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Novartis Research and Development

MBG453/Sabatolimab

Clinical Trial Protocol CMBG453B12201 / NCT03946670

A randomized, double-blind, placebo-controlled phase II multi-center study of intravenous MBG453 added to hypomethylating agents in adult subjects with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria

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List of abbreviations

ADA	Anti-drug Antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
ANA	Antinuclear antibodies
ASCO	American Society of Clinical Oncology
ASMA	Anti-smooth muscle antibodies
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BLQ	Below the Limit of Quantitation
BMA	Bone marrow aspirate
BSA	Body surface area
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulation
CG	Cockcroft-Gault
CMML	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
[redacted]	
COVID-19	Coronavirus disease of 2019
CR	Complete Remission
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EBV	Epstein–Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event Free Survival
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
[redacted]	

EOT	End of treatment
[redacted]	
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
ESA	Erythropoiesis Stimulating Agent
ESMO	European Society for Medical Oncology
FA	Final Analysis
FAS	Full Analysis Set
FDA	Food and Drug Administration
FUP	Follow Up
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma-glutamyl-transferase
GLDH	Glutamate dehydrogenase
HAV	Hepatitis A virus
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HI	Hematologic improvement
Hgb	Hemoglobin
HI-E	Erythroid
HI-P	Platelet
HI-N	Neutrophil
HIV	human immunodeficiency virus
HMA	Hypomethylating agent
HSCT	Hematopoietic stem cell transplantation
i.v.	intravenous
IA	Interim Analysis
ICF	informed consent form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig	Immunoglobulin (Ig-M; Ig-G; Ig-A; Ig-E)
INR	International normalized ratio
IPSS-R	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
LC-MS	Liquid Chromatography Mass Spectrometry
LDH	lactate dehydrogenase
LFT	Liver function test
LMWH	Low Molecular Weight Heparin
LPLV	Last Patient Last Visit
mAb	Monoclonal antibody
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mCR	marrow Complete Remission
MCV	mean corpuscular volume
MDS	Myelodysplastic syndromes
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
Mg	milligram(s)
mL	milliliter(s)
Ml	milliliter(s)
[redacted]	
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	
NK	Natural Killers
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
PFS	Progression free survival
[redacted]	
PK	pharmacokinetic(s)
PR	Partial remission
[redacted]	
PS	Performance status
PTA	Post Trial Access
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	red blood cell(s)

RNA	Ribonucleic acid
s.c.	subcutaneous
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SSC	Steering committee
SD	Stable disease
SOC	Standard of Care
[redacted]	
SUSAR	Suspected Unexpected Serious Adverse Reactions
T3	Triiodothyronine (thyroid hormone)
T4	Thyroxine (thyroid hormone)
TBL	total bilirubin
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TLS	Tumor lysis syndrome
TSH	Thyroid-Stimulating Hormone
ULN	upper limit of normal
WBC	white blood cell(s)
WoC	Withdrawal of Consent
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biological Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
[redacted]	
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed up or traced over time
Control drug	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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from the 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 subject permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Subject agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
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)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined 4 years after last subject randomized, which is the data cut-off date of the final OS analysis.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained The action of enrolling one or more subjects.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”

Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal data	Subject information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Re-screening	If a subject fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A 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 subjects as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
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 number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
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	Withdrawal of consent from the study occurs when the 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.

use of data/biological samples	This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 4 (02-Sep-2021)

As of the release of this amendment, enrollment has been completed on 10-Aug-2020 with 127 subjects randomized. The complete remission (CR) rate analysis (first of two primary endpoints) has taken place in May-2021 and the DMC recommended to continue the study blinded without changes. The study team, investigators and patients have not been made aware of any unblinded analysis result.

Amendment rationale

The main purpose of this amendment is to clarify that long-term safety and efficacy data is collected until 4 years after last subject was randomized, which is the time of the end of study and the data cut-off date for the final overall survival (OS) analysis. Further, based on the observed pooled Progression Free Survival (PFS) events, the pooled rate of discontinuations without PFS event, the limited number of subjects that are still at risk to have a PFS event and the predictions of future PFS events, the target number of PFS events for the final PFS analysis might not be reached at all or within a reasonable time frame. Thus, the final PFS analysis (FA) data cut-off date is now planned to be approximately 4 months after the interim PFS analysis (IA) data cut-off date (or after approximately 108 PFS events are observed if this is earlier) if PFS is not already significant at IA. The final PFS analysis if applicable, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date. Based on FDA's recommendation, the alpha spending function for PFS and OS analyses were modified to use O'Brien and Fleming boundaries.

Post Trial Access (PTA) language was included to clarify the provision of study treatment to trial subjects who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator's evaluation.

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.

Additional guidance for COVID-19 vaccinations was added to avoid overlapping adverse events with study treatment including update on risk and benefits session.

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.

Glossary: Glossary terms added and existing terms modified for clarity.

[redacted].

Section 3: Clarifies that long-term safety and efficacy data is collected until 4 years after last subject randomized.

Section 4.3.2:

- Clarification that MBG453 was well tolerated as a single agent or when it is administered intravenously in combination with decitabine or azacitidine to MDS/AML subjects.
- Additional efficacy data from study CPDR001X2105 with data cut-off 25-Jun-2020 included.

Section 4.3.3: Added information based on CPDR001X2105 study data.

Section 4.4: Clarifies timelines for final PFS analysis, interim OS analysis and final OS analysis.

Section 4.5:

- Added information based on CPDR001X2105 study
- Language added no substantial risk identified for subjects' safety due to the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Corona Virus) and the COVID-19 (Coronavirus disease of 2019) pandemic.

Section 4.7: Section added “Rationale for Public Health Emergency Mitigation Procedures”

Section 6.1.5: Addition of Post-Trial Access (PTA) information.

Section 6.2.2: Vaccination against COVID-19 is allowed during screening and during the treatment phase, unless these are live vaccines, but should not be administered on the same day of study treatment administration to avoid potential overlapping adverse events.

Section 6.4: Clarification on treatment unblinding criteria and parameters following PFS IA, PFS FA and Interim OS analysis.

Section 7: Allowance of informed consent discussion remotely due to Public Health Emergency (e.g. telephone, videoconference) if allowable by a local Heath Authority.

Section 8:

- Allowance of alternative methods of providing continuing care by the investigator due to Public Health Emergency as the situation dictates and if allowable by a local Health Authority and depending on operational capabilities. 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.
- Unscheduled pre-dose ECG timepoint moved from the Central ECG Collection Plan to Local ECG Collection Plan. Unscheduled timepoints should be performed on local ECG machine if clinically indicated. In case of new abnormalities, a cardiologist should be consulted, as needed.

Section 8.3.1:

- Clarifies that pathology reports should be collected and sent to the Novartis designated central laboratory for storage until final PFS analysis data cut-off date.
- Updated with new Withdrawal of Consent (WoC) language

Section 8.4: During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone

or virtual calls can occur as necessary for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

Section 8.4.1: 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, if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be required for patient's management and used.

Section 8.4.2: Unscheduled pre-dose ECG timepoint moved from the Central ECG Collection Plan to the Local ECG Collection Plan. Unscheduled timepoints should be performed on local ECG machine if clinically indicated. In case of new abnormalities, a cardiologist should be consulted, as needed.

Section 8.4.3: Updated with Public Health Emergency language as related to pregnancy testing.

[redacted]

Section 9.1.1: Updated with new WoC language

Section 9.1.2: Updated with new WoC language

Section 9.1.3: Updated with new WoC language

Section 9.1.4: Updated with new WoC language

Section 9.1.6: Updated with new WoC language

Section 9.2:

- Clarifies EOS definition
- Addition of PTA information

Section 10.1.1: Adverse Event (AE) duration and outcome reporting

Section 10.1.3: Clarification of SAE reporting requirements

Section 10.2.1: Clarification of DMC responsibilities and meeting frequency

Section 10.2.2: Clarification of SC unblinding plan

Section 12: Clarifies timelines for final PFS analysis, interim OS analysis and final OS analysis.

Section 12.5.1: Clarifies timelines for final PFS analysis, interim OS analysis and final OS analysis.

Section 12.7:

- Clarifies timelines for final PFS analysis, interim OS analysis and final OS analysis
- The O'Brien and Fleming spending function will be used for the interim and final analysis

Section 12.8.1: Clarifies timelines for final PFS analysis, interim OS analysis and final OS analysis

Section 15: References for the Rho Family and Pocock spending functions removed. Reference for the O'Brien and Fleming spending function added.

Appendix 2: Table 16-1 and Table 16-2 – update on liver events ALP to ≥ 2 × ULN instead of ALP to > 2 × ULN

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.

Amendment 3 (06-May-2020)

Amendment rationale

As of the release of this amendment, 61 sites have been initiated and 96 subjects have been randomized to the study.

The purpose of this amendment is to update the definitions of the RBC or platelet transfusion dependence and transfusion independence in Section 8.3, Table 8-2 based on FDA feedback. 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 high-risk MDS patients at baseline (IWG 2006, IWG 2018). Transfusion independence will be defined as absence of any transfusion during a given period of observation.

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.

Section 5.2: Exclusion criteria numbering was adjusted due to a typo on Amendment 2.

Section 6.1.1: Sentence was removed as instructions for the preparation and dispensation of MBG453 or placebo will be provided in the Pharmacy Manual.

Section 8.3.1 - Table 8-2: Transfusion independence and dependence definition were updated.

Section 8.4.1: Footnote was added to Table 8-5 to allow Troponin I to be performed in case Troponin T is not available.

Section 10.1.1: Adverse event collection language in patients starting new antineoplastic therapy was updated.

Section 12.3: Transfusions will be summarized using 8 weeks intervals prior and post baseline.

Section 12.5.1: Transfusion independence definition was updated as per Table 8-2.

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 trial specific model ICF.

Amendment 2 (13-Jan-2020)

Amendment rationale

As of the release of this amendment, 52 sites have been initiated and 39 subjects have been randomized to the study.

The primary purpose of this amendment is to address Heath Authorities' requests and Study Steering Committee's (SSC) recommendations.

Based on FDA feedback, Event Free Survival (EFS) was added as secondary endpoint. This endpoint is defined in analogy with the EFS definition used for AML. Events will include lack of reaching complete remission within the first 6 months, relapse from complete remission or death due to any cause, whichever occurs first.

In addition, PK and IG samples collection was prolonged and the time-points for collection were updated accordingly

The table 8-2 relating to efficacy response assessment has been updated as follows:

The SSC recommended to prohibit use of erythropoietin stimulating agents and thrombopoietic agents during the course of the study as their use could mask cytopenias. However, G-CSF cannot be prohibited, because it is part of the SOC in the context of infection or septicemia. Therefore, the note in the table for complete remission was updated accordingly. Confirmation of CR by peripheral blood at 4 weeks was removed as retreatment with HMA every 4 weeks could potentially bias results. CR is considered confirmed if progression or relapse from CR are not observed within 4 weeks (see Section 12.4.1.1). Assessment hematological improvements based on IWG 2006 criteria were added in the table and the definitions of transfusion independence/dependence status were adapted to reflect the IWG 2018 criteria. Reference values to determine significant increase in blasts or decrease in blood values have been added.

Change has been made in the inclusion criterion Nº 9 relating to the adequate renal function. The most recent Modification of Diet in Renal Disease (MDRD) formula instead of the Cockcroft-Gault (CG) formula should be used to estimate the renal function. MDRD formula is more accurate than the CG formula below an eGFR of 60 milliliters per minute per 1.73 meters squared and is generally more appropriate to identify renal impairment in older population such the MDS population (median age around 70 years old)

A modification has been made in the exclusion criterion Nº 14 relating to previous cancer to clarify that low-risk MDS subjects who were adequately treated with lenalidomide and failed are eligible. Per exclusion criterion Nº 2, lenalidomide must not have been administered for intermediate, high or very high-risk MDS

The safety information has been updated to be in alignment with the Investigator's Brochure Edition 5.1 (cut-off 15-Oct-2019).

In addition, clarifications and corrections are made throughout the protocol as well as editorial change to improve flow and consistency. Other minor editorial changes and corrections were made throughout the protocol for consistency and/or clarifications.

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: secondary objective, key inclusion and exclusion criteria, efficacy assessment were updated.

Section 2 - Table 2-1

- Secondary objective, to assess EFS in each treatment arm, was added
- Endpoint for secondary objective, Leukemia free survival was updated to add diagnosis of extramedullary acute leukemia as an event.
- Endpoint for secondary objective, to assess HI responses rate was added
- Endpoint for secondary objective, to assess the duration of RBC/platelet transfusion independence was added

Section 4.2 and 4.3.2 –Updated with the data from latest version of the Investigator Brochure Edition 5.1 (data cut-off, 15-Oct-2019)

Section 5.1

- Inclusion criteria Nº 4, 5, have been slightly modified to be more clearly aligned with the study population definition in section 5. Subjects who can be enrolled into the present trial are subjects who are not eligible for transplant or intensive chemotherapy).
- The adequate limit for bilirubin for isolated Gilbert Syndrome was added in inclusion criterion Nº 8
- Change has been made in the inclusion criterion Nº 9 relating to the adequate renal function

Section 5.2 – Exclusion criteria Nº 1, 2, 3, 10, 14, 15, 16, 18, 20 were updated. The exclusion Nº 11 has been deleted as it is not relevant in the MDS patient population. Such a criterion is more pertinent for AML patients, who are excluded per exclusion criterion Nº 8

Section 6.1.1 – Table 6-1 – footnote was added to include other locally available HMA dose strengths

Section 6.1.4 – Typo was corrected, to indicate the correct referenced section

Section 6.2.1 - Editorial changes to the protocol language to enhance clarity

Section 6.2.2 – Updated per SSC recommendation to prohibit use of erythropoietin stimulating agents and thrombopoietic agents during the course of the study. Editorial changes to the protocol language to enhance clarity

Section 6.3.1 - Editorial changes to the protocol language to enhance clarity

Section 6.4 – Added clarification for samples received by bio-analyst. Added [redacted]

Section 6.5.1 – Table 6-2 - Editorial changes to enhance clarity

Section 8 – Treatment window, laboratory test window (hematology and chemistry) and procedure window (bone marrow) were added. Clarity was provided for safety follow up

Table 8-1 – Assessment Schedule:

- Thyroid, urine pregnancy, PK and IG assessment collection time-points were added
- Row was added for Peripheral blood collection to enhance clarity
- Row for Antineoplastic therapies was updated
- Time points were updated for Prior/concomitant medications, surgery and medical procedures assessment; and Adverse Events assessments
- Screening time point was removed for Response Assessment
- Footnote Nº 2, 5, 9, 11, 12, 14, 18, 19 and 20 were updated to enhance clarity

Section 8.2 - Editorial changes to the protocol language to enhance clarity

Section 8.3 – Response criteria section was updated and hematological improvement definition was added. Editorial changes to the protocol language to enhance clarity

Section 8.3.1 – Response confirmation was removed. Editorial changes to the protocol language was added to enhance clarity

Section 8.3.1 - Table 8-2

- Response category: CR, definition was updated
- Response category: Relapse from CR, Disease progression were updated to enhance clarity. In order to ensure standardization, the reference values to determine significant increase in blasts or decrease in blood values have been added
- Hematological improvement category based on Modified Hematological Improvement per IWG-MDS criteria in MDS (Cheson et al 2006) were added. Transfusion independence and dependence definition were updated

Section 8.4.1 – Table 8-5 – Test category: Chemistry – Troponin T test; Additional tests – Free T3, Free T4, were added to the chemistry collection panel

Section 8.4.2 – Information related to ECG collection time points was updated

Section 8.4.3 – Urine / serum pregnancy test collection during safety follow up period was updated

Section 8.5.1 - Editorial changes were made

Section 8.5.2.1

- text related to PK, IG [redacted] collection time-point was updated
- Table 8-8: PK and IG collection time-points were updated. Footnote was added to clarify PK, IG [redacted] samples will be analyzed only in subjects receiving MBG453

Section 8.5.3.1 - Editorial changes to the protocol language to enhance clarity. Information regarding storage of biological samples was added

Section 9.1.5 - Editorial changes to the protocol language to enhance clarity

Section 9.2

- typo in the end of the study definition was corrected
- the paragraph, for the study treatment provision at the end, had a discrepancy, this discrepancy was removed

Section 10.1.1 - Details of the grade 3 & 4 AE reporting if occurred second time is deleted and AE monitoring details is added

Section 10.1.3 - Criteria for reporting of SAE was updated

Section 12.1 - typo corrected to enhance clarity and definition of the safety set was modified. Subjects who will never took MBG453 will be analyzed in the HMA + placebo arm.

Section 12.3 – number of cycles of each study drug component will not be summarized.

Section 12.4.1.1 – abbreviation updated and definition of a confirmed CR was modified. Response confirmation was removed

Section 12.4.1.2 – explanations for subjects that discontinuation from study due to lost to follow-up or withdrawal of consent were added. Abbreviation was updated

Section 12.4.2.1 - Editorial changes to the protocol language to enhance clarity

Section 12.4.3 - Editorial changes to the protocol language to enhance clarity

Section 12.5.1 - [redacted]

Section 12.5.2

- protocol language updated to enhance clarity
- on-treatment period for safety analyses updated
- description of summary tables for AE updated

Section 12.5.3 - Protocol language updated to enhance clarity

Section 12.7 - Editorial changes to enhance clarity; number of expected OS events at the PFS IA and information fraction were corrected.

[redacted]

IRB Section

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

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

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

Amendment 1 (10-Apr-2019)

Amendment rationale

As of the release of this amendment, no site has been initiated, no subject has been screened and no subject has received study treatment in this trial.

The primary purpose of this amendment is to add a general guideline for dosing modifications of the investigational drug (MBG453/placebo) in relation to non-hematologic non-immune-related toxicities that are clinically significant according to the investigator and possibly attributable to the investigational drug. This guideline does not apply to non-hematologic non-immune-related toxicities that are attributable to decitabine/azacitidine or the myelodysplastic syndrome and its complications.

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.

Section 4.5 – A reference was added to the general guideline in Section 6.5.1.

Section 6.5.1 – Table 6-2 – General guideline was added for non-hematologic non-immune-related toxicities possibly attributable to the investigational drug; and the text of the section has been updated accordingly.

Section 8 – Table 8-1 – Typo corrected related to antineoplastic therapies including transplant since discontinuation of study treatment.

IRB Section

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

The changes herein do NOT affect the trial specific model ICF.

Protocol summary

Protocol number	CMBG453B12201
Full Title	A randomized, double-blind, placebo-controlled Phase II multi-center study of intravenous MBG453 added to hypomethylating agents in adult subjects with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria.
Brief title	A Phase II efficacy and safety study of MBG453 in combination with hypomethylating agents in subjects with IPSS-R intermediate, high or very high-risk myelodysplastic syndrome (MDS).
Sponsor and Clinical Phase	Novartis Phase II
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 HMA (azacitidine or decitabine) in adult subjects with IPSS-R intermediate, high, very high risk MDS. The justification for a double blind randomized placebo-controlled trial is to determine the efficacy of adding MBG453 to the current standard of care on the primary efficacy endpoints (complete remission and progression free survival). The randomized, double-blind placebo-controlled design minimizes the risk of bias introduced by assessments of efficacy, safety [redacted].
Primary Objective(s)	The 2 primary objectives are as follow: To determine if MBG453 combined with standard HMA therapy improves complete remission in subjects with intermediate, high, or very high risk MDS. To determine if MBG453 combined with standard HMA therapy improves PFS in subjects with intermediate, high or very high risk MDS.
Secondary Objectives	The secondary objectives are as follow: • To assess Overall Survival in each treatment arm. • To assess EFS in each treatment arm. • To assess Leukemia-free survival in each treatment. • To assess responses rate in each treatment arm. • To assess duration of complete remission in each treatment arm. • To assess time to complete remission in each treatment arm. • To assess the improvement in RBC/platelets transfusion independence in each treatment arm. • To assess the safety profile of MBG453 when given in combination with HMA. • To characterize the pharmacokinetics of MBG453 when given in combination with HMA. • To evaluate immunogenicity of MBG453 when given in combination of HMA.

Study design	This Phase II is a multicenter, randomized, two-arm parallel-group, double-blind, placebo-controlled study of MBG453 or placebo added to hypomethylating agents (azacitidine or decitabine, as per investigators' choice based on local standard of care (SOC)) in adult subjects with IPSS-R intermediate, high or very high risk myelodysplastic syndrome (MDS) not eligible for HSCT or intensive chemotherapy. Approximately 120 subjects will be randomized in a 1:1 ratio to treatment arms as follow: MBG453 400 mg IV Q2W and decitabine or azacitidine Placebo IV Q2W and decitabine or azacitidine The randomization will be stratified by 2 stratification factors: a) HMA (decitabine or azacitidine) selected by the investigator as per the local standard of care (SOC) and b) IPSS-R prognostic risk categories (intermediate, high or very high) at randomization. Crossover between treatment arms is not permitted at any time during the study.
Population	The study population will include adult subjects to be treated in first-line setting, with intermediate, high or very high risk per IPSS-R prognostic risk categories for myelodysplastic syndromes who do not qualify according to medical judgement for intensive chemotherapy or HSCT. Subjects with chronic myelomonocytic leukemia are not eligible for this trial.

Key Inclusion criteria	Subjects eligible for inclusion in this study must meet all of the following criteria:
	• Signed informed consent must be obtained prior to participation in the study.
	• Age ≥ 18 years at the date of signing the informed consent form (ICF)
	• Morphologically confirmed diagnosis of a myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) by investigator assessment with one of the following Prognostic Risk Categories, based on the International Prognostic Scoring System (IPSS-R):
	  • Very high (> 6 points)
	  • High (> 4.5-6 points)
	  • Intermediate (> 3-4.5 points): a subject determined to be in the Intermediate Prognostic Risk Category is only allowable in the setting of ≥ 5% bone marrow blast
	• 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 decision
	• Not eligible at the time of screening, for allogeneic stem-cell transplantation (HSCT) according to the investigator, based on local medical practice and institutional guidelines for treatment decisions
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2

Key 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 check point inhibitors (e.g. anti-CTLA4, anti-PD-1, anti-PD-L1, or anti-PD-L2), cancer vaccines are allowed except if the drug was administered within 4 months prior to randomization.

	2. Previous first-line treatment for intermediate, high or very high risk myelodysplastic syndromes (based on IPSS-R) with chemotherapy or any other antineoplastic agents including lenalidomide and hypomethylating agent (HMAs) such as decitabine or azacitidine. 3. History of severe hypersensitivity reactions to any ingredient of the study treatment (azacitidine, decitabine or MGB453) or their excipients, or to monoclonal antibodies (mAbs). 4. Currently using or used 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. Investigational treatment for MDS received within 4 weeks prior to randomization. In case of a checkpoint inhibitor: 4 months minimum prior to randomization interval is necessary to allow enrollment. 6. Active autoimmune disease requiring systemic therapy (e.g. corticosteroids). 7. Live vaccine administered within 30 Days prior to randomization.
Study treatment	MBG453, placebo, decitabine, azacitidine.
Efficacy assessments	Efficacy assessments will be performed according to the IWG and WHO criteria for MDS (Cheson et al 2000, Cheson et al 2006, Arber et al 2016, Platzbecker et al 2018). Response criteria in MDS are described as Complete remission (CR), marrow Complete remission (mCR), Partial Remission (PR), Stable Disease (SD), Relapse from CR, Disease Progression including transformation to acute leukemia. Response assessment will be performed by investigator according to the assessment schedule. Investigators will assess and document response/progression at each time point as per the visit schedule. For efficacy analyses, baseline is defined as the last non-missing assessment on or before the date of randomization. Bone marrow assessments will be performed at screening and pre-dose during treatment period at C4D1, C7D1, C10D1, and C13D1 and hematology assessments will be performed at screening, D1, D8 and D22 of each cycle until end of treatment and if clinically indicated at any time during the study. After C13D1, bone marrow assessments are to be done every 6 cycles (C19D1, C25D1, etc.) and hematology assessments every 2 months and if clinically indicated at any time during the study. Subjects can be assessed for disease response (bone marrow assessment, hematology, transfusion) at any time if clinically indicated for example if there is a clinical suspicion of progression/relapse, in particular after a subject has achieved a CR. In order to confirm that a subject achieves a CR, no progression or relapse from CR should be reported within the following 4 weeks.
Pharmacokinetic assessments	Pharmacokinetic (PK) 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, 12-lead electrocardiograms (ECGs), monitoring of laboratory markers in blood and urine.
[redacted]	

[redacted]

Data analysis	The CR rate analysis is planned when the last randomized subject has reached cycle 7 (or discontinued earlier). No interim analysis (IA) is planned for CR rate. The intent of this CR rate analysis is to assess whether MBG453 + HMA has superior efficacy than Placebo + HMA based on the CR rate. The other primary endpoint PFS will not be tested at this time point and is following a group sequential design. One interim analysis for PFS is planned after approximately 81 of the targeted 108 PFS events (i.e. at approximately 75% information fraction) have been documented. If the PFS is not already significant at IA, the final PFS analysis will be conducted after observing approximately 108 PFS events or approximately 4 months after the PFS IA data cut-off date, whichever comes first. The final PFS analysis if applicable, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date. The final OS analysis will be conducted at end of study, i.e. with a data cut-off date of 4 years after the last subject randomized.
Key words	Phase II, MBG453, TIM-3, decitabine, azacitidine, placebo, myelodysplastic syndrome (MDS).

1 Introduction

1.1 Background

It is estimated that 15,000 to 20,000 new cases of Myelodysplastic Syndromes (MDS) are diagnosed annually in the USA (Klepin 2016). The incidence of MDS is more frequent in male patients and increases with age, with a median age at diagnosis of about 70 years.

MDS correspond to a heterogeneous group of hematopoietic diseases that are associated with impaired bone marrow function, ineffective hematopoiesis, elevated bone marrow blasts and persistent peripheral blood cytopenias. Cytogenetics abnormalities are frequently present at time of diagnosis. Patients with MDS have a predisposition to developing acute myeloid leukemia (AML) (Heaney and Golde 1999). Although progression to AML can frequently lead to death in patients with MDS, many deaths are consequences of cytopenias and marrow failure in the absence of leukemic transformation. To account for disease heterogeneity, assess the risk of progression to AML and estimate survival, MDS prognostication systems have been proposed. Prognosis is usually determined using the revised International Prognostic Scoring System (IPSS-R), which considers the percentage of bone marrow blasts, the number of cytopenias, and bone marrow cytogenetics. Patients with untreated MDS are stratified into five IPSS-R prognostic risk categories: very low, low, intermediate, high and very high, with median survival times of 8.8, 5.3, 3.0, 1.6 and 0.8 years, respectively and with 25% AML transformation rate of NR (not reached), 10.8, 3.2, 1.4, 0.73 years respectively (Greenberg et al 2012). In a large database of MDS patients (n = 7,012) distribution of patients across the 5 IPSS-R risk categories were as follows: Very low (19%), low (38%), intermediate (20%), high (13%) and very high (10%) (Greenberg et al 2012).

Current treatment guidelines for MDS recommend modification of the disease with hematopoietic stem cell transplantation (HSCT, treatment with a curative intent), hypomethylating agents (HMA: azacitidine or decitabine) or intensive chemotherapy (Fenaux et al 2014). Choice of therapy is mainly driven by the IPSS-R score, the overall general health status and clinical assessment of comorbidities. For patients eligible for intensive therapy, and for whom a donor is available for HSCT or for whom the marrow blast count requires reduction, intensive chemotherapy may be considered (Steensma 2018). HSCT remains the only curative option for MDS patients; however, many MDS patients are not candidates for HSCT (Passweg et al 2011; and see Section 4.1). In MDS patients without major co-morbidities who are classified as intermediate, high, very high risk by IPSS-R, and who do not qualify for HSCT or intensive chemotherapy, HMAs remain the first-line reference treatment. HMAs (azacitidine or decitabine) are generally administered for a minimum of 6 cycles (repeat cycle after 4 weeks), and continued for as long as the patient benefits. HMAs (azacitidine or decitabine) have a similar safety profile. In clinical practice, bone marrow suppression is the most common adverse reaction in demethylation therapy, and is also the main reason for the dose-reduction or discontinuations of decitabine or azacitidine. Supportive care, including blood transfusions, is frequently required.

HMAs have improved outcomes for patients with intermediate/high risk/very high risk MDS; especially for patients who are not candidates for intensive chemotherapy regimens or HSCT. However, despite these improvements, prognosis for patients treated with HMA remains poor.

Complete Remission rate (CR) with azacitidine or decitabine in higher-risk (IPSS; intermediate-2 & high, IPSS-R; intermediate, high & very high) MDS is rare. CR rate has been shown to be 9% for decitabine and 17 % for azacitidine in pivotal trials (Kantarjian et al 2006, Fenaux et al 2009). Other trials reported CR rate in MDS patients ranging from 7% to 25% with azacitidine and from 9% to 35% with decitabine (Saunthararajah 2013).

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 has transformed to AML, survival generally will not exceed 6 months. Thus, improved treatments in addition to HMA and/or as an alternative to HMAs are urgently needed in this patient population.

The primary goals for treatment of higher-risk (intermediate/high risk/very high risk) MDS patients are to improve overall survival (OS) and delay/prevent AML evolution. International Working Group (IWG) 2006 response criteria were developed to predict clinical outcomes in general practice and clinical trials for MDS patients treated with standard of care (HMA). Validation of IWG response criteria has shown that the best responses to first line therapy in higher-risk MDS correlate with OS. This finding suggests that CR rate may be considered as a relevant primary endpoint in Phase II clinical trials investigating novel therapies, especially when other time related endpoints will evaluate disease progression or transformation to acute leukemia (progression free survival (PFS)) or transfusion free intervals (Cheson et al 2006, Komrokji et al 2015, Nazha et al 2016, Bell et al 2018).

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 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. Overall response rate was observed in 15/20 (75%), 15/21 (71%), 2/15 (13%), and 7/20 (35%) of patients treated with azacitidine+nivolumab, azacitidine+ipilimumab, nivolumab, and ipilimumab, respectively; CR/CRp was observed in 10/20 (50%), 8/21 (38%), 0 (0%), and 3 (15%) in patients treated with azacitidine+nivolumab, azacitidine+ipilimumab, nivolumab, and ipilimumab, respectively. Main toxicities reported were as follows: skin rash (11%); fatigue (9%); pain (7%); infection (6%); febrile neutropenia (5%); pruritus (6%); diarrhea (5%); constipation, nausea (4% each), alanine aminotransferase (ALT) elevations, anorexia, cough (3% each). This provides preliminary evidence that checkpoint inhibition combined with hypomethylating agents is feasible in front-line MDS and may have clinical activity (Garcia-Manero et al 2018). A Phase Ib/II study involving azacitidine

and nivolumab has been conducted in 70 relapsed/refractory AML patients. The overall response rate (ORR) in this study was 33%: 23 clinical responses were reported including 4 complete remission, 11 complete remission with insufficient recovery of counts (CRi), 1 partial remission (PR), and 7 patients with hematologic improvement (HI) maintained > 6 months. The ORR was 58% and 22%, in HMA-naive (n = 25) and HMA pre-treated (n = 45) patients, respectively. Duration of response among responders was 5.2 months. 3 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 3/4 immune related adverse events (irAE) occurred in 8 (11%) patients (Daver et al 2018).

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 diseases were reported and transplants were possible in some patients. 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. 5 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 MDS patients and detection on blasts increases as MDS progresses. Therefore the blockade of this other immune checkpoint 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, ligand-blocking, 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).

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

1.2 Purpose

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

The humanized anti-TIM-3 IgG4 monoclonal antibody (mAb) 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 HMA (azacitidine or decitabine) in adult subjects with IPSS-R intermediate, high, very high risk MDS. This randomized, two-arm, parallel-group, double-blind, placebo-controlled study will compare MBG453 plus HMA or placebo plus HMA. Objectives and endpoints of the study are detailed in Section 2.

2 Objectives and endpoints

The objectives and associated endpoints are presented in 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 determine if MBG453 combined with standard HMA therapy improves complete remission in subjects with intermediate, high, or very high risk MDS	• Complete remission (CR) rate according to International Working Group (IWG) for MDS (Section 8.3) as per investigator assessment (Section 12.4.1.1)
• To determine if MBG453 combined with standard HMA therapy improves PFS in subjects with intermediate, high or very high risk MDS	• PFS is defined as time from randomization to disease progression (including transformation to acute leukemia per WHO 2016 classification), relapse from CR according to IWG-MDS (Section 8.3) or death due to any cause, whichever occurs first, as per investigator assessment (Section 12.4.1.2)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess Overall Survival in each treatment arm	• Time from randomization to death due to any cause
• To assess EFS in each treatment arm	• EFS is defined as time from randomization to lack of reaching CR within the first 6 months, relapse from CR or death due to any cause, whichever occurs first. CR and relapse from CR are defined according to International Working Group (IWG) for MDS (Section 8.3) as per investigator assessment.
• To assess Leukemia-free survival in each treatment	• 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 responses rate in each treatment arm	• Percentage of CR/mCR/PR according to IWG-MDS as per investigator assessment and HI according to IWG-MDS
• To assess duration of complete remission in each treatment arm	• Time from the date of the first documented CR to the date of first documented relapse from CR or death due to any cause, whichever occurs first
• To assess time to complete remission in each treatment arm	• Time from randomization to the first documented CR
• To assess the improvement in RBC/platelets transfusion independence in each treatment arm.	• Number and percent of subjects who are RBC/platelets transfusion independent and duration of transfusion independence (Section 8.3) after randomization as per IWG-MDS
• To assess the safety profile of MBG453 when given in combination with HMA	• Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs, incidence of notable ECG abnormalities

Objective(s)	Endpoint(s)
• To characterize the pharmacokinetics of MBG453 when given in combination with HMA	• Serum concentrations and pharmacokinetic parameters for MBG453
• To evaluate immunogenicity of MBG453 when given in combination of HMA	• Anti-drug Antibody (ADA) prevalence at baseline and ADA incidence on-treatment

[redacted]

3 Study design

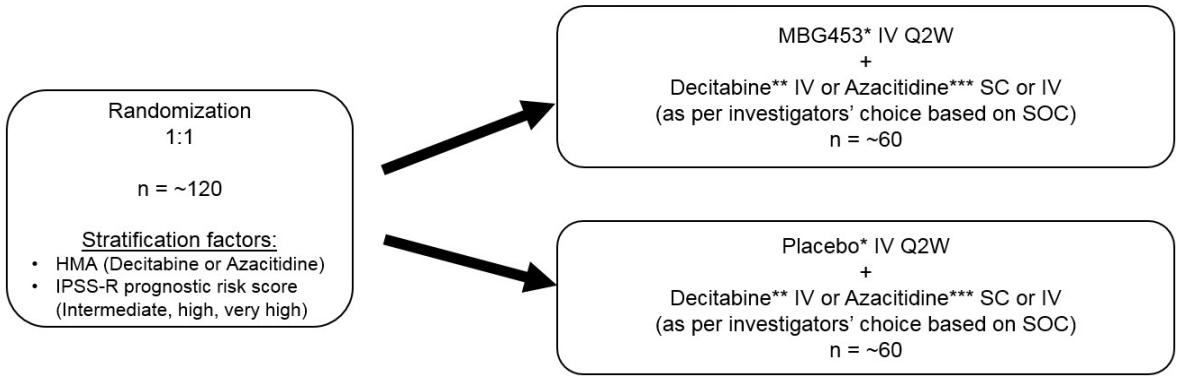
This Phase II is a multicenter, randomized, two-arm parallel-group, double-blind, placebo-controlled study of MBG453 or placebo added to hypomethylating agents (azacitidine or decitabine, as per investigators' choice based on local standard of care (SOC)) in adult subjects with IPSS-R intermediate, high or very high risk myelodysplastic syndrome (MDS) not eligible for HSCT or intensive chemotherapy.

Approximately 120 subjects will be randomized in a 1:1 ratio to treatment arms as described in the Figure 3-1. The randomization will be stratified by 2 stratification factors: a) HMA (decitabine or azacitidine) selected by the investigator as per the local standard of care (SOC) and b) IPSS-R prognostic risk categories (intermediate, high or very high) at randomization. Crossover between treatment arms is not permitted at any time during the study.

The study treatment consists of cycles of MBG453 or placebo in combination with HMA administered to the subjects until treatment discontinuation (Section 6.1.5 and Section 9.1.1). Treatment options and dosing information is provided in Section 6.1.1. The planned duration of a cycle is 28 days.

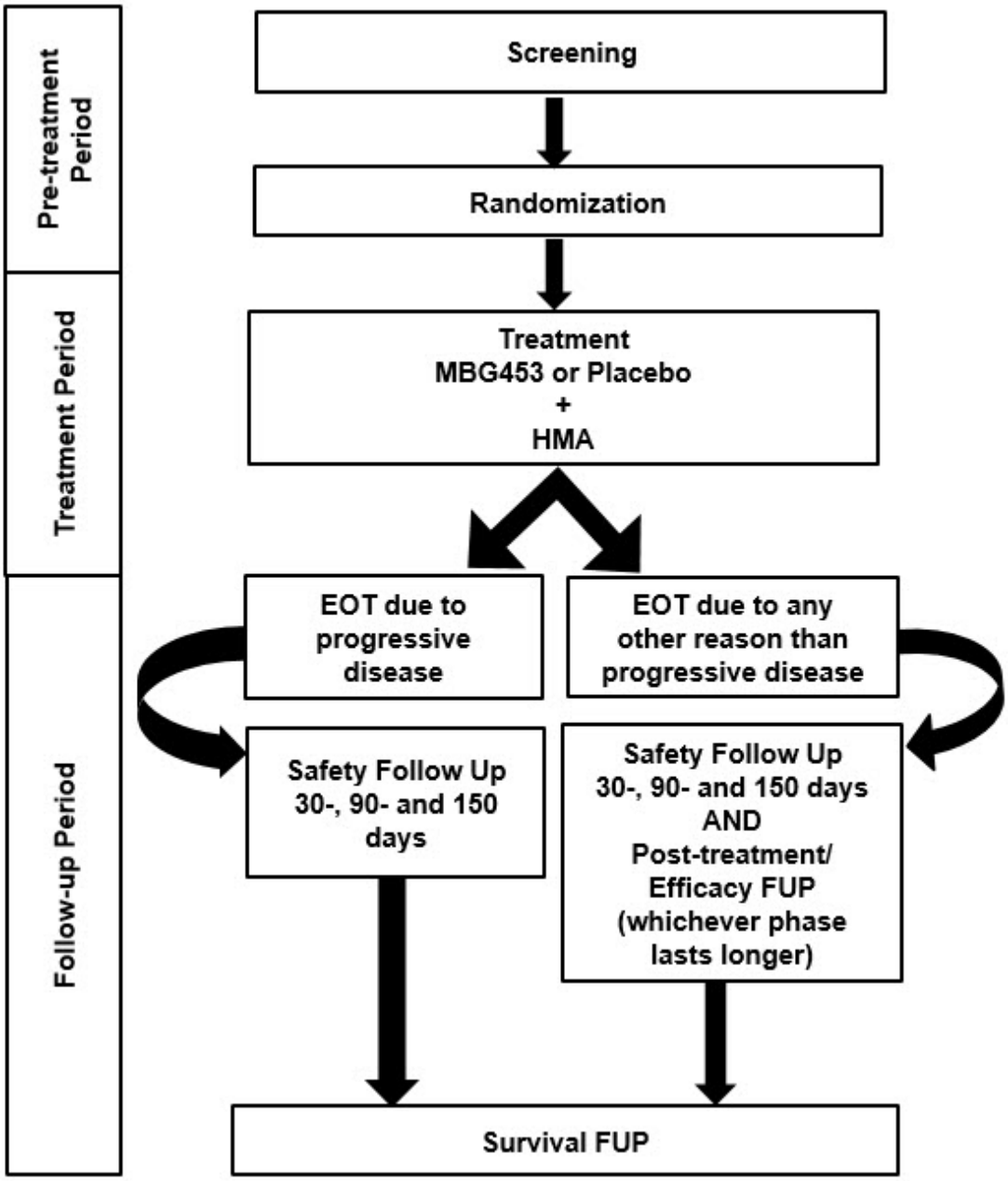
After the end of study treatment, all subjects must be followed for adverse events (AEs) for 30 days following the last dose of azacitidine or decitabine, or 150 days following the last dose of MBG453 or placebo, whichever is later. In addition, all subjects who discontinued study treatment will enter a long-term follow-up (for efficacy and/or survival status) for up to 4 years from the last subject randomized. Subjects who are scheduled for hematopoietic stem-cell transplant (HSCT) or intensive chemotherapy at any time during the course of the study will be discontinued from study treatment but will also enter a long term follow-up (for efficacy and/or for survival status) for up to 4 years from the last subject randomized (Section 12.8.1).

Figure 3-1 Study design



*MBG453 or placebo: 400 mg on D8 and D22
**Decitabine: 20 mg/m^2 from D1 to D5
***Azacitidine: 75 mg/m^2 from D1 to D7 or D1 to D5 + D8 to D9

Figure 3-2 Study flow



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 the current standard of care on the primary efficacy endpoints (complete remission and progression free survival). The randomized, double-blind placebo-

controlled design minimizes the risk of bias introduced by assessments of efficacy, safety [redacted].

In this trial, subjects with higher risk MDS (defined as very high risk, high risk, intermediate risk with ≥ 5% blasts present in the bone marrow at baseline) will be enrolled. The choice of HMA (decitabine or azacitidine) is left to the investigator's discretion in order to reflect the local approval and the local clinical practice. IPSS-R score at baseline is a crucial clinical indicator in the sense it will inform about the treatment outcomes and prognostic of each given subject. Each level of risk (intermediate/high/very high) is associated with a different survival length and potential of leukemic transformation (see Section 1.1). Azacitidine and decitabine used in monotherapy lead to similar clinical effectiveness and safety profiles (see Section 4.3.1). However, it cannot be ruled out treatment outcome of a novel compound given in a combination regimen may vary with nature of the partner drug. Therefore stratification will be used to balance allocation between treatment arms in terms of risk category per IPSS-R and type of hypomethylating agent (decitabine or azacitidine).

[redacted]

[redacted]

4.3 Rationale for choice of the combination drugs

4.3.1 Rationale for HMA (azacitidine or decitabine)

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

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

Higher risk MDS patients who are non-transplant candidates are commonly treated with HMA therapy. HMAs (azacitidine and decitabine) represent the only approved therapeutic agents and constitute the current standard 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.

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

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

Azacitidine and decitabine regimens used in this trial are the most studied regimens and recommended by international treatment guidelines (See Section 6.1.1.).

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

Safety data indicate that the compound was well tolerated overall in 291 subjects with solid tumors or hematological malignancies exposed to MBG453. Two trials are ongoing: one Phase I/II open label, multicenter study of the safety and efficacy of MBG453 as single agent and in combination with PDR001 in adult subjects with advanced malignancies [CMBG453X2101] and a Phase Ib multi-arm, open label study of PDR001 and/or MBG453 in combination with decitabine in subjects with AML or high risk MDS [CPDR001X2105].

In particular, the compound was well tolerated as a single agent or when it is administered intravenously in combination with decitabine or azacitidine to MDS/AML subjects. Please refer to Section 4.2 and the [MBG453 Investigator's Brochure] for more details.

Preliminary efficacy data reported in higher risk MDS subjects are showing high response rates. At the time of the latest data cut-off on 25-Jun-2020 among 35 evaluable patients with high-risk MDS, overall response rate (ORR) was 62.9% (22 patients) including 8 CR, 8 mCR (including 5 mCR with hematologic improvement [HI]) and 6 stable disease with HI. Median time to response was 2.0 months and estimated 6-month Duration of response rate for CR/mCR/PR was 90% (95% CI: 73.2-100%). Encouraging response rates were achieved in both patients with high-risk per IPSS-R MDS (ORR 50% [11/22]) and very high-risk per IPSS-R MDS (ORR 84.6% [11/13]) [CPDR001X2105].

4.3.3 Rationale for combining MBG453 with HMA (azacitidine and decitabine)

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

Combining HMAs with novel agents may improve their clinical efficacy and overcome resistance. The fact that immune checkpoint inhibitors have been able to generate deep and durable response in various cancers including hematologic malignancies together with emerging preclinical and clinical data (see Section 1.1) strongly supports the evaluation of the novel anti-TIM-3 antibody MBG453 combined with HMAs in MDS.

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

Emerging clinical data from the ongoing Phase I study [CPDR001X2105] enrolling high risk MDS subjects indicate that MGB453 plus decitabine or azacitidine combination is feasible, well tolerated and produces clinical responses (see Section 4.3.2). Please refer to Section 4.2 and to the [MBG453 Investigator's Brochure] for more details.

Azacitidine and decitabine exhibit a similar safety profile and share a similar mechanism of action. As a result, the combination of MBG453 with azacitidine is likely to be feasible and as tolerated as the combination MBG453 with decitabine. Immunomodulators, such as MBG453, may regulate CYP enzymes and may cause Drug-Drug Interaction (DDI) with small molecule drugs because of the potential to alter CYP mediated metabolism. However, cytochrome P450 mediated degradation is minor for HMA and therefore DDI between MBG453 and HMA is not expected. When MBG453 was administered in combination with decitabine in the CPDR001X2105 study, MBG453 PK were similar to that observed in the CMBG453X2101 study, while decitabine PK was similar to the label reported value.

In CPDR001X2105 study, a signal of a relevant clinical activity is being reported with high response rate, durable response and absence of disease progression in all high risk MDS and newly diagnosed AML subjects who were treated with MBG453 and HMA (see above).

4.4 Purpose and timing of interim analyses/design adaptations

The statistical basis for claim of efficacy in favor of the MBG453 arm is based on either statistical significance for CR rate or statistical significance for PFS as detailed in Section 12.4.2.

There was one analysis of the CR rate, with a data cut-off date fixed at 7 months after the last randomized subject. It has taken place in May-2021 and the DMC recommended to continue the study blinded without changes. PFS was not tested at this time point. A PFS interim analysis will be performed after 75% of the planned target PFS events have been observed. If the PFS is not already significant at IA, the final PFS analysis will be conducted after observing approximately 108 PFS events or at approximately 4 months after the PFS IA data cut-off date, whichever comes first. The final PFS analysis if applicable, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date. The final OS analysis will be performed with a data cut-off date of 4 years after the last subject randomized. The timing of the CR rate analysis, the interim and final PFS analyses and OS analyses are detailed in Section 12.4.2 and Section 12.7. Figure 12-2 described 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 [PDR001X2105], which showed achievement of durable complete remission or bone marrow CR in high risk MDS subjects 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 HMA 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 in combination with HMA, dose modifications must be applied per protocol based on clinical or laboratory findings, and a close safety monitoring will be performed during the study.

Occurrence of an immune-related event is an anticipated risk in subjects treated with checkpoint inhibitors, 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 guideline for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgement and that are possibly attributable to the investigational drug is also provided (see Section 6.5.1).

Based on currently available data, there are no known significant overlapping toxicities between decitabine or azacitidine and MBG453. However, there may be unforeseen risks from combining decitabine or 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 anti-tumor immune response, there is the potential for increased toxicity secondary to increase in cytokine release syndrome due to activation of T cells and macrophages, and there may also be changes in immune function that could lead to increased autoimmunity or risk of infection or risk of immune-related adverse events. All subjects enrolled will be monitored closely for these potential toxicities. Furthermore, as safety data of the azacitidine + MBG453 combination are not yet available from the ongoing [CPDR001X2105] study, the protocol of the trial stipulates that a data monitoring committee (DMC) (Section 10.2.1) will meet regularly to review safety data and initially when at least 10 subjects have received azacitidine combined with the study drug MBG453 or placebo for at least one cycle (approximately 5 subjects in each blinded treatment arm). Safety data from subjects receiving decitabine combined with the study drug MBG453 or placebo available will be reviewed as well at the same time.

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]

4.7 Rationale for Public Health Emergency mitigation procedures

In the event of a Public Health emergency as declared by Local or Regional authorities i.e. pandemic (eg COVID-19), epidemic or natural disaster, mitigation procedures may be required to ensure subject safety and trial integrity are listed in relevant sections of the present study protocol. 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 Population

The study population will include adult subjects to be treated in first-line setting, with intermediate, high or very high risk per IPSS-R prognostic risk categories for myelodysplastic syndrome who do not qualify according to medical judgement for intensive chemotherapy or HSCT. Subjects with chronic myelomonocytic leukemia (CMML) are not eligible for this trial.

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 a myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) by investigator assessment with one of the following Prognostic Risk Categories, based on the International Prognostic Scoring System (IPSS-R):
   - Very high (> 6 points)
   - High (> 4.5-6 points)
   - Intermediate (> 3-4.5 points): a subject determined to be in the Intermediate Prognostic Risk Category is only allowable with ≥ 5% bone marrow blasts at baseline
4. 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.
5. 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.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
7. AST and ALT ≤ 3 × upper limit of normal (ULN).
8. Total bilirubin ≤ 1.5 × ULN (except in the setting of isolated Gilbert syndrome where subjects may only be included with direct bilirubin ≤1.5 × ULN).
9. 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).
10. 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 check point inhibitors (e.g. anti-CTLA4, anti-PD-1, anti-PD-L1, or anti-PD-L2), cancer vaccines are allowed except if the drug was administered within 4 months prior to randomization.

2. Previous first-line treatment for intermediate, high or very high risk myelodysplastic syndromes (based on IPSS-R) with chemotherapy or any other antineoplastic agents including lenalidomide and hypomethylating agent (HMAs) such as decitabine or azacitidine.
3. History of severe hypersensitivity reactions to any ingredient of the study treatment (azacitidine, decitabine or MGB453) or their excipients, or to monoclonal antibodies (mAbs).
4. Currently using or used 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. Investigational treatment for MDS received within 4 weeks prior to randomization. In case of a checkpoint inhibitor: 4 months minimum prior to randomization interval is necessary to allow enrollment.
6. Active autoimmune disease requiring systemic therapy (e.g. corticosteroids).
7. Live vaccine administered within 30 days prior to randomization.
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 Chronic myelomonocytic leukemia (CMML), or primary or secondary myelofibrosis based on 2016 WHO classification (Arber et al 2016).
10. History of organ transplant or allogeneic hematopoietic stem cell transplant.
11. Exclusion criteria retired.
12. Any concurrent severe and/or uncontrolled medical condition. Subjects with active infection requiring parenteral antibacterial, antiviral or antifungal therapy which are controlled by treatment are eligible.
13. Cardiac or cardiac repolarization abnormality, including but not limited to any of the following:

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

    b) QTcF > 470 ms at screening, long QT syndrome or family history of unexplained cardiac death

    c) Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block).
14. 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 and failed lenalidomide are eligible

    c) Subjects with history of adequately treated malignancy for which no anticancer systemic therapy (namely chemotherapy, radiotherapy or surgery) is ongoing or required during the

course of the study. Subjects who are receiving adjuvant therapy such as hormone therapy are eligible.

15. Human immunodeficiency virus (HIV) infection not controlled by standard therapy and/or with known history of opportunistic infection.
16. Active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Subjects whose disease is controlled under antiviral therapy should not be excluded. For additional guidance regarding Hepatitis B, please refer to Section 16.4.
17. Other co-morbidity that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol.
18. Sexually active males unwilling to use a condom during intercourse while taking azacitidine or decitabine and for 3 months after stopping these drugs. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above, and their female partners will be instructed to use highly effective contraception.
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 during study treatment and for 3 months after the last dose of azacitidine or decitabine (or as per their respective local labels, 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 combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

    Women are considered post-menopausal and not of child-bearing potential if they have had over 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive

status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

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

6 Treatment

6.1 Study treatment

In this study, the "study treatment" refers to the combination of study drugs: MBG453 or placebo plus hypomethylating agent (HMA: decitabine or azacitidine).

The term "investigational drug" refers to the Novartis study drug, MBG453 or placebo. The choice of the HMA (as described in the following sections) will be selected by the investigator as per local standard of care (SOC) at randomization. The investigator choice for HMA must not be changed after randomization.

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

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	**Dose administration**	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply Type**	**Sponsor (global or local)**
MBG453 100mg/1ml /Placebo	400mg	Solution for infusion	Intravenous use	Double Blind	Sponsor (global)
MBG453 400mg/4ml /Placebo*	400mg	Solution for infusion	Intravenous use	Double Blind	Sponsor (global)
Decitabine 50mg single vial**	20mg/m^2	Lyophilized powder	Intravenous use	Open Label	Provided Locally
Azacitidine 100 mg single vial**	75mg/m^2	Lyophilized powder	Intravenous or subcutaneous use	Open label	Provided Locally
*During the study the MBG453 400mg/4ml/Placebo may be included as additional strength which will be globally supplied. **Other locally available dose strengths are acceptable					

Azacitidine and decitabine regimens used in this protocol were selected because they are the most studied regimens and recommended by international treatment guidelines (National

Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), Steensma 2018).

Decitabine should be administered according to standard clinical practice. A standard dose of decitabine (20 mg/m^2) will be given intravenously every day for five consecutive days on Days 1-5 out of a 28 day cycle (see local decitabine package insert). MBG453 or placebo infusions will be administered on Day 8 and Day 22 out of a 28 day cycle (Section 6.1).

Azacitidine should be administered according to standard clinical practice. A standard dose of azacitidine (75 mg/m^2) will be given subcutaneously or intravenously every day for seven consecutive days on Days 1-7 out of a 28 day cycle (see local azacitidine package insert). In keeping with standard clinical practice, the alternative schedule of 75 mg/m^2 for five consecutive days on Days 1-5, followed by a two-day break, then two consecutive days on Days 8-9 will also be permitted (alternative schedule). MBG453 or placebo infusions will be administered on Day 8 and Day 22 out of a 28 day cycle (Section 6.1).

If the alternative schedule is selected for azacitidine 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 Pharmacy Manual.

MBG453 or placebo will be administered at 400 mg via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated). There should be a period of at least 1 hour after the infusion whereby the subject requires close observation. Further instructions for the preparation and dispensation of MBG453 or placebo is described in the Pharmacy Manual.

6.1.2 Additional study treatments

Not applicable

6.1.3 Treatment arms/group

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

- MBG453 + HMA (decitabine or azacitidine) or
- Placebo + HMA (decitabine or azacitidine)

The randomization will be stratified by two stratification factors:

- Hypomethylating agents as per investigators' choice at randomization based on local standard of care (SOC): a) decitabine or b) azacitidine
- IPSS-R Prognostic Risk Categories: a) intermediate, b) high, c) very high

6.1.4 Guidelines for continuation of treatment

The study treatment consists of HMA plus MBG453 or HMA plus placebo (Section 6.1.1). Planned duration of a cycle is 28 days. 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

A subject may be discontinued from study treatment for reasons of unacceptable toxicity, progressive disease (including transformation to acute leukemia per WHO 2016 classification) , withdrawal of consent by the subject, pregnancy, failure to adhere the protocol or at the discretion of the investigator or if the study is terminated by the Sponsor. Continuation of treatment beyond progression (including transformation to acute leukemia) may be possible in selected subjects (Section 6.1.5.1).

Subjects 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 treatment to trial subjects following their completion of trial participation. PTA will be provided until one of the following is met: subject no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial subject's country, or the clinical program is discontinued for any other reason including toxicity.

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 with immunotherapy may get clinical benefit despite initial evidence of disease progression. Subjects will be allowed to continue the study treatment, HMA or MBG453 or placebo beyond disease progression if all following criteria are met:

- There is no overt transformation to acute leukemia with ≥ 30 % blast. Regarding subjects with low blast count (> 20% and < 30%), subjects may continue the study treatment if the benefit/risk remains positive according to the investigator
- There is a clinical benefit observed per investigator assessment
- No unacceptable toxicity is reported
- The subject continues to follow all protocol requirements

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. If a subject experiences a Grade 3 or Grade 4 infusion reaction, the investigational drug should be discontinued.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a subject experiences a Grade 3 or Grade 4 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 should be readily available.

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

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before 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 study treatment.

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

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 and 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, ongoing anticoagulant therapy should be temporarily discontinued to allow bone marrow sampling according to the institutional guidelines.

Anti-hypertensive therapy is allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to infusion with MBG453 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 replacement-dose steroids in the setting of adrenal insufficiency or transient exacerbation of other underlying diseases such as chronic obstructive pulmonary disease requiring treatment for ≤ 3 weeks. Systemic corticosteroids required for control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study administration. If more than 10 mg/day prednisone is used, study drug should be interrupted until the 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 during screening and during the treatment phase, but should not be administered on the same day of study treatment administration to avoid potential overlapping adverse events.

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

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

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 unless the subject is re-screened. The Subject identifier consists of the Center Number (Center No.), (as assigned by Novartis to the investigative site) with a sequential Subject No. suffixed to it, so that each subject 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.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information to register the subject. 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 IRT 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 Subject No. should be assigned for all re-screened subjects.

6.3.2 Treatment assignment, randomization

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

Following completion of screening procedures and prior to receive the first dose of study medication, the IRT system must be contacted to verify subject eligibility and randomize the subject to one of the treatment arms stratified by IPSS-R risk category and HMA use as determined by the investigator at randomization.

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. The IRT will specify a unique medication number for the first package of MBG453 or placebo to be dispensed 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 by:

- Hypomethylating agents as per investigators' choice at randomization based on local standard of care (SOC): a) decitabine or b) azacitidine
- IPSS-R Prognostic Risk Categories: a) intermediate, b) high, c) very high

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

6.4 Treatment blinding

At the time of the CR rate analysis, efficacy analyses will be performed by an independent statistician and reviewed by a data monitoring committee (DMC). Unblinded results from the CR rate analysis will not be communicated to the Novartis clinical team or to any party involved in the study conduct (apart from the independent statistician and DMC members) until the DMC has determined that either: (i) CR rate has crossed the pre-specified boundary for efficacy or (ii) the study needs to be terminated due to any cause including safety reasons.

[redacted]

[redacted]

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: independent biostatistician and programmer who will perform Data Monitoring Committee (DMC) analysis and PK bioanalyst. The study bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the samples in subjects receiving MBG453. The independent biostatistician, programmer and bioanalyst will keep treatment allocation information confidential until final PFS analysis or PFS IA if PFS is not significant at IA.

[redacted]

6.5 Dose modification

6.5.1 Dose modifications

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

Dose modifications for HMA 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 about management of immune-related AEs (Brahmer et al 2018). Additionally, the guidance indicated in Table 6-2 below provides instructions for infusion reaction, immune-related adverse events not covered by ASCO guidelines and a general guideline for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgement and possibly attributable to the investigational drug. This general guideline will not apply in case of non-hematologic non-immune-related toxicities that are attributable to HMA or MDS and its complications.

Deviations to mandatory dose interruptions, reductions and/or permanent discontinuations 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 seven days. If a dose cannot be administered within the planned window within the cycle then the dose should be skipped. Next scheduled dosing may resume once the adverse event has resolved to ≤ Grade 1 or baseline and the cycle will be shifted accordingly. Dose reductions for MBG453 or placebo are not allowed.

  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

- **Dose modifications for HMA**

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

- **Permanent discontinuation of MBG453 or placebo and HMA**

  If the study treatment (i.e. MBG453 + HMA or placebo + HMA) is interrupted for toxicities and the start of the subsequent study treatment cycle is delayed for more than 56 consecutive days (i.e. 2 planned consecutive cycles of study treatment for both, HMA and MBG453/placebo) the subject should be discontinued from study treatment.

- **Permanent discontinuation of only one component MBG453/placebo or HMA**

  If **one component only** of the study treatment (HMA 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 HMA alone) as long as the subject benefits per investigator's judgement.

  All dose changes must be recorded on the appropriate CRF.

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

Worst Toxicity CTCAE v5.0 Grade	Dose Modifications
Infusion Reaction*	
Grade 1	Decrease infusion rate until recovery
Grade 2	Stop infusion Before restarting – pre-medicate according to local institutional guidelines. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s) If the AE recurs at the reinitiated slow rate of infusion, and despite adequate pre-medication, then discontinue treatment
Grade 3 or 4	Discontinue MBG453/placebo
For toxicities thought to be immune-related 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 (400 mg) and schedule (Q2W)
Grade 2 or Grade 3 ≤ 7 days	Delay MBG453/placebo until toxicity resolved to ≤ Grade 1 or baseline. Then resume at the same dose (400 mg) and schedule (Q2W)
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 (400 mg) but with a longer treatment interval (Q4W). Return to the initial treatment interval (Q2W) may be possible but only after discussion and agreement with Novartis Medical Lead
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 possibly attributable to the investigational drug. This guideline does not apply for toxicities attributable to HMA (decitabine or azacitidine) or the underlying MDS including its complications.	
Grade 1	No change. Continue MBG453/placebo at the same dose (400 mg) and schedule (Q2W)
Grade 2 or Grade 3 ≤ 7 days	Delay MBG453/placebo until toxicity resolved to ≤ Grade 1 or baseline. Then resume at the same dose (400 mg) and schedule (Q2W)
Grade 3 > 7 days	Delay MBG453/placebo until toxicity resolved to ≤ Grade 1 or baseline. Then resume at the same dose (400 mg) but with a longer treatment interval (Q4W). Return to the initial treatment interval (Q2W) may be possible but only after discussion and agreement with Novartis Medical Lead

Worst Toxicity CTCAE v5.0 Grade	Dose Modifications
Grade 4	Discontinue MBG453/placebo
All dose modifications should be based on the available information and worst preceding toxicity. * Infusion related reaction or allergic reaction/anaphylaxis. See Section 6.2.1 for instructions regarding prophylaxis. ** Per investigator judgement.	

6.5.2 Follow-up for toxicities

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

All subjects must be followed up for AEs for 30 days following the last dose of azacitidine or decitabine, or 150 days following the last dose of MBG453 or placebo, whichever is later.

Immune – related AEs

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

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

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

Tumor lysis syndrome

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

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 (e.g., 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 3 days before or in the days following initiation of a treatment cycle:
  - Uric acid ≥ 8 mg/dL or 25% increase from baseline
  - Potassium ≥ 6 mEq/L or 25% increase from baseline
  - Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
  - Calcium ≤ 7 mg/dL or 25% decrease from baseline
- Regimen:
  - If none or one of the laboratory values above is abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g., febuxostat) and oral fluids. If uric acid remains elevated, consider 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

Subjects with transaminase increase combined with TBIL increase may be indicative of potential DILI and should be considered as clinically important events and should be assessed appropriately to establish diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 3.0 x baseline] OR [ALT or AST > 8.0 x ULN] combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed.

A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH), prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

Perform relevant examinations (Ultrasound or magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) as appropriate, to rule out if liver function tests (LFTs) are caused by cholestasis (defined as ALP elevation > 2.0 x ULN with R value < 2).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

Table 6-3 Guidance on specific clinical and diagnostic assessments to be (OR which can be) performed to rule out possible alternative causes of the observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs. old)	• Ceruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon the subjects' medical history (Hyperthyroidism/thyrotoxic hepatitis – T3, free T4, thyroid stimulating hormone (TSH); CVD / Ischemic hepatitis – electrocardiogram (ECG), prior hypotensive episodes; T1D/glycogenic hepatitis).

Obtain PK sample to determine exposure to study drug and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the drug is estimated as “probable” i.e. >50% likely, if it appears greater than all other causes combined. The term “drug-induced” indicates probably caused by the drug, not by something else, and only such a case can be considered DILI case and should be reported as an SAE.

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 and submit the triplicate for central review.
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities.
- Review concomitant medication use for possible causes for QT prolongation (refer to crediblemedicines.org). Record all concomitant medications in the appropriate eCRF page.
- Monitor ECG per the institutional standards.

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

IRT must be contacted to assign a medication (kit) number to the subjects every time the MBG453 or placebo is to be administered. The date and time of all study treatment administrations during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff on the appropriate study treatment dispensing form. Compliance with the study treatment and any protocol deviations will be assessed by the field monitor on an ongoing basis. All study treatment dispensed and returned (if applicable) must be recorded in the Drug Accountability Log.

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

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. 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
- Name (if available)
- 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.

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 for recurrence and survival as specified in the protocol (Section 9.1.5 and Section 9.1.6).

6.7 Preparation and dispensation

Novartis will supply each study site with the investigational drug (MBG453 or placebo) in packaging of identical appearance per product volume.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing 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

MBG453 (400 mg) or placebo will be administered i.v. Further instructions for the preparation and dispensation of MBG453 or placebo are described in the Pharmacy Manual.

All dosages for MBG453 or placebo prescribed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Decitabine

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

Azacitidine

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

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

6.7.1.2 Handling of additional treatment

Not applicable

6.7.2 Instruction for prescribing and taking study treatment

Refer to Section 6.1.1.

7 Informed consent procedures

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

If applicable, in cases where the 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 his/her level of 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.

The study includes the option for the subjects to continue MBG453 or placebo alone. These will require a separate informed consent 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.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the 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.

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

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

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.

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

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

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 Heath Authority.

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

8 Visit schedule and assessments

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

Each treatment cycle is 28 days. Screening evaluations should be performed within ≤ 28 days of Cycle 1 Day 1 (except for the pregnancy test which has to be performed within 72 hours before the first dose). Bone marrow aspirate (BMA) or biopsy performed prior to signing informed consent but within 28 days from the randomization, may be used. [redacted]

If the hematology and chemistry 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 visits, test and/or procedures should occur on schedule whenever possible. During the treatment phase a visit window of +/- 3 days is allowed, during the post-treatment follow up phase a visit window of +/-14 days is allowed. In case the infusion of MBG453 or placebo, azacitidine or decitabine cannot be administered at the scheduled visit, it has to be administered as soon as possible. Every effort should be made on C1D1 for the drug

to be administered on the same day as randomization. A visit window of + 3 days is allowed for treatment administration for reason other than toxicities. On PK collection days the windows are provided in Section 8.5.2.1.

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

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

For post-treatment follow-up and survival information, please refer to Section 8.3.1, Section 9.1.5 and Section 9.1.6.

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 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 subject´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the subject to visit the site again. 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.

Table 8-1 Assessment Schedule

Period	Screening	Treatment																		
Cycle		Cycle 1 (28d)			Cycle 2 (28d)			Cycle 3 (28d)			Cycle 4 (28d)			Cycle 5 (28d)			Cycle 6 (28d)			Cycle 7 (28d)
Days	-28 to -1	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1
Informed consent	X																			
IRT Screening	X																			
IRT Randomization[1]		X																		
Demography	X																			
Inclusion / Exclusion criteria	X																			
Medical history/current medical conditions	X																			
Disease History	X																			
Prior antineoplastic therapies	X																			
Prior/concomitant medications, surgery and medical procedures (including blood transfusions requirement)[2]	X	Continuous																		
Physical Examination	S	S	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	X	X
Body Height	X																			
BSA (use height from screening)		X			X			X			X			X			X			X
Body Weight	X	X			X			X			X			X			X			X

Period	**Screening**	**Treatment**																		
Cycle		**Cycle 1 (28d)**			**Cycle 2 (28d)**			**Cycle 3 (28d)**			**Cycle 4 (28d)**			**Cycle 5 (28d)**			**Cycle 6 (28d)**			**Cycle 7 (28d)**
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**
ECOG PS	X	X			X			X			X			X			X			X
Hematology[3]	X	X	X	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
Coagulation	X	X			X			X			X			X			X			X
Cytogenetics [4]	X																			
Thyroid function[5]	X				X									X						
Urinalysis dipstick and sediment	S	If clinically indicated																		
Serum vitamin B12, serum and erythrocyte folates, iron	X	If clinically indicated																		
Serum ferritin	X	If clinically indicated																		
Cytokines for safety IFN-γ, IL-6, IL-1,TNF-α[6]	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 [7]	S	S[8]																		
Urine Pregnancy Test OR Serum Pregnancy Test[7]					S			S			S			S			S			S
Efficacy - Bone marrow aspirate and/or biopsy and	X[10]										X									X

Period	Screening	Treatment																		
Cycle		Cycle 1 (28d)			Cycle 2 (28d)			Cycle 3 (28d)			Cycle 4 (28d)			Cycle 5 (28d)			Cycle 6 (28d)			Cycle 7 (28d)
Days	-28 to -1	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1
peripheral blood smears [9]																				
Response assessment[11]											X									X
12-Lead ECG (triplicates)[12]	X[13]	X	X		S			S	X		S			S			S			S
Adverse Events	X	Continuous																		
Decitabine infusion		on Days 1-5 of every cycle: IV 20mg/m2																		
Azacitidine infusion		on Days 1- 7 of each cycle OR on Days 1-5 and then on Day 8 and Day 9: IV or SC 75mg/m2																		
MBG453/Placebo infusion		on Day 8 and Day 22: 400 mg IV Q2W																		
IRT - Drug Dispensation MBG453/Placebo			X	X		X	X		X	X		X	X		X	X		X	X	
Blood sample for PK analysis[14]			X			X			X			X			X			X		
Blood sample for IG analysis[14]			X						X			X			X			X		
[redacted]																				

Period	Screening	Treatment																		
Cycle		Cycle 1 (28d)			Cycle 2 (28d)			Cycle 3 (28d)			Cycle 4 (28d)			Cycle 5 (28d)			Cycle 6 (28d)			Cycle 7 (28d)
Days	-28 to -1	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1	D8	D22	D1
[redacted]																				
Antineoplastic therapies including, HSCT and transfusions since discontinuation of study treatment[19]																				
Disposition	X																			
IRT Discontinuation																				
Survival Follow-up																				

Period	Treatment					EOT	Safety FU[18]	Post- treatment FU	Survival (every 3 months)
Cycle	Cycle 7 (28d)		Cycle 8 (and beyond) (28d)						
Days	D8	D22	D1	D8	D22	-		-	-
Informed consent									
IRT Screening									

Period	Treatment					EOT	Safety FU[18]	Post- treatment FU	Survival (every 3 months)
Cycle	Cycle 7 (28d)		Cycle 8 (and beyond) (28d)						
Days	D8	D22	D1	D8	D22	-		-	-
IRT Randomization[1]									
Demography									
Inclusion / Exclusion criteria									
Medical history/current medical conditions									
Disease History									
Prior antineoplastic therapies									
Prior/concomitant medications, surgery and medical procedures (including blood transfusions requirement)[2]	Continuous						X		
Physical Examination	S	S	S	S	S	S			
Vital Signs	X	X	X	X	X	X			
Body Height									
BSA (use height from screening)			X						
Body Weight			X			X			
ECOG PS			X			X			
Hematology[3]	X	X	X	X	X	X		Every 2 months and if clinically indicated	

Period	Treatment					EOT	Safety FU[18]	Post- treatment FU	Survival (every 3 months)
Cycle	Cycle 7 (28d)		Cycle 8 (and beyond) (28d)						
Days	D8	D22	D1	D8	D22	-		-	-
Chemistry			X			X			
Coagulation			X			X			
Cytogenetics [4]									
Thyroid function[5]			On cycle 8 and every 3 cycles thereafter			X			
Urinalysis dipstick and sediment	If clinically indicated								
Serum vitamin B12, serum and erythrocyte folates, iron	If clinically indicated								
Serum ferritin	If clinically indicated								
Cytokines for safety IFN-γ, IL-6, IL-1,TNF-α[6]	Anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of AE								
Virology hepatitis B and C	If clinically indicated								
HIV serology (only if required per local regulation)									
Serum Pregnancy test [7]						S	S[20]		
Urine Pregnancy Test OR Serum Pregnancy Test[7]			S				Monthly testing[20] S		
Efficacy - Bone marrow aspirate and/or biopsy and peripheral blood [9]			On cycle 10, 13, 19, 25 and beyond, and if clinically indicated[9]			X		At least every 6 months and if clinically indicated	
Response assessment[11]			On cycle 10, 13, 19, 25 and beyond, and if clinically indicated			X		Every 2 months and if clinically indicated	

Period	Treatment					EOT	Safety FU[18]	Post- treatment FU	Survival (every 3 months)
Cycle	Cycle 7 (28d)		Cycle 8 (and beyond) (28d)						
Days	D8	D22	D1	D8	D22	-		-	-
12-Lead ECG (triplicates)[12]			S			S			
Adverse Events	Continuous						Continuous		
Decitabine infusion	on Days 1-5 of every cycle: IV 20mg/m2								
Azacitidine infusion	on Days 1- 7 of each cycle OR on Days 1-5 and then on Day 8 and Day 9: IV or SC 75mg/m2								
MBG453/Placebo infusion	on Day 8 and Day 22: 400 mg IV Q2W								
IRT - Drug Dispensation MBG453/Placebo	X	X		X	X				
Blood sample for PK analysis[14]				On cycles 9, 12, 18 and 24		X	D30 and D150		
Blood sample for IG analysis[14]				On cycles 9, 12, 18 and 24		X	D30 and D150		
[redacted]									

Period	Treatment					EOT	Safety FU[18]	Post- treatment FU	Survival (every 3 months)
Cycle	Cycle 7 (28d)		Cycle 8 (and beyond) (28d)						
Days	D8	D22	D1	D8	D22	-		-	-
[redacted]									
Antineoplastic therapies including transplant, and transfusions since discontinuation of study treatment[19]							X	X	X
Disposition						X		X	
IRT Discontinuation						X			
Survival Follow-up									X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] At C1D1 IRT randomization will be performed. MBG453 / placebo will not be dispensed at this visit
[2] Blood transfusion administered within 16 weeks prior to randomization should be collected. [3] 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 2 months and if clinically indicated at any time

Period	Treatment					EOT	Safety FU[18]	Post- treatment FU	Survival (every 3 months)
Cycle	Cycle 7 (28d)		Cycle 8 (and beyond) (28d)						
Days	D8	D22	D1	D8	D22	-		-	-

during the study
[4] Cytogenetics will be performed locally. Assessment to be recorded in the clinical database
[5] Any deficiency should be corrected adequately and if possible before study Day 1. At Baseline: TSH, free T3 and free T4. During Treatment: TSH at time-points indicated in the table. If TSH is abnormal, then test free T3 and free T4
[6] Preferred cytokine panel should include IFN-γ, IL-6, IL-1, TNF-α, however it may be adjusted as per standard local practice. Please refer to Section 8.4.1
[7] This test will be performed only for women of child bearing potential
[8] Does not need to be performed if it was done in screening within 72 hours before first dose
[9] Bone marrow aspirate and/or biopsy and peripheral blood smears for efficacy assessments should be performed at screening and pre-dose during treatment period (C4D1, C7D1, C10D1, C13D1), after that every 6 cycles (C19D1, C25D1, etc.) and when clinically indicated at any time during the study
[10] If bone marrow results are available 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
[11] During post-treatment follow-up response assessments must continue to be performed every 2 months as per hematology assessment and at least every 6 months as per bone marrow assessment or as clinically indicated any time during the study. For more information please refer to Section 8.3.1.
[12] ECGs should be collected as per schedule of assessment prior to PK samples collection (if applicable). Central ECG will be collected at C1D1 predose, C1D8 post-dose, and C3D8 pre-dose. Remaining time-points will be collected locally including unscheduled ECGs if clinically indicated. Collect three serial ECGs approximately 3 minutes apart after the subject has been resting comfortably in a supine position for about 10 minutes (it should be obtained before blood collection if a blood sample is scheduled at the same time point). Pre-dose ECG to be collected prior to any study drug dosing. Post-dose ECG to be collected at the end of study drug infusion. Please refer to Section 8.4.2 for ECG collection time-points
[13] Screening ECG will be performed locally, however data will be recorded in the clinical database.
[14] For PK, IG [redacted] analysis, a single blood sample will be collected and then aliquoted into different tubes for PK analyte anti-drug antibody (ADA) [redacted] PK, IG [redacted] samples will be collected pre-MBG453 infusion at all specified time points. PK samples will also be collected at the end of MBG453 infusion on C1D8 and C3D8. [redacted] Beyond C6, samples should be collected every 3 cycles up to Cycle 12, and every 6 cycles after up to two years (Cycle 18 and Cycle 24), while the subject is on-treatment. PK and IG will be collected on D30 and D150 during safety follow up (D150 follow up samples can be collected at the investigator's discretion, if follow up visit is done at the site). Please refer to section 8.5.2.1 for blood collection timepoints

[redacted]

[18] Follow-up can be done by telephone call if assessment is not required at the visit on 30-day, 90-day, and 150-day safety follow-up
[19] Antineoplastic therapy, HSCT and Transfusion should be collected every 2 months during post-treatment follow-up. Antineoplastic therapy and HSCT information should be collected at survival.

Period	Treatment					EOT	Safety FU[18]	Post- treatment FU	Survival (every 3 months)
Cycle	Cycle 7 (28d)		Cycle 8 (and beyond) (28d)						
Days	D8	D22	D1	D8	D22	-		-	-

[20] Should be performed for women of child bearing potential monthly up to D90 after the last dose of azacitidine or decitabine; monthly up to D150 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, the urine test can be performed at home or at a local doctor's office, and the results must be communicated to the site staff. If the urine test is positive, then the subject will be asked to report to the clinic for a serum test. Please refer to Section 8.4.3.

8.1 Screening

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 from the ICF signature if such parameters does not meet the eligibility criteria. If the repeat value remains outside of the specified ranges, the subject must be discontinued from 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 perform when the subject is re-screened for participation in the study.

Bone marrow and peripheral blood pathology specimens (i.e. bone marrow slides, bone marrow biopsy block if applicable, peripheral blood smears) prepared locally for establishing the MDS diagnosis at the time of screening, should be sent to the Novartis designated central laboratory for storage. A copy of the corresponding pathology reports should be collected and sent to the Novartis designated central laboratory for storage. Central morphology review of the pathology specimens may be performed, if deemed necessary.

8.1.1 Eligibility screening

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 sign 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 is to be notified as soon as possible that the subject was not randomized. Subjects who are randomized are not considered screening failures regardless of eligibility.

8.2 Subject demographics/other baseline characteristics

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

Other background, relevant medical history or current medical conditions

- Disease history (MDS), including date of diagnosis, confirmation of MDS diagnosis, IPSS-R risk classification for MDS subjects at time of screening, prior antineoplastic therapies. IPSS-R risk score for MDS subjects should be calculated based on the hematology values obtained at screening. If multiple hematology tests were performed during screening to confirm eligibility, the lab values closest to randomization should be used (last available values during screening)
- All prior and concomitant medications and medical procedures
- Blood transfusion **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:

- After all applicable study ICFs are signed the subject will be registered with the IRT
- Physical examination
- ECOG Performance Status, body height, weight, vital signs (blood pressure (supine position preferred when ECGs are collected) and pulse and body temperature).
- Laboratory - hematology, chemistry, coagulation, urinalysis, serum pregnancy test for women of child-bearing potential, thyroid function, serum ferritin, serum vitamin B12, serum and erythrocyte folate, iron, virology hepatitis B and C, HIV serology (only if required per local regulation)
- Cardiovascular assessments (i.e., triplicate 12-lead central ECG)
- [redacted]
- Bone marrow biopsy or aspirate will be performed locally to establish diagnosis (If a bone marrow aspirate or biopsy was conducted during the regular work-up of the 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).
- Cytogenetics will be performed locally as per local standard
- [redacted]
- Cytokines (Preferred cytokine panel should include, IFN-γ; IL-6, IL-1, TNF-α, however it may be adjusted as per standard local practice)
- Adverse events
- [redacted]

8.3 Efficacy

8.3.1 Efficacy assessments

Efficacy assessments will be performed according to the IWG and WHO criteria for MDS (Cheson et al 2000, Cheson et al 2006, Arber et al 2016, Platzbecker et al 2018). Response

criteria in MDS are described in Table 8-2. Investigators will assess and document response/progression at each time point as per the visit schedule. For efficacy analyses, baseline is defined as the last non-missing assessment on or before the date of 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 criteria in MDS (Platzbecker et al 2018, Cheson et al 2006, Cheson et al 2000)

Response category	Definition[#]
Complete remission (CR)	**Bone marrow:** ≤ 5% blasts with normal maturation of all cell lineages. (Note: Persistence of dysplasia will be noted but does not preclude achievement of complete remission [CR]) **Peripheral blood** 1. Hgb ≥ *10 g/dL* AND 2. Platelets ≥ $100*10^9$/L AND 3. Neutrophils ≥ $1.0*10^9$/L AND 4. Blasts 0% *Note: the 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*10⁹/L. Note:*

Response category	Definition[#]
	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*10⁹/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*10⁹/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*10⁹/L* 3. Reduction *from maximum remission/response*** *levels* in Hgb by ≥ 2g/dL *AND Hgb < 10g/dL* **Becoming transfusion dependent**** ***Occurrence of acute leukemia or extramedullary leukemia per investigator's judgement***
Modified Hematological Improvement per IWG-MDS criteria in MDS (Cheson et al 2006)	
HI category	**Definition[#] (HI must last at least 8 weeks)**
Erythroid response (HI-E) (pretreatment*, <11 g/dL)	1. Hgb increase from baseline by ≥ 1.5 g/dL, in at least 2 consecutive Hgb measurements and maintained over at least 8 weeks 2. Relevant reduction from baseline of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of < 9 g/dL pre-treatment will count in the RBC transfusion response evaluation.

Response category	Definition[#]
Platelet response (HI-P) (pretreatment*, <100 x 10^9/L)	1. Absolute increase from baseline of ≥ 30 x 10^9/L for subjects starting with > 20 x 10^9/L platelets 2. Increase from baseline from < 20 x10^9/L to > 20 x10^9/L and by at least 100% for 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 MDS (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 aspirate or biopsy and peripheral blood will be collected per Table 8-1 for assessment of disease. [redacted] Bone marrow assessments will be performed at

screening and pre-dose during treatment period at C4D1, C7D1, C10D1, and C13D1 and hematology assessments will be performed at screening, D1, D8 and D22 of each cycle until end of treatment and if clinically indicated at any time during the study. After C13D1, bone marrow assessments are to be done every 6 cycles (C19D1, C25D1, etc.) and hematology assessments every 2 months and if clinically indicated at any time during the study. Screening bone marrow aspirates or biopsies (BMA/BMB) must be collected within 28 days of randomization. If a subject's screening BMA/BMB was collected >28 days before randomization, then the subject must agree to have a repeat BMA/BMB performed. Clinical suspicion of relapse or disease progression at any time after randomization will require a disease evaluation promptly, rather than waiting for the next scheduled assessment. In case of an unscheduled or delayed disease evaluation for any reason, subsequent assessments should be performed according to the original planned schedule.

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

Post-treatment efficacy follow-up

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

8.3.2 Appropriateness of efficacy assessments

Not applicable.

8.4 Safety

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

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ‘‘baseline" assessment.

For details on AE collection and reporting, refer to AE Section 10.1.

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 limits or prevents on-site study visits, regular phone or virtual calls can occur as necessary for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

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,

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

Performance status:

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

Table 8-4 ECOG performance status

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

8.4.1 Laboratory evaluations

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

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

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

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

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 limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be required for patient's management and used.

Table 8-5 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands), Blasts, *Other* (*absolute value preferred , %s are acceptable*)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH),Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Troponin T****
Virology*	HBsAg, HBcAb, HBV DNA (in subjects positive for HBcAb), HCV RNA (PCR) HIV (Only if required by local regulation)
Coagulation	International normalized ratio (INR), Activated partial thromboplastin time (aPTT)
Cytokines***	IFN-γ, IL-6, IL-1, TNF-α
Urinalysis dipstick and sediment*	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated
Pregnancy Test*	Serum / Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' section)
Additional tests	Ferritin, iron, vitamin B12, erythrocyte and/or serum folates **, TSH, Free T3, Free T4

*Virology, urinalysis and pregnancy test will only be reported in the source documentation.
**Preferred method is erythrocyte folate but in case is not available then serum should be performed. However, every effort should be made to perform both test.
***Preferred cytokine panel should include IFN-γ, IL-6, IL-1, TNF-α, however it may be adjusted as per standard local practice.
****If Troponin T is not available, Troponin I may be performed.

8.4.2 Electrocardiogram (ECG)

Standard triplicate 12-lead ECG recording will be performed according to Table 8-6 and Table 8-7. The Fredericia QT corrected (QTcF) values should be used for clinical decisions.

The ECGs are to be collected with ECG machines supplied by the central laboratory during the following timepoints: C1D1 predose, C1D8 post-dose, and C3D8 predose. At the remaining time-points ECG will be collected locally including unscheduled ECGs. When triplicate ECG is required, collect three serial ECGs approximately 3 minutes apart after the subject has been resting comfortably in a supine position for about 10 minutes (it should be obtained before blood collection if a blood sample is scheduled at the same time point). Pre-dose ECG to be

collected prior to any study drug dosing. Post-dose ECG to be collected at the end of study drug infusion.

Clinically significant ECG abnormalities present at screening should be reported on the appropriate CRF and 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. All ECGs recorded using the machines supported by the central laboratory must be transmitted electronically to the central laboratory and should be centrally reviewed by an independent reviewer.

Any identifier details must be redacted e.g. subject initials, date of birth where local regulations require it.

Additional ECGs may be repeated at the discretion of the investigator locally at any time during the study as clinically indicated. In case of new abnormalities, a cardiologist should be consulted, as needed.

Refer to section 'Dose modification' in case of QTcF prolongation (Section 6.5).

Table 8-6 Central ECG collection plan

Cycle	Day	Time	ECG Type
1	1	Pre-dose	12 Lead Triplicate
1	8	Post-dose**	12 Lead Triplicate
3	8	Pre-dose***	12 Lead Triplicate

**ECG to be collected after dose of MBG453 or placebo
***ECG to be collected prior to any study drug dosing

Table 8-7 Local ECG collection plan

Cycle	Day	Time	ECG Type
Screening**	-28 to -1	Anytime	12 Lead Triplicate
2	1	Pre-dose	12 Lead Triplicate
3	1	Pre-dose	12 Lead Triplicate
4 and subsequent cycles	1	Pre-dose	12 Lead Triplicate
EOT	NA	Anytime	12 Lead Triplicate
Unscheduled	Any	Anytime	12 Lead Triplicate

**Results will be collected in the eCRF

8.4.3 Pregnancy and assessments of fertility

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

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

During the study, a urine/serum pregnancy test should be done locally at Day 1 of each cycle (except if for Cycle 1 a pregnancy test was performed within 72 hours of the first dose) and at EOT visit. Additionally, during the safety follow up, women of child bearing potential will be

tested monthly with urine or serum pregnancy tests up to Day 90 after the last dose of azacitidine or decitabine. They will also be tested monthly with urine or serum pregnancy tests up to Day 150 after the last dose of MBG453/placebo, and a serum pregnancy test should be performed on Day 150 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 natural disaster, that limits or prevents on-site study visits, the test can be performed at home or at a local doctor's office, and the results will be communicated to the site staff.

A positive urine pregnancy needs to be confirmed with a serum test. Confirmed positive pregnancy test requires immediate discontinuation of study treatment and discontinuation from study see Section 10.1.4 for pregnancy reporting.

The pregnancy tests will be recorded only in the source documentation, not in the CRF.

Women of childbearing potential should employ the use of highly effective contraception during study treatment, for 3 months after the last dose of azacitidine or decitabine (or as per their respective local labels, whichever is longer) and 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.

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

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

8.5 Additional assessments

[redacted]

[redacted]

8.5.2 Pharmacokinetics

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

8.5.2.1 Pharmacokinetic blood collection and handling

PK, [redacted] IG blood sampling schedule is outlined in 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] IG assessment will be recorded on the appropriate eCRF.

After permanent discontinuation of MBG453 or placebo, the samples scheduled for pre-MBG453/placebo and end of MBG453/placebo infusion (within 2 hours) should no longer be collected with exception of 30 days and 150 days safety follow-up. Refer to the [MBG453B12201 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK, IG [redacted] samples.

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

Cycle	Day	Scheduled Time Point (h)	PK Sample	IG Sample	[redacted]
1	1	Pre-HMA infusion*			
1	8	Pre-MBG453 infusion	x	x	
1	8	End of MBG453 infusion (within 2 hours)	x		
2	8	Pre-MBG453 infusion*	x		
3	8	Pre-MBG453 infusion*	x	x	
3	8	End of MBG453 infusion (within 2 hours)	x		
4	8	Pre-MBG453 infusion*	x	x	
5	8	Pre-MBG453 infusion*	x	x	
6	8	Pre-MBG453 infusion*	x	x	
9	8	Pre-MBG453 infusion*	x	x	
12	8	Pre-MBG453 infusion*	x	x	
18	8	Pre-MBG453 infusion*	x	x	

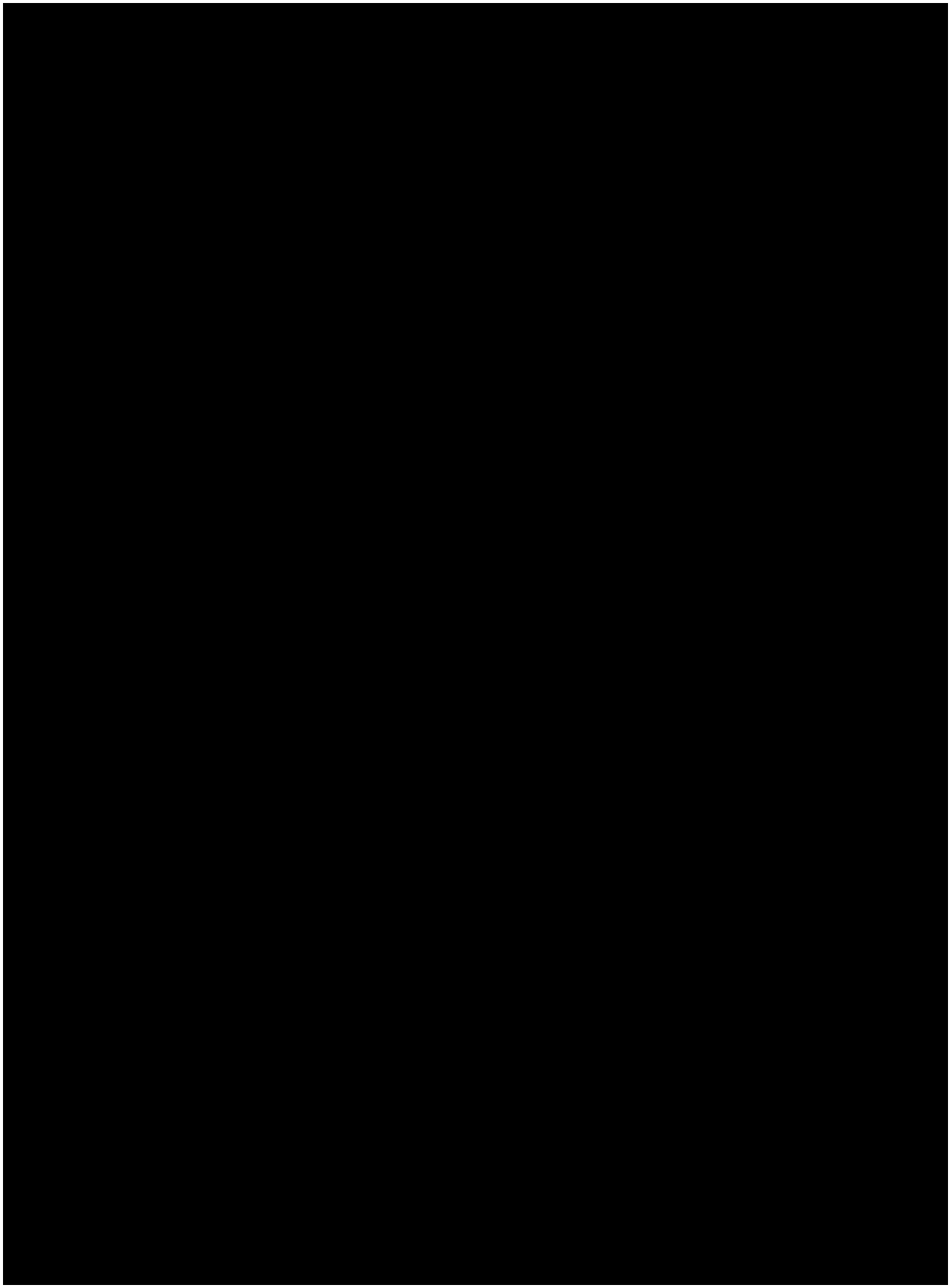
Cycle	Day	Scheduled Time Point (h)	PK Sample	IG Sample	[redacted]
24	8	Pre-MBG453 infusion*	x	x	
EOT		Anytime	x	x	
At least 30 day Follow up		Anytime	x	x	
150 day** Follow up		Anytime	x	x	
Unscheduled***		Anytime	x	x	
*All pre-dose samples must be collected within 30 min before the infusion begins					
**150-day Follow up samples can be collected at the investigator's discretion, if follow up visit is done at the site.					
***An unscheduled PK samples and IG samples should be collected upon confirmation of disease progression, may be collected at any time if clinically indicated or at the Investigator's discretion.					
PK, IG [redacted] samples will be analyzed only in subjects receiving MBG453					

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. The details of the assay will be documented in the [CMBG453B12201 Laboratory Manual].
- The assay to quantify and assess the IG against MBG453 will be a validated homogeneous bridging enzyme-linked immunosorbent assay (ELISA). The details of the assay will be documented in the [CMBG453B12201 Laboratory Manual].

[redacted]



9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

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 treatment 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 judgement of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Protocol-defined reasons for discontinuation (see Section 6.1.4 and Section 6.1.5)
- 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 from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's discontinuation from study treatment and record this information.

Subjects who discontinue from 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 9.1.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section (Section 9.1.3). This contact should preferably be done according to the study visit schedule.

If the 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.

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.

For subjects who discontinue from study treatment for reasons other than documented disease progression, pregnancy, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, efficacy assessments must continue to be performed every 2 months as per hematology assessment and at least every 6 months as per bone marrow assessment or as clinically indicated until documented disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples..

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 from study treatment.

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

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)

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 subject 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 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. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons.

In taking the decision to terminate, Novartis will always consider the subjects' welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a subject who has discontinued from study treatment.. 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.

9.1.5 Survival follow-up

Subjects will enter the survival follow-up period once they complete the safety follow-up period or have disease progression on the post treatment FUP phase whichever is longer. Subjects will be contacted by telephone every 3 months (12 weeks) to follow-up on their survival status. Any new antineoplastic therapies and transfusions that have been started since the previous contact will be collected. HSCT information will also be collected during these phone calls.

9.1.6 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 [redacted] assessments, [redacted] as per Table 8-1 until progressive disease/relapse, withdrawal of consent/opposition to use data/biological samples, lost to follow-up, or death.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes 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 or decitabine, or 90 and 150 days following the last dose of MBG453 or placebo, whichever is the latest. The safety follow-up can be done by telephone call or visit. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

[redacted]

After the cut-off date for the CR rate analysis (if CR rate is significant or not), the study will continue as planned until the final OS analysis. Ongoing subjects will continue to receive study

treatment and be followed as per the schedule of assessments. The end of study is defined as 4 years after the last subject randomized; which is the data cut-off date for the final OS analysis and a final CSR will be produced (Section 12.4). Also, in the event of an early study termination decision, the end of the study is the date of that decision.

At the end of the study, in alignment with local regulations, Post Trial Access (PTA) will be set up to continue provision of the study treatment outside this study through an alternative setting to subjects who 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 reported by the subject during, between visits or through physical examination findings, laboratory test findings, or other assessments.

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

1. The adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0,
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single 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:

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

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

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

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

Conditions that were already present at the time of informed consent should be recorded in medical history of the 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 should be continued for at least:

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in 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 judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the 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 malignant neoplasms will be assessed as serious medically significant if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent to 30 days after the date of the last actual administration of HMA or 150 days after the last dose of MBG453 or placebo, whichever is later and it must be reported to Novartis safety immediately, without undue delay, and under no circumstances later than within 24 hours of learning of its occurrence. Any SAEs experienced after the 150 day safety follow-up period should only be reported to Novartis safety database if the investigator suspects a causal relationship to study treatment 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.

The following SAE reporting timeframes apply:

1. 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
2. Randomized OR Treated Subjects: SAEs collected between the time the subject signs ICF to 30 days after the date of the last actual administration of HMA or 150 days after the last dose of MBG453 or placebo, whichever is later or stopped study treatment

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

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

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring in a female study subject after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to 12 months after the estimated date of delivery to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

Pregnancy data will not be collected for the female partners of any male 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 (European Medicines Agency (EMA) definition).

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

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

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

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

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

10.2 Additional Safety Monitoring

Not applicable

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 and recommend to the sponsor whether to continue, modify, or terminate a trial. The DMC will be responsible to periodically review safety data after the first enrolled subject has started study treatment. The DMC will review also efficacy (CR rate and PFS) at the time of the CR rate analysis and interim PFS analysis.

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 be responsible to review CR rate and PFS data of subjects randomized into the study at the time of CR rate analysis.

It is envisioned that the DMC may make recommendations, namely:

- Recommendation to continue the study blinded as planned, no details about the efficacy results will be revealed
- Recommendation to continue the study blinded as planned but proposing to the Sponsor to unblind the interim results, if CR rate is statistically significant

If CR rate analysis is not statistically significant, the DMC will be responsible to review CR rate and PFS data of subjects randomized into the study at the time of PFS IA.

It is envisioned that the DMC may make recommendations, namely:

- Recommendation to continue the study blinded as planned, no details about the efficacy results will be revealed
- Recommendation to continue the study blinded as planned but proposing to have the Sponsor unblinded to the interim results, if PFS IA is statistically significant

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 issues prior to the finalization of DMC charter and the study analysis plan.

The second meeting will occur when at least 10 subjects have received azacitidine combined with the study drug MBG453 or placebo for at least one cycle (approximately 5 subjects in each blinded treatment arm). Safety data from subjects receiving decitabine combined with the study drug MBG453 or placebo available will be reviewed during this meeting as well.

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

The DMC will review also efficacy (CR rate and PFS) at the time of the CR rate analysis and interim PFS analysis.

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

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. The Study Steering Committee will not have access to unblinded trial data at the time of the CR rate analysis. The SC will be unblinded after the interim OS analysis.

11 Data Collection and Database management

11.1 Data collection

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

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

After final database lock, the investigator will receive copies of the 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.

11.2 Database management and quality control

Novartis personnel 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.

Randomization codes and data about all study treatment(s) 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.

Once all the necessary actions have been completed and the database has been declared 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.

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. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of 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

The CR rate analysis is planned when the last randomized subject has reached cycle 7 (or discontinued earlier). No interim analysis (IA) is planned for CR rate. The intent of this CR rate analysis is to assess whether MBG453 + HMA has superior efficacy than Placebo + HMA based on the CR rate. The other primary endpoint PFS will not be tested at this time point and is following a group sequential design.

One interim analysis for PFS is planned after approximately 81 of the targeted 108 PFS events (i.e. at approximately 75% information fraction) have been documented.

If PFS is not already significant at the interim analysis, the final PFS analysis will be performed after approximately 108 PFS events have been documented or at approximately 4 months after the interim PFS analysis data cut-off date, whichever comes first. The final PFS analysis if applicable, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date.

The final OS analysis will be performed with the data cut-off date of 4 years after the last subject randomized.

All data will be summarized by treatment group: 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.

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 1 dose of any component of the study treatment (MBG453 + HMA or placebo + HMA). Subjects will be analyzed according to the study treatment they received, either MBG453 + HMA or placebo + HMA. If the subject never

received the study drug (i.e. MBG453 or placebo) and took at least 1 dose of HMA, subjects will be analyzed in the placebo + HMA treatment arm.

Pharmacokinetic Analysis Set: PAS

The Pharmacokinetic Analysis Set (PAS) includes all subjects in the Safety Set, who had at least 1 evaluable PK concentration.

For a concentration to be evaluable:

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

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 HMA (azacitidine and decitabine)). The dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized for each study drug component by descriptive statistics.

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

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

RBC and platelets transfusions will be summarized for the period of 8 weeks prior to baseline and post-baseline.

12.4 Analysis of the primary endpoint(s)

The 2 primary objectives of the study are to compare complete remission (CR) rate and progression-free survival (PFS) as per investigator assessment between the two treatment arms.

12.4.1 Definition of primary endpoint(s)

The primary endpoints are CR rate and PFS as per the International Working Group (IWG) criteria for MDS (Cheson et al 2006, Platzbecker et al 2018; Table 8-2):

- CR rate is defined as the percentage of subjects with best overall response equal to confirmed complete remission (CR)

- PFS is defined as the time from the date of randomization to the date of the first documented progression/relapse from CR or death due to any cause

To conclude for efficacy, the treatment effect needs to be demonstrated in any (or both) of the primary endpoints CR rate and/or PFS. The type I error control for this primary endpoint family is described in Section 12.7.

12.4.1.1 Complete remission rate

The primary endpoint CR rate is the percentage of subjects with best overall response of complete remission (CR) as per the International Working Group (IWG) criteria for MDS per investigator assessment (Cheson et al 2006, Platzbecker et al 2018; Table 8-2)

Complete Remission is defined as a confirmed response. CR is considered confirmed if progression or relapse from CR (see Table 8-2) are not observed within 4 weeks.

A subject with CR is classified as a responder.

[redacted]

12.4.1.2 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 acute leukemia transformation as per WHO 2016 classification. Relapse after CR and progression will be assessed by the investigator (Section 8.3). A subject without PFS event will have their PFS censored at the time of the last adequate assessment performed on or before the cut-off date.

[redacted]

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

[redacted]

[redacted]

12.4.2.2 Complete remission rate

The following statistical hypotheses will be tested to address the primary efficacy objective for CR at the 1-sided alpha-CR level of significance:

$$H_{01}: CR_{MBG453+HMA} \leq CR_{PLB+HMA} \text{ versus } H_{a1}: CR_{MBG453+HMA} > CR_{PLB+HMA},$$

where $CR_{MBG453+HMA}$ is the probability of CR rate on MBG453 + HMA and $CR_{PLB+HMA}$ is the probability of CR rate on placebo + HMA.

CR rate will be provided with exact 95% confidence intervals (CI) (Clopper and Pearson 1934). The analysis will be performed using data up to the analysis data cut-off date, which will be 7 months after the last subject is randomized.

CR rate and its 95% CI will be presented by treatment group. The exact Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor of IPSS-R categories (very high vs. high vs. intermediate), will be used to compare CR rate between the two treatment arms. Since only a low proportion of subjects is expected to have received decitabine, the primary analysis will not be stratified by the HMA randomization stratification factor.

12.4.2.3 Progression Free Survival

The following statistical hypotheses will be tested to address the primary efficacy objective for PFS at the 1-sided alpha-PFS level of significance:

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

Where $\theta 1$ is the hazard ratio (HR) of PFS in the MBG453 + HMA arm vs. Placebo + HMA arm.

The analysis to test this hypothesis will consist of a stratified log-rank test at the alpha-PFS level of significance. The same stratification factor as for the primary CR rate analysis will be used.

The PFS distribution will be estimated using the Kaplan-Meier method. The Kaplan-Meier curves, medians and 95% CI of the medians will be presented for each treatment group. A stratified Cox regression will be used to estimate the HR of PFS, along with the 95% confidence interval using the same strata information as for the primary CR rate analysis.

[redacted]

[redacted]

12.4.4 Supportive analyses

PFS will be analyzed with the same statistical methods but considering the following different censoring method:

- If disease progression/relapse from CR or death is documented after two or more missing response assessments, the subject will be considered with an event at the documented event date.

Subgroup analyses for CR rate and PFS

If the primary endpoint analyses for CR rate and/or PFS are statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across randomization stratification factors will be performed for the subgroups as shown below:

- IPSS-R risk categories (very high vs. high vs. intermediate) as per randomization
- Hypomethylating agents (azacitidine vs. decitabine) as per randomization

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Efficacy endpoints will be calculated and summarized for the FAS.

Time-to-event endpoints will be analyzed using Kaplan-Meier method as described above. Hazard ratio and 95% CIs from the stratified Cox-model will be provided.

The overall survival will be tested [redacted] only if the primary endpoint CR is statistically significant and if, and when the primary endpoint PFS is statistically significant at either IA or final PFS analysis. The final PFS analysis if PFS is not already significant at IA, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date. The final OS analysis data cut-off date will be defined as 4 years after last subject randomized.

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

[redacted]

Overall Survival (OS)

OS is defined as the time from date of randomization to date of death due to any cause. 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). All deaths will be taken into account [redacted]

Event Free Survival (EFS)

EFS is defined as time from randomization to lack of reaching CR within the first 6 months, relapse from CR or death due to any cause, whichever occurs first. CR and relapse from CR are defined according to International Working Group (IWG) for MDS (Section 8.3) as per investigator assessment. A subject without EFS event will have their EFS censored at the time of the last adequate response assessment performed on or before the cut-off date. For subject without reaching CR within the first 6 months, an EFS event at day 1 will be considered.

Leukemia-free survival

Leukemia-free survival is defined as the time from date of randomization to ≥ 20% blast in bone-marrow/peripheral blood as per WHO 2016 classification or diagnosis of extramedullary acute leukemia or death 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 (CR/mCR/PR/HI)

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) as per investigator assessment according to modified MDS-IWG (Table 8-2). Response rates will be provided with exact 95% confidence intervals (Clopper and Pearson 1934). Stable Disease (SD) rate is defined as the proportion of subjects with best overall response of SD per investigator assessment. Any hematologic improvement rate, based on Table 8-2, will be reported separately with exact 95% confidence intervals (Clopper and Pearson 1934).

Duration of CR

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

Time to CR

Time to CR is defined as the time from the date of randomization to the first documented CR. Subjects without a CR will be censored at the study-maximum follow-up time (i.e. Last Patient Last Visit (LPLV)) for subjects with a PFS event (i.e. disease progression or death due to any cause), or at the date of the last adequate assessment for subjects without a PFS event.

Red blood cells (RBC)/Platelets 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 (Table 8-2). The number and percentage of subjects will be shown for the overall FAS and then also in only those with transfusion dependence at baseline as defined in Table 8-2. Percentages will be provided with exact 95% confidence intervals (Clopper and Pearson 1934). For subjects with at least one period of transfusion independence post-baseline, the total duration of all transfusion independence periods (which all individually must be at least 8 weeks) will be also summarized. The duration of each period of transfusion

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

12.5.2 Safety 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:

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

Overall safety period: from date of first administration of study treatment to 30 days after the date of the last administration of HMA 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. 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.

Selected summaries of adverse events will be produced for the overall safety period.

All deaths (on-treatment and post-treatment) will be summarized.

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

Vital signs

All vital signs abnormalities will be summarized by treatment group.

12-lead ECG

HR and QTcF will be obtained from 12-lead ECGs for each subject at screening and during the study.

Categorical analysis of QTcF interval and HR data will be based on the summary of number of subjects meeting or exceeding predefined limits.

Clinical laboratory evaluations

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

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

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

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

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

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

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

Other safety evaluations

ECOG PS

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

[redacted]

12.5.3 Pharmacokinetics

PAS will be used for all pharmacokinetic data analyses. 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 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.

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. [redacted]

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.

Immunogenicity

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

[redacted]

12.7 Interim analyses

The null hypothesis for CR rate will be tested at alpha-CR significance level (Figure 12-1), and the analysis will be scheduled approximately 7 months after the last subject has been randomized in the study. This analysis is expected to take place approximately 18 months after the date that the first subject is randomized, assuming a recruitment duration of approximatively 11 months. No interim analysis (IA) is planned for CR rate.

A maximum of two analyses will be performed for PFS. The interim analysis will be scheduled when approximately 81 PFS events (75% of the target number) have been documented, expected to occur approximately 28 months after the first subject randomized. Based on the pooled observed PFS events, the rate of discontinuations without PFS event, the limited number of subjects still at risk to have a PFS event and the predictions of future events, there is a risk that the targeted 108 PFS events for FA will not be observed at all or within a reasonable time frame. Therefore, the PFS final analysis will be performed using the pre-defined cut-off date of approximately 4 months after the PFS IA with the number of PFS events documented by this date, if PFS is not already significant at IA. The final OS analysis will be conducted with a data cut-off date of 4 years after the last subject randomized.

[redacted]

The overall type I error probability, alpha-PFS, will be controlled by using an alpha spending function for the interim and the final PFS analysis. A fixed 1-sided alpha of 0.00001 will be spent at the CR rate analysis. The O'Brien and Fleming spending function will be used for the interim and final analysis (O'Brien and Fleming 1979).

[redacted]

The secondary endpoint OS will be tested only if the primary endpoint CR is statistically significant and if, and when the primary endpoint PFS is statistically significant at either IA or final PFS analysis. The final PFS analysis if PFS is not already significant at IA, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date. [redacted]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size of the study is based on the 2 primary endpoints CR rate and PFS.

It will be concluded that the study drug is efficacious if at least one of the two null hypothesis for the primary endpoints CR rate and PFS is rejected.

[redacted]

Complete remission rate

One of the primary endpoints compares the complete remission rate between the two treatment arms using an exact Cochran-Mantel-Haenszel (CMH) test in the Full Analysis Set.

The randomization is stratified by use of HMA (azacitidine or decitabine) and the IPSS-R risk categories (intermediate, high and very high). It is anticipated that approximately 80% of subjects will use azacitidine. The CR rate will be tested using a stratified exact Cochran-Mantel-Haenszel chi-square test at the significance level [redacted] The CR rate in the placebo + HMA treatment arm is expected to be 18% (azacitidine or decitabine), based on the literature for previous trials using azacitidine (Fenaux et al 2009) and decitabine (Kantarjian et al 2006) in MDS subjects. [redacted]

Progression Free Survival

PFS is the other primary endpoint. The hypotheses to be tested and details of the testing strategy are provided in Section 12.4.2.3 and Section 12.7. Based on available data from the literature for previous trials using azacitidine (Fenaux et al 2009) in MDS subjects, in which the median time to PFS was 14.1 months for azacitidine. The median PFS in the placebo + HMA arm is expected to be 12 months (for azacitidine or decitabine) as the study population is expected to have a poorer prognosis than in the reference publication. [redacted]

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.

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 subject 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).

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of 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.

15 References

References are available upon request

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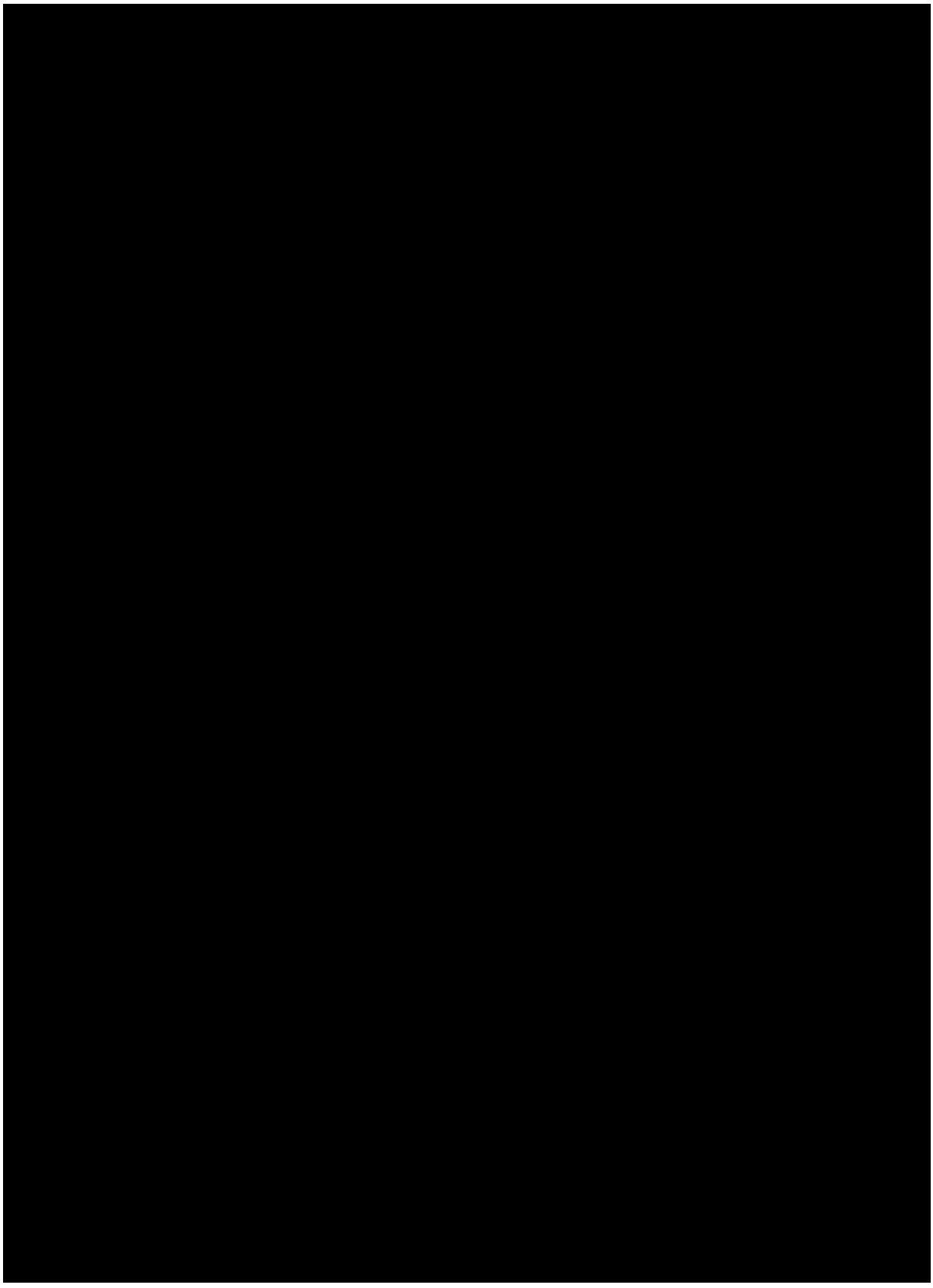
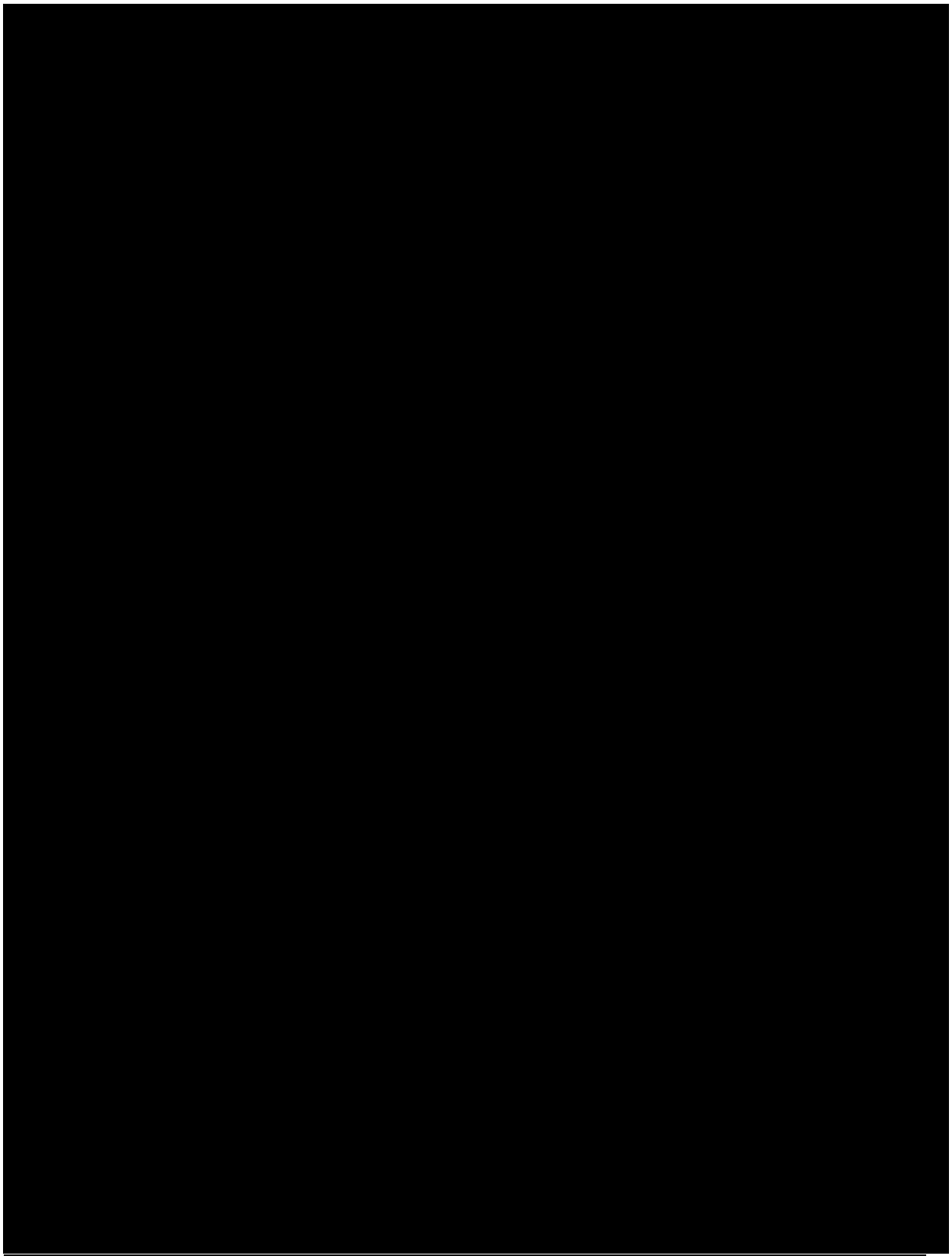
16 Appendices

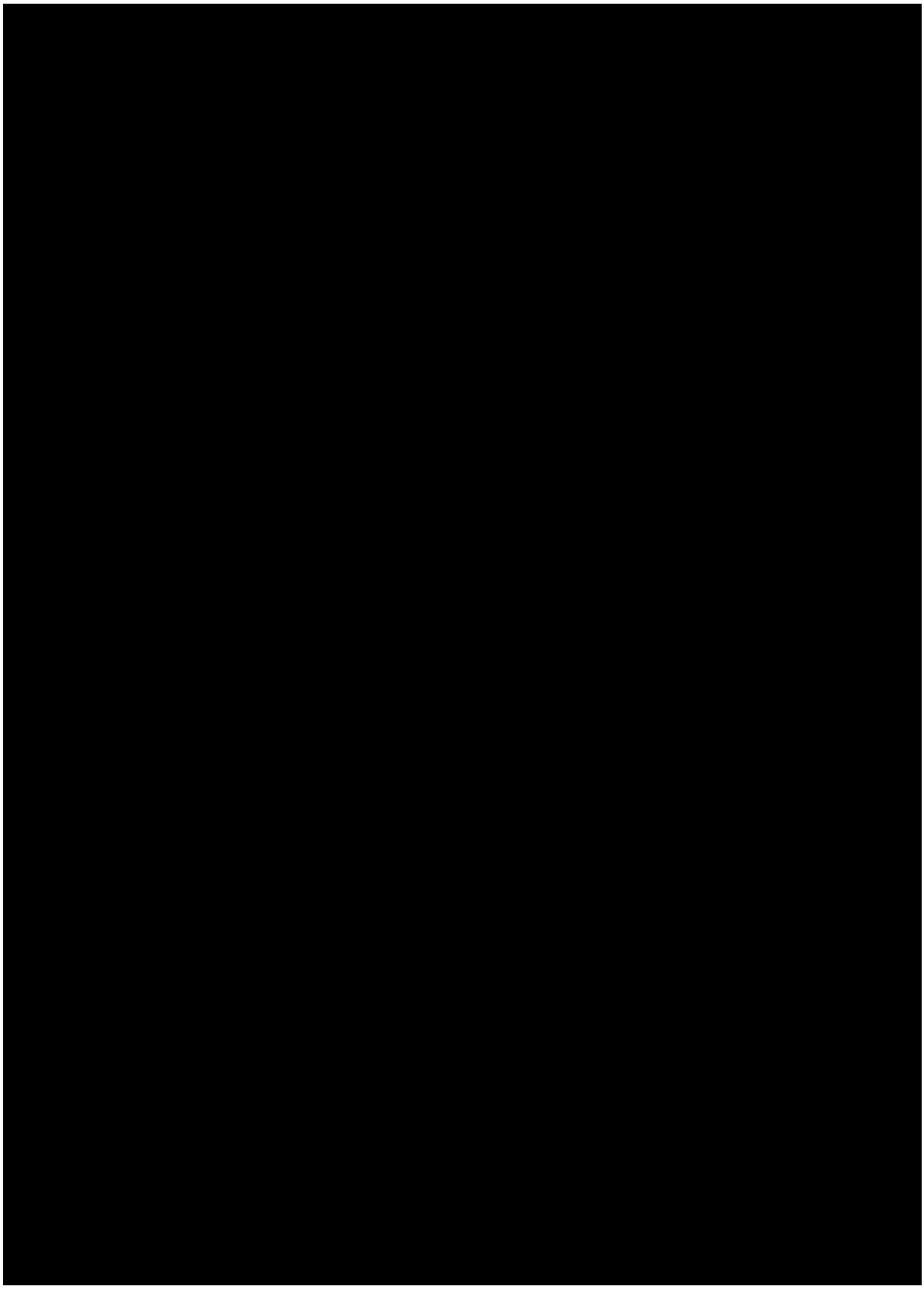
16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

[redacted]







[redacted]

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

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

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