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MBG453

Clinical Trial Protocol CMBG453C12201 / NCT04150029

A phase II multi-center, single arm, safety and efficacy study of MBG453 in combination with azacitidine and venetoclax for the treatment of Acute Myeloid Leukemia (AML) in adult patients unfit for chemotherapy

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List of abbreviations

ADA	Anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	Acute Myeloid Leukemia
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BMA	Bone marrow aspirate
BSA	Body Surface Area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
COA	Clinical Outcome Assessment
CR	Complete Remission
CRF	Case Report/Record Form (paper or electronic)
CRi	Complete Remission with incomplete hematologic recovery
CRh	Complete Remission with partial hematologic recovery
CRO	Contract Research Organization
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
CV	coefficient of variation
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
DLCO	Diffusing Capacity for Carbon Monoxide
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event-free Survival
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
ELN	European Leukemia Network
EMA	European Medicines Agency
EMD	Extramedullary disease
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire
EOT	End of treatment

[redacted]

ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol Group - standardized measure of health status questionnaire
ESA	Erythropoiesis Stimulating Agent
eSAE	Electronic Serious Adverse Event
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV 1	Force Expiratory Volume Force 1
GCP	Good Clinical Practice
GCSF	Granulocyte-Colony Stimulating Factor
GLDH	Glutamate dehydrogenase
HbcAb	Hepatitis B core antibody
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HMA	Hypomethylating agent
HR	Hazard Ratio
HSCT	Hemopoietic Stem Cell Transplant
HSV	Herpes-simplex virus
i.v.	intravenous
ICF	Informed consent form
ICH	International Council forHarmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
irAE	Immune related adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWG	International Working Group
LDH	lactate dehydrogenase
LFT	Liver function test
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
MFC	Multiparameter Flow Cytometry
MFC-MRD	Multiparameter Flow Cytometry-Measurable Residual Disease
Mg	milligram(s)
mL	milliliter(s)
MLFS	Morphologic Leukemia-Free State
MRD	Measurable residual disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NK	Natural killer
OS	Overall Survival

[redacted]

PAS	Pharmacokinetic Analysis Set
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PGIS	Patient Global Impression of Severity
PGITS	Patient Global Impression of Treatment Satisfaction
PK	pharmacokinetic(s)
PR	Partial remission
PRO	Patient Reported Outcome
PS	Performance status
Q4W	Every 4 weeks
RBC	red blood cell(s)
RFS	Relapse Free Survival
RNA	Ribonucleic acid
SC	Steering Committee
SAE	serious adverse event
SCT	Stem cell transplant
SD	Stable Disease
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TFQ	Trial Feedback Questionnaire
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TLS	Tumor lysis syndrome
TSH	Thyroid-Stimulating Hormone
ULN	upper limit of normal
USPI	United States Prescribing Information
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
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)
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 response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (CRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Investigational drug/treatment	The study drug whose properties are being tested in the study
Investigational treatment / study 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/ study 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 medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare professional	A qualified healthcare professional who performs certain protocol procedures for the subject in an off-site location such as a subject's home.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
[redacted]	[redacted]
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.

[redacted]

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis/Sponsor for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias
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
Screen Failure	A subject who is screened but is not treated or randomized
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
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 drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

[redacted]

Amendment 5 (08-Dec-2022)

Amendment rationale

At the time of release of this amendment, all subjects (n= 90) have been enrolled to this trial.

The main purpose of the present amendment is to revise the timing of the primary analysis (CR analysis) in order to capture potential late responders and more robust duration of response to study treatment. The CR rate analysis, initially planned when all subjects completed at least 7 treatment cycles or discontinued earlier, will now be performed when all subjects completed at least 12 treatment cycles or discontinued earlier. As recent publications highlighted the high variability of time to/duration of response in patients receiving venetoclax plus azacitidine; it is necessary to allow sufficient follow-up time before conducting the CR rate analysis (Jonas et al 2022; Pratz et al 2022).

In addition, the following secondary endpoints were added: CR/CRh rate and duration of CR/CRh that will be derived by the Sponsor. These changes are made to reflect the updated ELN 2022 diagnosis and management of AML guidelines (Döhner et al 2022).

Furthermore, the following changes were made to the protocol:

Changes to the protocol

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

- Updated glossary of terms and list of abbreviation with respect to latest Novartis protocol template and amended text
- Updated protocol summary with respect to changes in protocol body
- Section 1.1 – Background
  - Added data from a recent Phase III study on venetoclax+azacitidine combination (DiNardo et al 2020)
- Section 1.2 – Purpose
  - Added reference to recent phase III trial (DiNardo et al 2020)
- Section 2 – Objectives and endpoints
  - Table 2-1 – Objectives and related endpoints
    - Added timepoint for primary endpoint
    - Updated to use duration of CR and duration of CR/CRi instead of the terminologies of "RFS in CR patients" and "RFS in CR/CRi patients", respectively.
    - CR/CRh rate, duration of CR/CRh and MRD negativity rate in subjects in CR/CRh were added as secondary endpoints
    - [redacted]
    - These changes are made to reflect the revised ELN 2022 AML guidelines. CRh related endpoints will be derived by the Sponsor
- Section 4.4.1 – Rationale for MRD assessments

[redacted]

  - Data updated according to recent study update (Pratz et al 2022)
  - Reference to the revised ELN 2021 MRD guidelines was added
- [redacted]
  - [redacted]
  - [redacted]
- Section 4.5 – Purpose and timing of interim analyses/design adaptations
  - Updated to revise the timing of primary analysis (CR analysis). The CR analysis, initially planned when all subjects completed at least 7 treatment cycles, will now be performed when all subjects completed at least 12 treatment cycles or discontinued earlier
- Section 4.6 - Risks and benefits
  - Paragraph on contraception requirement for women with child-bearing potential was updated for consistency with language in exclusion criterion 20
- Section 4.7 - Rationale for Public Health Emergency mitigation procedures
  - Language updated according to most recent Novartis protocol standard language for clarification
- Section 6.1.1 – Investigational and control drugs
  - Paragraph – Azacitidine, clarification added on Azacitidine administration per standard local clinical practice and local regulations
- Section 7 - Informed consent procedures
  - Added requirement for compliance with 21 CFR 50, privacy and data protection regulations
  - Added paragraph regarding guidance on remote consent in cases of public health emergencies
  - Updates done to reflect latest Novartis protocol template language
- Section 8 – Visit schedule and assessments
  - Language for disruption proofing was updated to clarify Investigator's responsibilities and oversight for off-site assessments
- Section 8.3.1 – Efficacy assessments
  - Paragraph – Post treatment efficacy follow-up, updated to align with Table 8-1 Assessment Schedule regarding criteria to enter the post-treatment follow-up phase
- Section 8.5.2 – Pharmacokinetics
  - Pre-dose sampling window is relaxed from 30 min to 2 hours in Table 8-9 footnote, considering the long half-life of MBG453
- [redacted]
  - [redacted]
  - [redacted]
- Section 9.1.1.1 – Safety Follow-up

[redacted]

  - Updated to clarify the safety monitoring for patients continuing on MBG453 through an alternative setting after the end of the study
- Section 9.1.2 - Withdrawal of informed consent/opposition to use data/biological samples
  - Section language updated as per latest Novartis protocol template language for further clarification
- Section 9.1.3 -Lost to follow up
  - Language updated as per latest Novartis protocol template language for further clarification
- Section 9.2 – Study completion and post-study treatment
  - Updated to reflect the revised timing of primary analysis (CR analysis)
- Section 10.1.1 – Adverse Events
  - Updated to clarify the safety monitoring for patients continuing on MBG453 through an alternative setting after the end of the study
- Section 10.1.3 – SAE reporting
  - Updated to clarify the safety reporting for patients continuing on MBG453 through an alternative setting after the end of the study
- Section 11.2 - Database management and quality control
  - Paragraph added to state minimal required retention period for study records and documents
- Section 12 – Data analysis and statistical methods
  - Updated to reflect the revised timing of primary analysis (CR analysis)
- Section 12.4.2 – Statistical model, hypothesis, and method of analysis
  - CR analysis (safety run-in and expansion parts) paragraph, updated to reflect the revised timing of primary analysis (CR analysis)
- Section 12.5 – Analysis of secondary endpoints
  - CR/CRh rate was added as a secondary endpoint
  - Duration of response (CR, CR/CRi, CR/CRh) was used to replace RFS
- Section 12.5.1 – Efficacy endpoint(s)
  - Updated to clarify that all response assessments used for efficacy analysis will be based on investigator assessment, unless otherwise stated
  - Duration of response paragraph, updated to use duration of CR and duration of CR/CRi instead of the terminologies of “RFS in CR patients” and “RFS in CR/CRi patients”, respectively
  - Duration of CR/CRh was added as secondary endpoint
  - Added criteria for derivation of CRh
  - CR/CRh rate was added as a secondary endpoint
  - MRD negativity rate in subjects in CR/CRh was added as secondary endpoint
- [redacted]
  - [redacted]

[redacted]

- [redacted]
- [redacted]
- Section 12.7 – Interim analyses
  - Updated to reflect the revised timing of primary analysis (CR analysis)
- Section 13 - Ethical considerations and administrative procedures
  - Update to reflect latest Novartis protocol template language and added language for potential transition to European Clinical Trial Regulation (EU CTR)
- Section 15 – References
  - Following references were added: DiNardo et al 2020, Jonas et al 2022, Pratz et al 2022, Döhner et al 2022, Heuser et al 2021

This amendment also includes minor editorial changes and additional clarifications.

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.

[redacted]

Amendment 4 (22-Dec-2021)

Amendment rationale

At the time of release of this amendment, 29 subjects have been enrolled to this trial. Part 1 (safety run-in) has been completed, and following investigator's recommendation from the Safety Review Meeting held on 26-Oct-2021, the expansion phase has opened to enrollment.

The main purpose of this amendment is to modify the guidance on permanent discontinuation of treatment for patients experiencing prolonged cytopenias. Cytopenia is a common adverse event with the triplet combination of MBG453, venetoclax, and azacitidine and may take longer than 28 days to recover. For patients experiencing prolonged cytopenias, the study treatment may be interrupted for up to 42 days. This change will allow patients the opportunity to stay on study treatment while their blood counts recover.

In addition, the DLT criteria related to prolonged hematologic toxicities, applicable during the safety run-in phase, were modified. A CTCAE Grade 4 neutropenia, thrombopenia or pancytopenia, not related to leukemic infiltration, persisting beyond 42 days (instead of 56 days previously) from start of treatment cycle constitutes a DLT. This change was implemented consistently for pertinent combination studies within the MBG453 program. Furthermore, the following changes were made to the protocol:

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 3 – Study Design
  - Updated to clarify subjects' hospitalization is recommended during venetoclax rampup period and anytime at investigator's discretion.
- Section 4.2 – Rationale for dose/regimen and duration of treatment
  - Updated to implement latest MBG453 Investigator Brochure (v.7 dated 26-Nov-2021) updates
- Section 4.6 – Risks and Benefits
  - Reference to ASCO Guidelines updated to 2021 version
- Section 6.1.5 – Treatment duration
  - Permanent discontinuation criterion for subjects experiencing prolonged cytopenias updated to indicate that in absence of clinical benefit for the patient per investigator assessment subjects without recovery within 42 days should be discontinued
- Section 6.2.1.1 - Permitted concomitant therapy requiring caution and/or action
  - Table 6-3 – Management of potential interactions of CYP3A and P-gp inhibitors with venetoclax
    - Dosing schedule of the ramp-up period, for subjects on moderate CYP3A4 or P-gp inhibitor, was updated to reflect USPI for venetoclax
- Section 6.2.2 - Prohibited medication

[redacted]

  - Updated to note that vaccination against COVID-19, unless these are live vaccines, is allowed during the study. However, it was clarified that SARS-CoV-2 vaccines should not be administered the same day as study treatment as recommended by the ASCO guidelines 2021 version
- Section 6.5.2 – Definitions of dose limiting toxicities (DLTs)
  - Table 6-4 - Criteria for defining dose-limiting toxicities during the safety run-in updated
    - DLT for hematologic toxicities shortened to 42 days
    - Minor edit was performed for DLT for liver toxicities
- Section 6.5.3 – Dose modifications
  - Paragraph - Dose interruption at the start of a new treatment cycle and Table 6-6 - Dose modification for venetoclax, updated to include reference to the local label for dose modifications for venetoclax,
  - Permanent discontinuation criterion for subjects experiencing prolonged cytopenias updated to indicate that - in absence of clinical benefit for the patient per investigator assessment - subjects without recovery within 42 days should be discontinued
  - Reference to ASCO Guidelines updated to 2021 version in Table 6-5 and within paragraph of dose modifications for MBG453
- Section 6.5.4.1 – Follow-up for immune related AEs
  - Reference to ASCO Guidelines updated to 2021 version
- Section 8 – Visit Schedule and Assessments
  - The allowed visit window for BMA procedures was updated to +/- 8 days from the planned visit date. Further the maximum days allowed between BMA efficacy, extramedullary disease assessment and hematology assessments of the same visits was updated to 8 days.
  - Table 8-1 – Assessment Schedule - footnote 21 was added to clarify that the Trial Feedback Questionnaire (TFQ) is not considered study data and will be received electronically outside the clinical database
- Section 8.3.1 – Efficacy assessment
  - Updated to provide clarification on how hematology assessments should be performed in the absence of count recovery at C2D1 and beyond
  - Table 8-2 – Response classification in AML at a given evaluation time (based on IWG Cheson et al 2003, ELN 2017 Döhner et al 2017)
    - CRi definition was edited to reflect accurately ELN 2017 guidelines
- Section 8.5.1.2 Trial Feedback Questionnaire (TFQ)
  - Updated to clarify that the Trial Feedback Questionnaire (TFQ) is not considered study data and will be received electronically outside the clinical database
- Section 10.1.3 – SAE reporting
  - Updated to note if more stringent, local regulations regarding reporting timelines for initial or follow-up AEs prevail

[redacted]

  - Updated to note that initial and follow-up SAEs, must be reported, without undue delay and under no circumstances later than within 24 hours of obtaining knowledge of the initial event or receiving the follow up information.
- Section 15 – References
  - Reference Brahmer et al 2018 deleted
  - Reference for 2021 ASCO Guideline update added
  - Reference for Version 3.2021 NCCN Acute Myeloid Leukemia Clinical Practice Guidelines added

This amendment also includes minor editorial changes and additional clarifications

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.

[redacted]

Amendment 3 (08-Apr-2021)

Amendment rationale

At the time of release of this amendment, 5 subjects have been enrolled to this trial.

The main purpose of this amendment is to modify the exclusion criteria to permit enrollment of patients with therapy-related AML. This change will align eligibility criteria with VIALE-A, the Phase III study that demonstrated the efficacy of venetoclax and azacitidine in patients with AML not suitable for intensive chemotherapy.

In addition, the following notable changes were made:

- Exclusion criterion #6 was modified to allow enrollment of patients who have been treated for a malignancy and have been disease free (absence of residual disease) for at least 1 year; previously a disease free period of 2 years was required.
- Requirements for evaluation of extramedullary disease were modified to allow imaging modalities and techniques to be selected based on institutional standard of care. The previous specifications for use of CT scan or MRI have been removed.
- Venetoclax ramp-up dosing was updated based on Venclexta® (Venetoclax) USPI 2018 (Section 2.1). The 4-day ramp-up dosing was amended to 100 mg (D1), 200 mg (D2), 400 mg (D3), 400 mg (D4) compared to the original protocol which noted 4-day ramp-up dosing as 100 mg (D1), 200 mg (D2), 300 mg (D3), 400 mg (D4).
- New, Novartis standard language, referred to as disruption proofing language, has been added to address trial conduct during public health emergencies. The added language addresses study participant safety and trial integrity. In addition, updates to the new version of Novartis protocol CTP template were made.
- This amendment also includes minor editorial changes and additional 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.

- Updated glossary of terms and list of abbreviation further to protocol version 4.0 template
- Section 4.6 Evaluation of risk due to COVID-19 pandemic added
- Section 4.7- Rationale for Public Health Emergency mitigation procedures was added

Section 5.0 - Population

- Clarified that therapy-related AML patients may be included

Section 5.2 - Exclusion criteria

- Exclusion criterion # 3 was removed
- Exclusion criterion #6 was amended to specify subject with history of adequately treated malignancy for which the subject has been disease free (absence of residual disease) for at least 1 year can enter the study if all other criteria are met.

[redacted]

Section 6.1 - Study treatment

- Table 6-2 Dosing schedule for ramp-up of venetoclax in Cycle 1was updated to note ramp-up period and dosing schedule per USPI
- Updated to move the dosing interval recommendations for days of coadminstration of venetoclax with other study treatment to the venetoclax section, and to add reference to the pharmacy manual for detailed instructions on drug administration on coadministration days with MBG453

Section 6.2.1 - Concomitant therapy

- Updated to provide a window of when concomitant medications should be collected
- Updated to allow the use of cytarabine as a standard of care

Section 6.2.2 - Prohibited medication

- Updated to allow prophylactic intrathecal chemotherapy

Section 6.6.1 - Treatment Compliance

- Added the possibility of an off-site healthcare personnel to confirm compliance of administration of azacitidine, where applicable

Section 6.7 - Preparation and Administration

- Added the possibility to administer azacitidine off-site if requested by an Investigator

Section 8 - Visit schedule and assessments

- Added the option of a contingency plan if the patient cannot come onsite (phone calls)
- Added Patient Reported Outcomes must be completed before any clinical assessments are performed at any given visit

Table 8.1 - Assessment schedule

- CT scan/MRI replaced with Imaging assessment for extramedullary disease
- Footnote #4: Updated to specify suspected to be related to treatment AEs and SAEs and concomitant medication collection window
- Footnote #7: Updated to allow the use of preexisting cytogenetics results for the screening

Section 8.2 - Subject demographics/other baseline characteristics

- Modified language regarding race/ethnicity baseline characteristics to match CTP template v4.0
- CT scan/MRI removed to allow for appropriate imaging determined by the investigator

Section 8.3.1 - Efficacy assessments

- CT scan/MRI removed to allow for appropriate imaging of extramedullary disease to be determined by the investigator as clinically indicated and per standard of care

Table 8-6 Local clinical laboratory parameters collection plan

- Updated to allow the assessment of Troponin-I, if Troponin-T is not available

Section 8.4.2 Electrocardiogram (ECG)

- Providing clarification on how many minutes apart triplicate ECGs should be performed

[redacted]

Section 8.4.4 - Additional safety monitoring and considerations during venetoclax ramp-up

- Ramp-up period for venetoclax updated as lasting 3 or 4 days per USPI

Section 9.1.2, Section 10.1.3, Section 10.1.4 - Updated relevant sections to match new Novartis protocol standard language (CTP template v4.0)

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.

[redacted]

Amendment 2 (19-May-2020)

Amendment rationale

As the release of this amendment, no sites have been initiated, and no subject has been screened or has received study treatment in this trial.
The main purpose of this amendment is to allow enrollment of patients receiving moderate or strong CYP3A4 inhibitors or Pg-p inhibitors, in order to allow use of prophylactic antifungal medications (e.g. posaconazole, fluconazole or other azoles) commonly used in this patient population. This amendment expands the pool of eligible subjects, allowing enrollment of subjects more representative of the overall population with AML not suitable for intensive chemotherapy. Venetoclax is metabolized via the CYP3A4 system. Inhibitors of CYP3A4 administered concurrently with venetoclax result in higher, potentially toxic plasma levels of venetoclax. This has been studied extensively and is reflected in the prescribing information for venetoclax. It is allowed to co-administer venetoclax with strong CYP3A inhibitors, but venetoclax doses need to be reduced. As many antifungal drugs commonly used for prophylaxis or treatment of fungal infections in AML are strong CYP3A inhibitors, this amendment removes the strict ban of co-administration in lieu of dose-reduction rules for venetoclax.

In addition, the following updates have been implemented:

- Extend the restrictions on the use of live vaccines until the end of the follow-up period after the last dose of MBG453.
- Guidance has been added on the criteria for MBG453 dose management for dermatological adverse drug reactions (ADRs) and non-immune related toxicities to align with the MBG453 Investigator's Brochure.
- Guidance has been added that subjects should be monitored carefully for any skin toxicity or mucositis, and that study treatment should be discontinued for any suspected case of Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN) to align with the MBG453 Investigator's Brochure.

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

- Exclusion criterion # 10 removed to allow enrollment of subjects receiving CYP3A4 inhibitors or Pg-p inhibitors

Section 6.1 - Study treatment

- Updated to refer to the latest Pharmacy Manual for detailed administration instructions to ensure consistency between documents and compliance with compounding standards and internal guidance.

Section 6.2 - Other treatment(s)- Updated to clarify that subjects who received a reduced dose of venetoclax due to co-administration of moderate or strong CYP3A or P-gp inhibitors, as per

[redacted]

venetoclax USPI (see information in Table 6-3), will be considered to have received the planned dose of venetoclax.

Section 6.2.2 - Prohibited medications - The restriction of the use of live vaccines has been extended to 150 days after the last dose of MBG453.

- Table 6-3 - Management of potential interactions of CYP3A and P-gp inhibitors with venetoclax has been updated to allow concomitant use of venetoclax and posaconazole. Also, strong or moderate CYP3A4 inhibitors and P-gp inhibitors can now be used during venetoclax ramp-up phase.

Section 6.5.2.1 - Guidelines for assessing tolerability - Updated to clarify that subjects receiving a reduced dose of venetoclax due to co-administration of strong or moderate CYP3A4 inhibitors or P-gp inhibitors will be considered to have received the planned dose.

Section 6.5.3: Table 6-5 has been updated to add dose modification guidance for MBG453 for dermatological adverse drug reactions (ADRs) and non-immune related toxicities.

Section 6.5.4.1 - Follow-up for immune-related AE(s) - Guidance has been added for subjects on MBG453 that subjects should be monitored carefully for any skin toxicity or mucositis, and that study treatment should be discontinued for any suspected SJS/TEN.

[redacted]

- [redacted]

IRBs/IECs

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

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

The changes herein do not affect the Informed Consent.

[redacted]

Amendment 1 (10-Feb-2020)

Amendment rationale

As of release of this amendment, no site has been initiated, no subject has been screened and no subject has received study treatment in this trial. This amendment incorporates the US FDA recommendations following an End of Phase 1 meeting held on 22 November 2019.

There are two primary purposes of this amendment; to further evaluate subject safety during the safety run-in part of the trial by exploring a lower dose level of MBG453 (400 mg Q4W) in combination with azacitidine and venetoclax prior escalating to the higher MBG453 dose level of 800 mg Q4W, and to ensure consistency in the enrolled subject population across sites by modifying I/E criteria to more precisely define the population not suitable for intensive chemotherapy.

As the combination of MBG453, azacitidine and venetoclax has not been tested in the clinic, the safety run-in will initially enroll a cohort of 3 - 6 evaluable subjects at a starting dose of MBG453 of 400 mg Q4W in combination with azacitidine and venetoclax. This initial cohort will be observed and evaluated for safety using the criteria specified in the original protocol. Provided this initial dose level is considered safe, a cohort of approximately 12 subjects will be enrolled at the higher MBG453 dose level of 800 mg Q4W in combination with azacitidine and venetoclax, and the safety run-in will proceed as specified in the original protocol. The same doses and regimens of azacitidine and venetoclax will be used across cohorts.

In the original protocol, selection of subjects with first-line AML not suitable for intensive chemotherapy was determined by investigator decision. To ensure consistency in the enrolled subject population and alignment with similar studies involving venetoclax therapy, the I/E criteria will be modified to more precisely define the eligible population according to age and/or the presence of specific cardiac, pulmonary, hepatic or renal comorbidities.

In addition, the definition of the secondary endpoint event free survival (EFS) will be modified to implement US FDA feedback and to align with other MBG453 studies as well as with studies with other agents in this subject population, [redacted] The modified definition of EFS will include treatment failure, defined as failure to achieve CR after 7 cycles of treatment, death due to any cause, and relapse from CR as events; disease progression and start of new therapy will no longer be considered events. [redacted]

Finally, clarification is provided on the scope of the Steering Committee (including recommendation of study termination).

This amendment also includes minor editorial changes and additional clarifications to address investigators' questions as described in the list of changes below.

[redacted]

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

- Primary objectives updated to reflect the addition of one safety cohort (400 mg Q4W)
- Secondary objectives: EFS definition updated
- Study design updated to reflect the addition of one safety cohort (400 mg Q4W)
- Key inclusion criteria updated to add a definition of the criteria for patients to be assessed as unfit for intensive chemotherapy based on age and pre-existing comorbidities and to include subjects with ECOG performance status of 3 to align with the respective comorbidity criteria in other inclusion criterion.
- Language added for primary CR analysis that will be done on patients treated with MBG453 at 800 mg Q4W.

Section 2 - Objectives and endpoints

- Primary objectives: language added to specify that CR rate will be assessed on patients receiving MBG453 at 800 mg Q4W only. Incidence of DLTs will be assessed at the two tested dose levels.
- Secondary objectives: EFS definition updated.
- [redacted]

Section 3- Study Design

- Updated with the addition of one safety cohort.
- Figure 3-1 updated

Section 4.1 - Rationale for study design

- Language updated to include a safety review meeting at each dose level.

Section 4.2 - Rationale for dose/regimen and duration of treatment

- Language updated to reflect the addition of a safety cohort
- Clinical safety data updated based on most recent safety data.

Section 4.4.1 - Definition of MRD was updated.

Section 4.5 - Purpose and timing of interim analyses/design adaptations

- Updated with the addition of one safety cohort.
- Updated timing of interim analysis to be performed after all subjects have completed 7 months (previously 6 months) to align with the definition of treatment failure and assessment schedule for CR.

Section 4.6 - Risks and benefits

- Updated with the addition of one safety cohort.

Section 5 - Population

- Updated with the addition of one safety cohort

[redacted]

Section 5.1 - Inclusion criteria

- Inclusion criterion # 3 updated with addition of a definition of the criteria for patients to be assessed as unfit for intensive chemotherapy based on age and pre-existing comorbidities
- Inclusion criterion # 5 updated to include subjects with ECOG performance status of 3 to align with the respective comorbidity criteria in inclusion criterion # 2
- Inclusion criterion # 7 updated to include subjects with total bilirubin up to 3 x ULN (Grade 2) (except in the setting of isolated Gilbert syndrome, in which case higher total bilirubin is allowed provided that conjugated bilirubin is ≤ 3.0 x ULN) to align with the respective comorbidity criteria in inclusion criterion # 2

Section 6.1.1 - Investigational and control drugs

- Table 6-1 updated wording for dose strength used for MBG453 for better illustration of formulations used
- Language updated to reflect the addition of a safety cohort
- Added formula for body surface area (BSA) calculation

Section 6.5 - Dose escalation and dose modification

- Language updated to reflect the addition of a safety cohort and a safety review meeting.
- Table 6-4: Immune toxicity: Language updated for better clarity. Footer added to the table regarding organ specific immune toxicity.

Section 6.5.4.2 - Follow-up for TLS: updated instruction for maintaining adequate hydration

Section 6.5.3 - Dose modification

- Correction to add condition of subjects with CR requiring dose interruption at the start of a treatment cycle in case of Grade 4 neutropenia and /or Grade 4 thrombocytopenia

Section 8 - Visit schedule and assessments

- Language added to specify that a maximum of 7 days is allowed between BMA efficacy, extramedullary disease assessment (if applicable) and hematology assessments of the same visit.
- Table 8-1 updated the description urinalysis to align with updated table 8-6 and typos corrected related to PK sample collection not done at Cycles 4 and 5 and to efficacy response assessment not done at screening.

Section 8.2 - Language updated to clarify that racial and ethnic information will be collected in this study in order to allow for signal detection for differences and to allow for racial/ethnic sensitivity reports required for registration in multiple countries· Table 8-6 updated to clarify that detailed urinalysis as per local practice is required only for patient with abnormalities during the dipstick analysis, if clinically indicated.

- Table 8-7 updated to specify IL1 subunit
- Section 8.5.2.1- language added to clarify that PK sample collection for pre-MBG453 infusion is no longer needed after permanent discontinuation of MBG453.

[redacted]

Section 9.1.1.3 - Survival follow-up

- Language updated to add that information about the remission status and the date of progression/relapse from CR for patients who receive a HSCT will also be collected during follow-up phone calls.

Section 9.1.4 - Early study termination by the sponsor

- Updated to clarify scope and the role of the steering committee in the study termination process.

Section 9.2 - Study completion and post study treatment: Updated information regarding complete remission rate analysis to be conducted after completion of 7 cycles by the last patient enrolled.

Section 10.2 - Additional Safety Monitoring

- Section 10.2.1 - Data Monitoring Committee updated to reflect the addition of a safety cohort
- Section 10.2.2 - Steering Committee updated to clarify the scope and role of the Steering Committee in the monitoring of study conduct (including study termination)

Section 12 - Data analysis and statistical methods

- Language updated to reflect the addition of a safety cohort
- Language updated for the primary analysis on CR rate that will be performed after all subjects have completed at least 7 cycles of treatment with MBG453+ azacitidine + venetoclax

Section 12.4 updated to specify that overdose criteria will be assessed at the two tested dose levels. CR rate will be assessed on patients receiving MBG453 at 800 mg Q4W only.

- EFS definition has been updated
- MRD definition has been updated

Section 12.5.1 - Efficacy endpoint(s):

- MRD definition has been updated
- RFS definition has been updated for subject without any event

Section 12.5.2 - Safety endpoints updated to specify that safety analyses will be summarized for the safety set and by dose level of MBG453.

[redacted]

Section 12.7 - Interim analyses updated to reflect the addition of a safety cohort

Section 12.8 - Sample size calculation

- Language updated to reflect the addition of a safety cohort
- Information updated to clarify that CR analysis will be performed in patient receiving MBG453 at 800 mg Q4W only from both safety run-in and expansion parts.

[redacted]

Section 16.1 - Appendix 1: Statistical Details for Safety Run-in Part: Bayesian model: prior and design properties for hypothetical data scenarios

Sections 16.1.1 to 16.1.3 updated to consider the new Bayesian model including the two doses tested of MBG453 in the safety run-in part: 400 mg Q4W and 800 mg Q4W.

IRBs/IECs

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

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

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

[redacted]

Protocol summary

Protocol number	CMBG453C12201
Full Title	A phase II multi-center, single arm, safety and efficacy study of MBG453 in combination with azacitidine and venetoclax for the treatment of Acute Myeloid Leukemia (AML) in adult patients unfit for chemotherapy
Brief title	A study of MBG453 in combination with azacitidine and venetoclax in AML patients unfit for chemotherapy
Sponsor and Clinical Phase	Novartis Phase II
Study Indication	Acute Myeloid Leukemia (AML)
Investigation/Treatment type	Drug; Biological
Study type	Interventional
Purpose and rationale	MBG453, a novel monoclonal antibody inhibitor of TIM-3, has shown preliminary evidence of clinical activity as a single-agent in patients with relapsed/refractory AML. The study will be conducted in two parts. The primary purpose of Part 1 (Safety Run-in) is to rule out excessive toxicity of MBG453, when administered in combination with azacitidine and venetoclax. The primary purpose of the combined Part 1 and Part 2 (Safety run-in and Expansion Part) is to evaluate efficacy of MBG453, when administered in combination with azacitidine and venetoclax in adult patients with newly diagnosed AML, who are not suitable for treatment with intensive chemotherapy. The current trial will seek to extend the preliminary findings of efficacy of MBG453 in combination with hypomethylating agents (HMA) by evaluating MBG453 in combination with the HMA azacitidine and the Bcl-2 inhibitor venetoclax. The doublet of venetoclax and azacitidine has demonstrated improved efficacy relative to azacitidine alone in early phase Ib and phase III trials (DiNardo et al 2019, DiNardo et al 2020), and recently has received approval by the FDA for treatment of unfit AML. Despite the improved efficacy demonstrated by the venetoclax-azacitidine, a significant unmet medical need remains as a substantial number of patients do not achieve CR (complete remission), the CRs which are observed are only of limited duration and MRD negativity is achieved by a minority of patients.
Primary Objective(s)	• The primary objective for the safety run-in part is to determine whether MBG453 at the two tested dose levels (400 mg and 800 mg Q4W) is not meeting the overdose criteria when added to azacitidine + venetoclax in subjects with AML not suitable for chemotherapy by measuring the incidence of dose-limiting toxicities (DLTs) between Cycle 1 Day 8 and the end of Cycle 2 of treatment. • The primary objective for the overall study (safety-run-in + expansion) is to assess the complete remission rate (CR) of MBG453, administered at 800 mg Q4W, in combination with azacitidine and venetoclax in subjects with AML not suitable for chemotherapy by determining the proportion of subjects achieving a complete remission (CR) as per investigator assessment.

Secondary Objectives	• To assess the CR/CRi rate and the duration of CR/CRi by measuring the proportion of subjects achieving a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) and the time from the date of the first documented CR/CRi to the date of first documented relapse or progressive disease or death due to any cause, whichever occurs first, as per investigator assessment • To assess the duration of complete remission (CR) by measuring the time from the date of the first documented CR to the date of first documented relapse or progressive disease or death due to any cause, whichever occurs first, as per investigator assessment • To assess the CR/CRh rate and the duration of CR/CRh by measuring the proportion of subjects achieving a complete remission (CR) or complete remission with partial hematologic recovery (CRh) and the time from the date of the first CR/CRh to the date of first relapse or progressive disease or death due to any cause, whichever occurs first, as per derivation • To assess the Event-free Survival (EFS) by measuring the time from start of treatment until date of death due to any cause, relapse from CR, or treatment failure, whichever comes first. • To assess Overall Survival (OS) by measuring the time from start of treatment to death due to any cause • To determine safety and tolerability of MBG453 when administered in combination with azacitidine and venetoclax by evaluating the incidence and severity of AEs and SAEs, changes in laboratory values and vital signs, incidence of notable ECG abnormalities • To characterize the pharmacokinetics (PK) of MBG453 when administered in combination with azacitidine and venetoclax by determining the serum concentrations for MBG453 and plasma concentrations for venetoclax • To evaluate immunogenicity of MBG453 when given in combination of azacitidine and venetoclax by measuring Anti-drug Antibody (ADA) prevalence at baseline and ADA incidence on-treatment • To assess the MRD negativity rate by determining the proportion of subjects with MRD negativity (a MRD negative sample determined by Multiparameter Flow Cytometry-Measurable Residual Disease (MFC-MRD) and a bone marrow remission) in the full study population and/or any subgroup of interest (CR, CR/CRi, CR/CRh, etc...) • To assess the effect of MBG453 in combination of venetoclax + azacitidine on transfusion independence by measuring the number and percent of all subjects who achieve transfusion independence on treatment, and from baseline respectively
Study design	This phase II, open-label, single-arm, multi-center study of MBG453 in combination with azacitidine and venetoclax in adult subjects with AML will be conducted in two parts. Part 1 is a Safety Run-in of approximately 18 subjects, to assess whether MBG453 at the two tested dose levels (400 mg and 800 mg Q4W) is safe when given in combination with azacitidine and venetoclax. Following the observation period a Safety Review Meeting will be conducted. If no safety concerns are identified with the tested combination of MBG453, azacitidine and venetoclax, Novartis will provide notification to the investigational sites that Part 2 (expansion) is open to enrollment. Enrollment to Part 2 will continue until a total enrolment of approximately 80 subjects treated with MBG453 at 800 mg Q4W (including those in the safety run-in) has been achieved.
Population	The study population will include approximately 86, adult subjects with newly diagnosed AML, who are not suitable for intensive chemotherapy and not eligible for HSCT, based on the medical judgment of the investigator.
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • Age ≥ 18 years at the date of signing the informed consent form (ICF)Newly diagnosed with AML (based on WHO 2016 classification (Arber et al 2016), who

	are not suitable for intensive chemotherapy based on one or more of the following criteria:
	• age ≥ 75 years
	• ECOG performance status of 2 or 3
	• or at least one of the following comorbidities:
	  • severe cardiac comorbidity (including congestive heart failure requiring treatment, left ventricular ejection fraction ≤ 50%, or chronic stable angina)
	  • pulmonary comorbidity (including DLCO ≤ 65% or FEV1 ≤ 65%)
	  • moderate hepatic impairment with total bilirubin > 1.5 to 3 times the upper limit of normal
	  • eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2 (estimation based on Modification of Diet in Renal Disease (MDRD) formula, by local laboratory)
	  • any other comorbidity (to be documented in the CRF) that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the Novartis Medical Monitor before study enrollment.
	• Patients with antecedent MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera are eligible, provided no prior therapy, as specified in the exclusion criterion #1.
	• No planned hematopoietic stem-cell transplantation (HSCT).
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, 2 or 3.WBC < 25x10^9/L (may be reduced with leukopheresis or hydroxyurea)

Key Exclusion criteria	• Previous treatment with any of the following antineoplastic agents, approved or investigational; checkpoint inhibitors, venetoclax and hypomethylating agents (HMAs) such as decitabine or azacitidine. Previous treatment for AML, MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera is permitted with hydroxyurea, growth factors or ruxolitinib • Prior exposure to TIM-3 directed therapy at anytime • Subjects with AML-M3 / APL (Acute promyelocytic leukemia) with PML-RARA and patients with AML secondary to Down's syndrome • Subjects with CNS leukemia or neurologic symptoms suggestive of CNS leukemia (unless CNS leukemia has been excluded by a lumbar puncture) • Subjects with concurrent or prior malignancy, **except**: a) subject with history of MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera b) subject with history of adequately treated malignancy for which the subject has been disease free (absence of residual disease) for at least 1 year and if no anticancer systemic therapy (namely chemotherapy, radiotherapy or surgery) is ongoing or required during the course of the study. Patients who are receiving adjuvant therapy such as hormonotherapy are eligible
Study treatment	MBG453 + azacitidine + venetoclax
Efficacy assessments	Bone marrow aspirate and peripheral blood will be collected at screening and at regular intervals during treatment for assessment of disease. Response evaluation will be per Investigator's assessment, based on standardized criteria as proposed by the European Leukemia Network (ELN) and International Working Group (IWG) for AML (Cheson et al 2003; Döhner et al 2017). Disease classification at baseline and evaluation of response during study treatment will rely on bone marrow or peripheral blood assessment, as well as on the presence or absence of extramedullary disease, and status of transfusion dependence.
Pharmacokinetic assessments	Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects.

[redacted]

Key safety assessments	• Adverse event monitoring, • Physical examination, • Vital signs, • ECOG PS, • Monitoring of laboratory evaluations in blood and urine, • 12-lead electrocardiograms (ECGs)
Other assessments	[redacted] **Immunogenicity:** Immunogenicity samples will be obtained and evaluated in all subjects.
Data analysis	For subjects included in the safety run-in part, the tolerability of MBG453 administered in combination with venetoclax and azacitidine will be guided by a Bayesian analysis and the DLT incidence reported during the two first cycles. The probability that the true DLT rate exceeds 33% will be modeled using a Bayesian Model. For all subjects (safety run-in and expansion parts) treated with MBG453 at 800 mg Q4W, the efficacy of MBG453 in combination with venetoclax and azacitidine will be based on the proportion of subjects achieving a complete remission (CR) as per investigator assessment. Trial success will be assessed based on dual decision criterion with a null value (no effect) of 50% (statistical criteria) and a minimum estimated effect size (clinical relevance) of 61% (clinical criteria) for the CR rate. If the statistical and clinical criteria are both met, the trial will be declared successful.
Key words	Phase II, MBG453, TIM-3, venetoclax, azacitidine, Acute Myeloid Leukemia (AML).

[redacted]

1 Introduction

1.1 Background

Acute myeloid leukemia (AML) is a malignant disease characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood and extramedullary tissues. AML is the most common form of acute leukemia in adults; an estimated 21,450 new cases of AML and 10,920 deaths from the disease will occur in the United States, in 2019 (American Cancer Society 2019). AML is primarily a disease of older patients, with approximately two-thirds of patients above the age of 60, and a median age at presentation of 68 years (Noone et al 2018). Patients aged 65 and older typically have AML associated with adverse cytogenetic characteristics, inferior performance status, and lower complete response (CR) rates, in addition to higher treatment-related mortality and shorter overall survival (OS).

Intensive chemotherapy, which is standard of care for first line treatment, is not considered suitable for many elderly AML patients due to higher toxicity, especially in patients with significant comorbidities and adverse cytogenetic risk AML. The subpopulation of patients with AML not considered suitable for intensive chemotherapy or HSCT, are often referred to as unfit AML, a term that will be used in this protocol.

Low dose cytarabine was the first agent reported to prolong survival and improve the quality of life of these unfit AML patients (Burnett et al 2007). More recently, decitabine (Dacogen®) and azacitidine (Vidaza®) have been approved in the EU for patients aged 65 years and above with newly-diagnosed leukemia who are not candidates for standard induction chemotherapy (or HSCT in the case of azacitidine) based upon phase 3 clinical trial results showing clinically meaningful improvements in OS (Kantarjian et al 2012, Dombret et al 2015). In addition, the use of azacitidine for elderly or unfit AML patients is included in the NCCN AML treatment guidelines version 3.2017 (O'Donnell et al 2017).

In 2018, venetoclax, a small molecule inhibitor of BCL-2, the over-expression of which has been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics (Konopleva et al 2006), has received accelerated approval by the FDA in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who are unfit for intensive induction chemotherapy. Approval was based on two open-label, non-randomized trials, and efficacy was established based on the rate of complete remission (CR) and CR duration. In a most recent data update (DiNardo et al 2019), it is reported that the CR and CRi rates were 37% and 30% respectively, for patients treated with venetoclax in combination with azacitidine or decitabine, with a median observed time in remission (CR or CRi) of 11.3 months (95% CI, 8.9 months-not reached). Furthermore, only 29% of patients in remission achieved levels of MRD below 0.1%, suggesting that deep leukemic clearance (< 0.1%) remains a challenge for a majority of the patients. In the randomized, placebo-controlled Phase III study comparing venetoclax plus azacitidine to azacitidine plus placebo (control group) in previously untreated and ineligible to standard induction patients with AML (DiNardo et al 2020) overall survival was significantly longer with median survival of 14.7 months in the azacitidine+ venetoclax group versus 9.6 months in the control group with HR= 0.66 (95% CI, 0.52 to 0.85; P<0.001). Although the incidence of complete remission was higher (36.7% vs. 17.9%; P<0.001) among patients who received azacitidine plus venetoclax than among those who received azacitidine

[redacted]

alone, significant number of patients still did not achieve a complete remission. Furthermore, MRD negativity rate occurred only in 23.4% of the patients receiving azacitidine plus venetoclax (DiNardo et al 2020). Thus, although these results represent an advance in treatment of the unfit AML population, complete remission achievement, remission duration and leukemic clearance to MRD levels below 0.1% are still modest, and an unmet need remains for new therapy options for this patient population.

Inhibition of immune checkpoints, including PD-(L)1 and CTLA4, have demonstrated durable objective responses in multiple tumor types, and 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 are used in daily clinical practice. However, the optimal immunotherapy for AML has not yet been identified.

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

MBG453 is a high-affinity, ligand-blocking, humanized anti-TIM-3 IgG4 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 in AML and in high and very high risk MDS subjects (see clinical responses in Section 4.3).

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

1.2 Purpose

The current study will be conducted in two parts. The primary purpose of Part 1 (Safety Run-in) is to rule out excessive toxicity of MBG453 when administered in combination with azacitidine and venetoclax. The primary purpose of the combined Part 1 and Part 2 (Expansion Part) is to evaluate the efficacy of MBG453 at 800 mg Q4W when administered in combination with azacitidine and venetoclax in adult patients with newly diagnosed AML who are not suitable for treatment with intensive chemotherapy or HSCT. In addition, Part 2 will evaluate safety and tolerability and characterize the pharmacokinetics of MBG453 when administered in combination with azacitidine and venetoclax.

MBG453, a novel monoclonal antibody inhibitor of TIM-3, has shown preliminary evidence of clinical activity as a single-agent in patients with relapsed/refractory AML. More importantly,

[redacted]

in study [CPDR001X2105] MBG453 has shown promising evidence of efficacy, including durable CRs of up to15 months in ongoing patients, when administered in combination with the HMA decitabine to patients with newly diagnosed AML and high-risk MDS.

The current trial will seek to extend these preliminary findings of efficacy by evaluating MBG453 in combination with the HMA azacitidine and the Bcl-2 inhibitor venetoclax. The doublet of venetoclax and azacitidine has demonstrated improved efficacy relative to azacitidine alone in early phase Ib and phase III trials (DiNardo et al 2019, DiNardo et al 2020), and recently has received approval by the FDA for treatment of unfit AML. Despite the improved efficacy demonstrated by the addition of venetoclax to HMA, a significant unmet medical need remains as a substantial number of patients do not achieve CR (complete response), the majority patients in remission still retain leukemic burden (detection of MRD >0.1%), and the CRs which are observed are only of limited duration.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Safety run in + Expansion:** To assess the complete remission (CR) rate of MBG453, administered at 800 mg Q4W, in combination with azacitidine and venetoclax in subjects with AML not suitable for chemotherapy	• Proportion of subjects achieving a complete remission (CR) as per investigator assessment (Cheson et al 2003, Döhner et al 2017) will be determined when all subjects have completed at least 12 cycles of treatment with MBG453 + azacitidine + venetoclax or discontinued earlier.
• **Safety run-in:** To determine whether MBG453 at the two tested dose levels is not meeting overdose criteria when added to azacitidine + venetoclax in subjects with AML not suitable for chemotherapy.	• Incidence of DLTs between Cycle 1 Day 8 and end of cycle 2.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the MRD negativity rate	• Proportion of subjects with MRD negativity (a MRD negative sample determined by MFC-MRD and a bone marrow remission) in the full study population and/or any subgroup of interest (CR, CR/CRi, CR/CRh, etc.)
• To assess the CR/CRi rate and the duration of CR/CRi	• Proportion of subjects achieving a CR or CRi, as per investigator assessment (Cheson et al 2003, Döhner et al 2017) • Time from the date of the first documented CR/CRi to the date of first documented relapse or progressive disease or death due to any cause, whichever occurs first, as per investigator assessment (Cheson et al 2003, Döhner et al 2017),
• To assess the duration of complete remission (CR)	• Time from the date of the first documented CR to the date of first documented relapse or progressive disease or death due to any cause, whichever occurs first, as per investigator assessment (Cheson et al 2003, Döhner et al 2017)
• To assess the CR/CRh rate and the duration of CR/CRh	• Proportion of subjects achieving a CR or CRh, as per derivation (Döhner et al 2022)

Objective(s)	Endpoint(s)
	• Time from the date of the first CR/CRh to the date of first relapse or progressive disease or death due to any cause, whichever occurs first, as per derivation (Döhner et al 2022)
• To assess the Event-free Survival (EFS)	• The time from start of treatment until date of death due to any cause, relapse from CR, or treatment failure, whichever occurs first.
• To assess Overall Survival (OS)	• The time from start of treatment to death due to any cause
• To determine safety and tolerability of MBG453 when administered in combination with azacitidine and venetoclax	• Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs, incidence of notable ECG abnormalities
• Characterize the pharmacokinetics (PK) of MBG453 when administered in combination with azacitidine and venetoclax	• Pharmacokinetic parameters (serum concentrations for MBG453 and plasma concentrations for venetoclax)
• To evaluate immunogenicity of MBG453 when given in combination of azacitidine and venetoclax	• Anti-drug Antibody (ADA) prevalence at baseline and ADA incidence on-treatment
• To assess the effect of MBG453 in combination of venetoclax + azacitidine on transfusion independence	• Number and percent of all subjects who achieve transfusion independence on treatment, and from baseline respectively.
[redacted]	

[redacted]

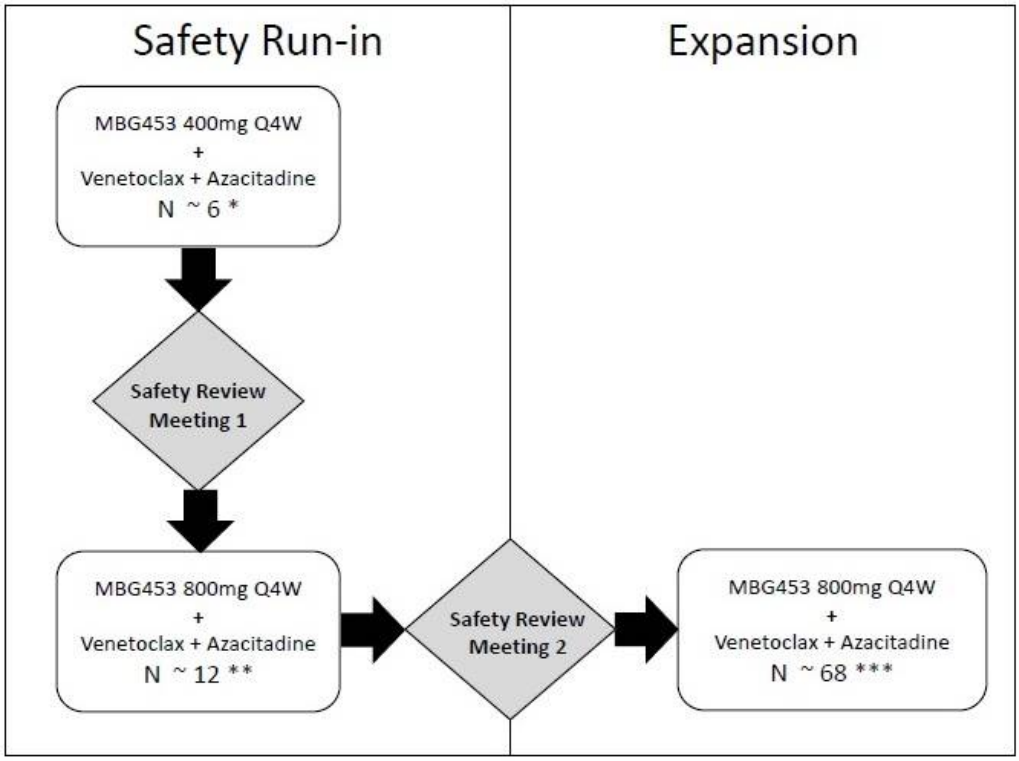
[redacted]

3 Study design

This Phase II, open-label, single-arm, multi-center study of MBG453 in combination with azacitidine and venetoclax in adult subjects with AML not suitable for intensive chemotherapy is described in Figure 3-1 below. The study will enroll a total of approximately 86 subjects and will be conducted in two parts. Part 1 is a Safety Run-in to assess whether MBG453 is safe when given in combination with azacitidine and venetoclax. A total of approximately 18 subjects will be enrolled to Part 1 across two dose levels. Approximately 6 subjects will be enrolled at the starting dose level, 400 mg Q4W, in order to obtain 3 to 6 evaluable subjects (see Section 6.5 for evaluability criteria). Provided the starting dose level is determined to be safe, approximately 12 subjects will be enrolled at the second dose level (800 mg Q4W), in order to obtain at least 9 evaluable subjects (see Section 6.5 for evaluability criteria). For each dose level, once the required number of evaluable subjects has been confirmed, enrollment will be halted until subjects have completed the DLT observation period (see Section 6.5), and a Safety Review Meeting has been conducted (see Section 6.5.1). If no safety concerns are identified at either dose level, Novartis will provide notification to the investigational sites that Part 2 (expansion) is open to enrollment. Enrollment to Part 2 will continue until a total enrollment of approximately 80 subjects at the 800 mg Q4W dose level (including those in the safety run-in) has been achieved.

[redacted]

Figure 3-1 Study Design



* The safety run-in cohort MBG453 400 mg Q4W requires 3 to 6 evaluable subjects (approximately 6 enrolled subjects) to have been observed for at least 2 cycles

**The safety run-in cohort MBG453 800 mg Q4W requires at least 9 evaluable subjects (approximately 12 enrolled subjects) to have been observed for at least 2 cycles

*** To achieve a total of 80 subjects at the 800 mg Q4W dose level

Study treatment will be administered in cycles with a planned duration of 28 days, and study treatment may continue until the subject experiences disease progression (as defined by ELN 2017; Döhner et al 2017) or unacceptable toxicity.

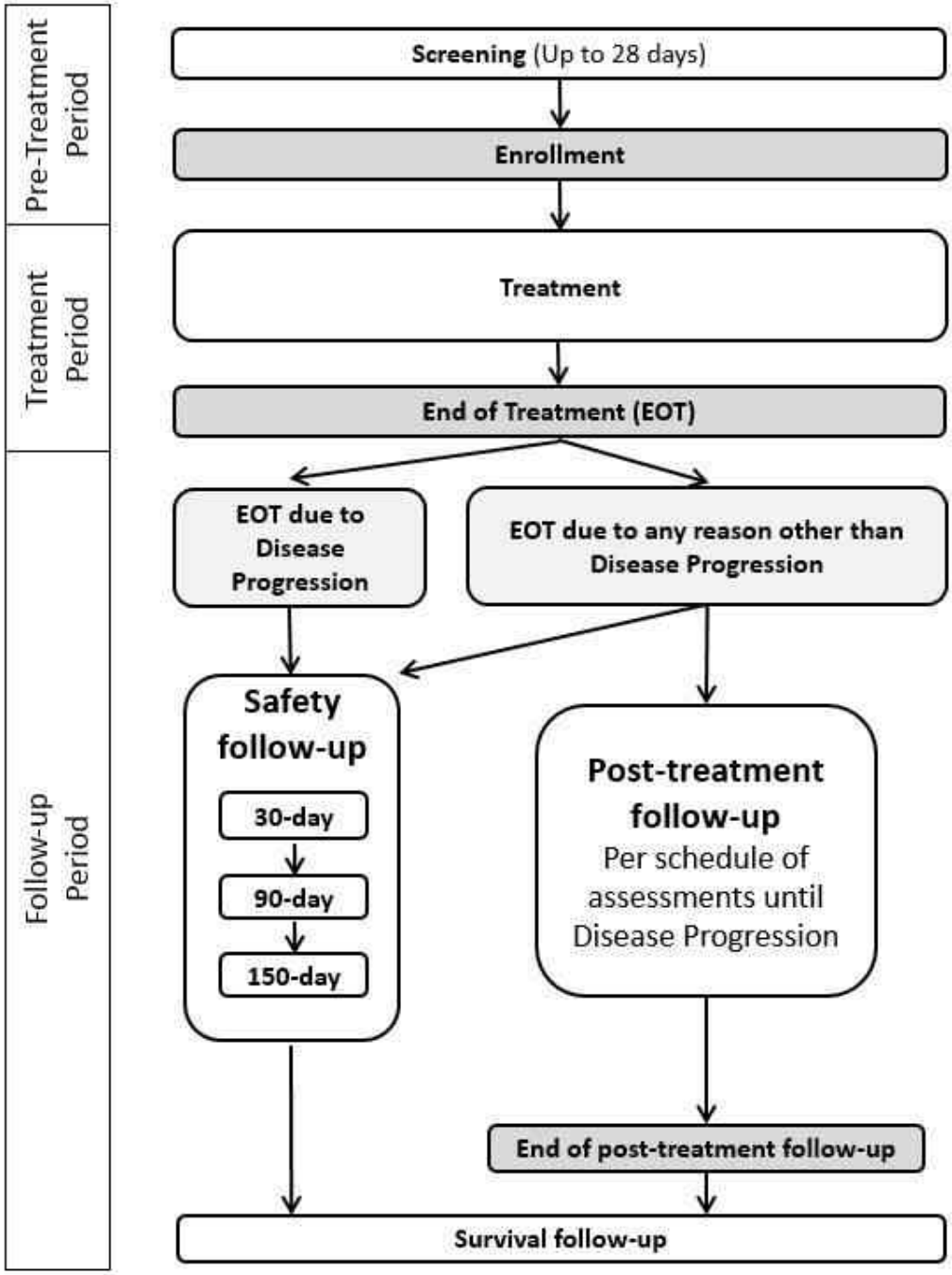
In each cycle, azacitidine will be administered intravenous or subcutaneous at 75 mg/m^2 on Days 1 to 5 and Days 8 and 9 (or, at discretion of the investigator on Days 1-7, or Days 1-6 and Day 8 respectively), and venetoclax will be administered orally at 400 mg daily (following ramp-up (see Table 6-2 and Section 6.1.1 for details), starting on Day 1). MBG453 will be administered intravenously at 400 mg (safety run-in cohort 1) or 800 mg (safety run-in cohort 2 and expansion) on Day 8 (Q4W) of every 28-day cycle. Hospitalization during Cycle 1 from Day 1 to Day 3 is recommended at investigator's discretion in order to monitor closely occurrence of TLS, (see Section 6.5.4.2), and thereafter is at the discretion of the investigator.

At any time during the study, patients unable to tolerate one or two of the study treatment drugs, may continue study treatment with only the tolerated drug(s). In addition, for patients who achieve a CR and have received at least 18 cycles of study treatment, treatment with venetoclax and azacitidine may be discontinued at the discretion of the investigator, and the patient continues on study receiving only single agent MBG453.

[redacted]

After the end of study treatment, all patients must be followed for adverse events (AEs) for 30 days; in addition, follow-up for AEs will be conducted for 150 days following the last dose of MBG453. All subjects who discontinued study treatment will enter a long-term follow-up (for efficacy and/or survival status) as described in the study flow diagram below (Figure 3-2) and outlined in Section 9.1.

Figure 3-2 Study Flow



Study Flow

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

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

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

All subjects will be followed for survival as per Section 9.1.1.3.

4 Rationale

4.1 Rationale for study design

The overall study design, Phase II, single-arm, open-label, multi-center, is a design to evaluate safety, tolerability and efficacy of a novel combination. To avoid overdosing of MBG453 in combination with azacitidine and venetoclax, the study does employ a two-part design with a halt to enrolment between Part 1 (Safety Run-in) and Part 2 (Expansion part). This design element allows, in Part 1, a Safety Review Meeting at each dose level, with evaluation of DLTs, and review of available safety data to confirm that MBG453 in combination with azacitidine and venetoclax, which has not been evaluated clinically, is safe, prior to opening enrollment to a larger patient population. A Steering Committee (Section 10.2.2) will be convened to review the safety during the course of study.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dose/regimen of MBG453

The study will start with a cohort of 3 to 6 evaluable subjects treated with MBG453 at a dose level of 400 mg Q4W in order to minimize the risk for unexpected toxicities of this novel combination of MBG453 in combination with venetoclax and azacitidine. The proposed MBG453 dose level for evaluation of efficacy in the study is 800 mg Q4W based on data accumulated from 2 phase 1 studies. [CMBG453X2101] in solid tumor patients has a wide MBG453 dose range. In MBG453 single agent arms, MBG453 doses ranged from 80 to 1200 mg every 2 weeks (Q2W) or every 4 weeks (Q4W), with a lower 20 mg Q2W MBG453 dose additionally tested in combination with PDR001. Because of the data obtained in [CMBG453X2101], [CPDR001X2105] study started evaluating MBG453 at 240 mg Q2W, 400 mg Q2W and 800 mg Q4W in combination with decitabine.

Clinical Pharmacology:

The pharmacokinetics (PK) of MBG453 were similar between studies [CMBG453X2101] in solid tumor patients and [CPDR001X2105] in AML and high risk MDS patients. At lower doses (at 80 mg and below for Q2W dosing or at 240 mg and below for Q4W dosing), the PK was nonlinear, with faster elimination at lower concentrations. PK appeared linear with an

approximate proportional dose-exposure (AUC and Cmax) relationship at doses of 240 mg and above for Q2W dosing and at doses of 800 mg and above for Q4W dosing. Accumulation of MBG453 was observed with repeated administrations, and for the Q2W regimen, AUCtau during cycle 3 ranged between 1.01-2.78 fold higher than during cycle 1. A dose of 800 mg Q4W has similar AUCtau as 400 mg Q2W at the steady state.

Clinical Efficacy:

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

Clinical Safety:

MBG453 was found to be safe and well tolerated across all dose levels tested in both studies. In study [CMBG453X2101], up to date, a total of 133 subjects with solid tumors have been treated with MBG453 single agent therapy. There were no adverse events attributed to study treatment with an incidence >10%. The most frequently reported adverse events attributed to study treatment included fatigue (9%), followed by decreased appetite and nausea (4.5% each). There were no DLTs during the first cycle. No subjects discontinued study treatment due to treatment-related AEs.

In study [CPDR001X2105], as of 01-Apr-2021, a total of 187 subjects with hematological malignancies have been treated with MBG453 as a single agent (n=26) or in combination with decitabine (n=82) or azacitidine (n=79). In the 26 subjects treated with MBG453 single agent, there were no adverse events attributed to study treatment with an incidence >10%. The most frequently reported adverse events attributed to study treatment were AST increased, diarrhea and rash in two subjects (8%), each. All other adverse events attributed to study treatment were single occurrences. There were no DLTs during the first cycle. No subjects discontinued study treatment due to treatment-related AEs. In the 82 subjects treated with MBG453 in combination with decitabine, the most frequent adverse events (all grades, >10%) attributed to study treatment have included thrombocytopenia, anemia, neutropenia, nausea, and fatigue. One subject experienced a DLT during the first 2 cycles, which consisted of hepatitis manifesting as Grade 3 ALT increase. One subject discontinued study treatment due to a treatment-related AE of possible hemophagocytic lymphohistiocytosis. In the 79 subjects treated with MBG453 in combination with azacitidine, the most frequent adverse events (all grades, >10%) attributed to study treatment have included nausea, vomiting, anemia, constipation, diarrhea, fatigue, neutrophil count decrease and platelet count decrease. One participant experienced a DLT during the first 2 cycles, which consisted of a Grade 4 acute febrile neutrophilic dermatosis (Sweet's syndrome), and discontinued the study treatment. One subject with neutropenic colitis reported as suspected to be related to study treatment died of septic shock. No other study treatment-related deaths were observed in any of the studies mentioned above.

[redacted]

Preliminary analysis revealed no relationship between dose, incidence and severity of adverse events across the different treatment groups. No relationship was observed between Cmax and the incidence of potentially immune related adverse events, providing additional support for 800 mg Q4W regimen, which has the highest Cmax among the doses tested. Please refer to the Investigator's Brochure for additional information of AEs reported in subjects with solid tumors or with hematologic malignancies treated with MBG453 as a single agent or in combination with other drugs.

Predicted Target Engagement:

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

In summary given the excellent safety and tolerability seen across all doses and schedules in [CMBG453X2101] and [CPDR001X2105], the activity seen at all three doses tested in study [CPDR001X2105]; the predicted saturation of TIM-3 from the soluble TIM-3 data and the receptor occupancy model; and the lack of clear dose-response or exposure-response relationship for MBG453, 800 mg Q4W was selected as the target dose regimen for this study.

4.3 Rationale for choice of combination drugs

Rationale for combining MBG453 with azacitidine and venetoclax

Venetoclax in combination with azacitidine or decitabine or low dose cytarabine has recently received accelerated approval from FDA based on efficacy and safety, demonstrated in two open-label trials (see Section 1.1). Based on these trial results, venetoclax in combination with HMA is emerging as a potential new standard of care.

The rationale for combining the MBG453 with azacitidine and venetoclax is based on the following:

Data from allogeneic HSCT and donor lymphocyte infusions have demonstrated a role for the immune system in the treatment of AML. However, the optimal immunotherapy has yet to be defined, and to date PD-1 inhibitors have demonstrated minimal single-agent activity, suggesting exploration of alternative approaches.

TIM-3 is a checkpoint inhibitor that plays a complex role in the negative regulation of innate and adaptive immune responses. Further, TIM-3 is expressed on leukemic stem cells and leukemic progenitor cells but not on normal hematopoietic stem cells. This suggests that TIM-3 inhibition by MBG453 may have immunomodulatory as well as direct anti-leukemic effects.

Hypomethylating agents induce broad epigenetic effects including downregulating genes involved in cell cycle, cell division and mitosis, and upregulating genes involved in cell differentiation. However, these potentially anti-leukemic effects are accompanied by increased

[redacted]

expression of TIM-3 as well as PD-1, PD-L1, PD-L2 and CTLA4, potentially downregulating immune-mediated anti-leukemic effects. These latter effects justify the exploration of novel checkpoint inhibitors to decrease an immunosuppressive tumor microenvironment (Yang et al 2014, Ørskov et al 2015).

Venetoclax is an inhibitor of BCL-2. BCL-2 inhibits apoptosis of factor-deprived cells, but does not prevent apoptosis of immune cell mediated killing, indicating different mechanisms of apoptosis induction (Vaux et al 1992). Therefore, blockage of both BCL2, which promotes direct leukemic cell apoptosis, and TIM-3, which may promote both immune cell mediated killing and direct leukemia-stem cell targeting, may induce cancer cell elimination via different pathways and possibly create a synergistic effect.

Study [CPDR001X2105] has demonstrated that MBG453 can be administered safely in combination with an HMA, decitabine, and that this combination demonstrates preliminary efficacy including durable responses in patients with AML and high-risk MDS (see Section 4.2).

Further, as a mAb, MBG453 is not metabolized by cytochrome P450 (CYP450) enzymes, or transported by P-glycoprotein (Pgp) or related ABC membrane transporters, therefore an impact of DDIs on the PK of MBG453 by azacitidine, or venetoclax is not anticipated. Cytokines produced by activated lymphocytes may impact the levels of Pgp and the activity of CYP450 enzymes (Renton 2005, Dumais et al 2008, Harvey and Morgan 2014); the clinical relevance to MBG453 is unknown. However, preliminary data from the clinical study [CPDR001X2105], which has shown that the co-administration of MBG453 with decitabine did not result in changes in their PK parameters. Therefore, a clinically relevant DDI effect is considered unlikely.

Taken together, these data suggest that the combination of MBG453, venetoclax and azacitidine, can be administered safely with little overlapping toxicity contributed by MBG453, and that MBG453 may improve the efficacy of azacitidine and venetoclax.

4.4 Rationale for MRD assessment [redacted]

4.4.1 Rationale for MRD assessments

Measurable Residual Disease (MRD) in AML refers to the presence of leukemic blasts at a sensitivity of detection below the threshold of conventional morphologic methods. Patients who experience a CR according to morphologic assessments (<5% blasts in the bone marrow) can potentially still harbor a large number of leukemic cells in the bone marrow which can confer a poor outcome. Detection of MRD in AML has shown prognostic relevance in several studies (Freeman et al 2013, Terwijn et al 2013, Ivey et al 2016, Jongen-Lavrencic et al 2018, Freeman et al 2018), indicating that depth of leukemic clearance should be considered as a relevant prognostic endpoint in this setting. A recent study investigating efficacy of venetoclax in combination with HMA in unfit AML showed that, despite the impressive rate of morphological remission (CR/CRi: 190/286 (66.4%)), only a fraction of patient in remission had MRD levels below 0.1% (67/164 (41%) CR/CRi MRD-negative), as determined by Multiparameter Flow Cytometry (MFC) (DiNardo et al 2019; Pratz et al 2022). This indicates that addition of venetoclax to HMA, while delaying progression of AML, does not seem to effectively eradicate leukemic disease in the majority of responding patients. In addition, among

[redacted]

patients CR/CRi MRD negative, the median duration of remission (DoR), event-free survival (EFS), and overall survival were not reached (NR) compared to 9.7, 10.6 and 18.7 months (respectively) for patients in CR/CRi MRD positive, suggesting that CR/CRi MRD negativity is a good prognostic factor.

To investigate in detail the depth of leukemic clearance, we will perform MRD assessments using both phenotypic and molecular methods. At present, MFC represents the most adequate, clinically validated technology to robustly monitor MRD in the large majority of AML patients (~90%), being recommended in the European Leukemia Net (ELN) 2018 and 2021 MRD guidelines (Schuurhuis et al 2018, Heuser et al 2021). For this reason, we plan to use MFC-MRD data as a secondary efficacy endpoint. Molecular methods for MRD (using the most adequate markers and technology at time of analysis) will also be investigated as part of the exploratory biomarker plan, due to their potential to achieve higher sensitivity compared to MFC and allow identification of molecular biomarkers linked to drug efficacy and/or relapse. Monitoring of MRD will be performed at baseline, during treatment, and EOT and/or until disease progression, if applicable (see Table 8-1 and Section 8.3.2 and Section 8.5.3 for details), to sensitively assess the depth and duration of response and to provide prognostic information on risk of relapse.

[redacted]

[redacted]

4.5 Purpose and timing of interim analyses/design adaptations

No formal interim analyses are planned (see Section 12.7).

However, the study design foresees that during and at the conclusion of Part 1 (Safety Run-in), decisions based on emerging data are taken at safety review meetings following completion of enrollment at each dose level (or earlier if required) and prior to starting the expansion part. At the Safety Review Meetings, the decision to escalate to the 800 mg Q4W dose level or to open the expansion part at the MBG453 dose level of 800 mg Q4W will be guided by a Bayesian analysis based on the incidence of dose limiting toxicity (DLT) data, and supported by all available data, including safety data, clinical pharmacology data, tolerability data, and recommendations from participating investigators. The decision to enroll further patients at the MBG453 800 mg Q4W in the safety run-in part and to open Part 2 (Expansion Part) to enrollment will be communicated to investigators.

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

The primary analysis on CR rate will be performed after all subjects have completed at least12 cycles of treatment with MBG453 + azacitidine + venetoclax or discontinued earlier see Section 12.7

4.6 Risks and benefits

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. Further, dose modifications are provided and must be applied per protocol based on clinical or laboratory findings (see Section 6.5.3).

Occurrence of an immune-related adverse event is an anticipated risk in subjects treated with immune-oncology drugs such as MBG453. In the case of an immune-related event, there are dose modification and management guidelines, including detailed plans for follow-up of toxicities. In addition, the protocol references and will adhere to recent American Society of Clinical Oncology (ASCO) practices guidelines for management of immune-related adverse events in patients treated with checkpoint inhibitors (Schneider et al 2021) (see Section 6.5.3 and Section 6.5.4.1).

Based on currently available data, there are no known significant overlapping toxicities between the combination of venetoclax and azacitidine and MBG453. However, this novel combination treatment may have unforeseen risks, which could be serious. In particular, there is the potential for increased toxicity secondary to cytokine release syndrome due to activation of T cells and macrophages, and there may also be changes in immune function that could lead to autoimmunity or other immune-related adverse events as well as increased risk of infection. All subjects enrolled will be monitored closely for these potential toxicities.

Furthermore, as the safety of MBG453 administered in combination with azacitidine + venetoclax has not been assessed previously, the protocol stipulates that consecutive safety run-

[redacted]

in cohorts at 400 mg Q4W and 800 mg Q4W will be observed for at least 2 treatment cycles followed by a Safety Review Meeting, before opening enrollment to a larger patient population in Part 2. See Section 6.5.1. In addition, a Steering Committee (see Section 10.2.2) will review the safety during the course of the study.

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 a pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria until at least 30 days after the last dose of venetoclax, 90 days after the last dose of azacitidine (or as per respective local labels, whichever is longer) and 150 days after the last dose of MBG453, whichever is later. 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 to patients' safety due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified with MBG453 based on the available knowledge at this time. In case of active COVID-19 infection, a careful benefit risk evaluation needs to be performed by the investigator to determine whether the subject should remain on study medication or not.

There is no contraindication for the use of an inactivated, viral-vector-, or mRNA based SARS-CoV-2 vaccine in cancer patients on sabatolimab therapy.

COVID-19 vaccines have not been tested in patients treated with MBG453, therefore any additional risks are unknown at this time. Before receiving any vaccine, the risks and benefits should be evaluated by the investigator.

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, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the 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 with newly diagnosed AML, who are not suitable for intensive chemotherapy and not eligible for HSCT. Approximately 18 subjects across two dose levels, are expected to be enrolled in the safety run-in; additional subjects will be enrolled in the expansion part to achieve total enrollment of approximately 86 subjects.

Subjects with secondary AML, including therapy-related AML, may be included provided Inclusion criterion #3 is met and Exclusion criterion #4 is not met.

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.

[redacted]

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. Newly diagnosed with AML (based on WHO 2016 classification (Arber et al 2016), who are not suitable for intensive chemotherapy based on one or more of the following criteria:
   - age ≥ 75 years
   - ECOG performance status of 2 or 3
   - or at least one of the following comorbidities:
     - severe cardiac comorbidity (including congestive heart failure requiring treatment, ejection ≤ 50%, or chronic stable angina)
     - pulmonary comorbidity (including DLCO ≤ 65% or FEV1 ≤ 65%)
     - moderate hepatic impairment with total bilirubin > 1.5 to 3 times the upper limit of normal
     - eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2 (estimation based on Modification of Diet in Renal Disease (MDRD) formula, by local laboratory)
     - any other comorbidity (to be documented in the CRF) that the physician judges to be incompatible with intensive chemotherapy must be reviewed and approved by the Novartis Medical Monitor before study enrollment.

   Patients with antecedent MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera may be included, provided no prior therapy, as specified in exclusion criterion # 1.
4. No planned hematopoietic stem-cell transplantation (HSCT).
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, 2, or 3
6. AST and ALT ≤ 3 × upper limit of normal (ULN)
7. Total bilirubin ≤ 3.0 × ULN (except in the setting of isolated Gilbert syndrome, in which case higher total bilirubin is allowed provided that conjugated bilirubin is ≤ 3.0 x ULN)
8. Estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min/1.73 m^2 (estimation based on Modification of Diet in Renal Disease (MDRD) formula, by local laboratory)
9. Subject is able to communicate with the investigator, and has the ability to comply with the requirements of the study procedures
10. WBC < $25x10^9$/L (may be reduced with leukopheresis or hyroxyurea)

5.2 Exclusion criteria

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

1. Previous treatment at any time, with any of the following antineoplastic agents, approved or investigational; checkpoint inhibitors, venetoclax and hypomethylating agents (HMAs) such as decitabine or azacitidine. Previous treatment for AML, MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera, with the exception of hydroxyurea, growth factors, and supportive care ruxolitinib
2. Prior exposure to TIM-3 directed therapy at any time.

[redacted]

4. Subjects with AML-M3 / APL (Acute promyelocytic leukemia) with PML-RARA and patients with AML secondary to Down's syndrome
5. Subjects with CNS leukemia or neurologic symptoms suggestive of CNS leukemia (unless CNS leukemia has been excluded by a lumbar puncture)
6. Subjects with concurrent or prior malignancy, **except:**
   a) subject with history of MDS, myelofibrosis, essential thrombocythemia, or polycythemia vera
   b) subject with history of adequately treated malignancy for which the subject has been disease free (absence of residual disease) for at least 1 year and if no anticancer systemic therapy (namely chemotherapy, radiotherapy or surgery) is ongoing or required during the course of the study. Patients who are receiving adjuvant therapy such as hormonotherapy are eligible
7. History of severe hypersensitivity reactions to any ingredient of study drug(s) (azacitidine, venetoclax, MBG453) or monoclonal antibodies (mAbs) and/or their excipients
8. Any concurrent severe and/or uncontrolled medical condition e.g., active uncontrolled infection or severe infectious disease requiring parenteral antibacterial, antiviral or antifungal therapy (such as severe pneumonia, meningitis, or septicemia)
9. Active autoimmune disease requiring systemic therapy (e.g. corticosteroids)
11. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment (C1D1).
12. Current use, or use within 14 days prior to enrollment, of systemic steroid therapy or any immunosuppressive therapy (≥ 10 mg/day prednisone or equivalent). Topical, inhaled, nasal and ophthalmic steroids are not prohibited. Replacement therapy is allowed and not considered a form of systemic treatment
13. Live vaccine administered within 30 days prior to the first day of study treatment (C1D1)
14. Cardiac or cardiac repolarization abnormality, including but not limited to any of the following:
   a) History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
   b) QTcF > 470 ms at screening (based on mean of triplicate ECG), 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)
15. HIV infection not controlled by standard therapy (as permitted per protocol Section 6.2.1.1) and/or with known history of opportunistic infection. For countries where HIV status is mandatory: HIV status will be tested during screening using a local test
16. Active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Subjects whose disease is controlled under antiviral therapy should not be excluded
17. Other co-morbidity that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol

[redacted]

18. Sexually active males unless they use a condom during intercourse while taking azacitidine and for 3 months after stopping this drug. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants must not donate sperm for the time period specified above.
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 30 days after the last dose of venetoclax, 90 days after the last dose of azacitidine (or as per their respective local labels, whichever is longer) and 150 days after the last dose of MBG453. It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening/baseline). For female subjects on the study the vasectomized male partner should be the sole partner
    - Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

Women 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 [generally age from 40 to 59 years], history of vasomotor symptoms) in the absence of other medical justification or have had surgical bilateral oophorectomy (with or without hysterectomy) or bilateral tubal ligation at least 6 weeks ago. 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.

[redacted]

6 Treatment

6.1 Study treatment

In this study, the term “investigational drug” refers to the Novartis study drug, MBG453. The term "study treatment” refers to the combination of study drugs: MBG453 plus venetoclax plus azacitidine.

All dosages prescribed, dispensed to the subject and all dose changes during the study including the reason for any component of the study treatment must be recorded on the appropriate eCRF page.

6.1.1 Investigational and control drugs

Table 6-1 Study Treatment

Investigational/ Combination Drug (Name and Strength)	Strength	Pharmaceutical dosage form and route of administration	Supply Type	Sponsor (global or local)
MBG453	100 mg in 1ml and/or 400 mg in 4 ml	solution in vial for i.v. infusion	Open Label	Sponsor (global)
Venetoclax	100 mg and/or 50 mg and/or 10 mg (or as per local supply)	tablet for oral use	Open Label	Sponsor (global) or provided locally (US)
Azacitidine*	as per local supply	solution for i.v. infusion or subcutaneous administration	Open Label	Provided locally
* Formulation for generic azacitidine as approved by local regulations				

MBG453

MBG453 will be administered at a dose of 400 mg Q4W (safety run-in cohort 1) or 800 mg Q4W (safety run-in cohort 2 and expansion) via i.v. infusion over 30 minutes on Day 8 of every 28-day cycle.

If the alternative schedule is selected for azacitidine by the investigator, azacitidine and MBG453 will be given on the same day (day 8 of the 28-day cycle). Azacitidine should be administered first, followed by MBG453. The first dose of MBG453 should be administered after the subject has received at least 5 doses of azacitidine.

Further instructions for the preparation, dispensation, and administration of MBG453 are described in the Pharmacy Manual.

Venetoclax

Venetoclax film-coated tablets should be administered at a dose of 400 mg orally or corresponding reduced dose for concomitant use with P-gp inhibitors or moderate or strong CYP3A4 inhibitors (see Table 6-3 and Venclexta® (Venetoclax) USPI 2018) , once a day, on

[redacted]

each day of the 28-day cycle. Subjects should be instructed to swallow the tablets whole (tablets should not be crushed or broken), with water, at approximately the same time each day. The tablets should be taken with a meal (ideally at breakfast).

In Cycle 1, the dose of venetoclax will be ramped-up over a period of 3 or 4 days (C1D1 - C1D3 or C1D4) to achieve the dose of 400 mg per day (see Table 6-2), or corresponding reduced dose per day for concomitant with P-gp inhibitors or moderate or strong CYP3A4 inhibitors (see Table 6-3 and Venclexta® (Venetoclax) USPI 2018). During the ramp-up period, venetoclax should be taken in the morning to facilitate laboratory monitoring. See Section 8.4.4 for additional considerations during ramp-up and Section 6.5.4.2. For guidance on prophylaxis and follow-up for suspected TLS.

Table 6-2 Dosing schedule for ramp-up of venetoclax in Cycle 1

Day	Daily dose of venetoclax
Day 1	100 mg
Day 2	200 mg
Day 3 and beyond	400 mg

If a subject misses doses of venetoclax within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible on the same day. If the subject misses a dose by more than 8 hours, the subject should not take the missed dose and should resume the usual dosing schedule at the usual time the following day. In the event that the missed dose occurs during the ramp-up period of venetoclax, the subject should resume on the following day at the dose that was missed in order not to skip any dose increase of venetoclax during the ramp-up. If a patient vomits after taking venetoclax, the dose should not be re-administered and the subject should take their next dose at the usual time the following day.

On the days of PK sampling, the subject will be instructed to bring his/her drug supply to the site, and take the dose in the clinic, under supervision of the site personnel. The exact time for dose administration and breakfast (if applicable) intake must be recorded in the source documents and electronic Case Report Form (CRF). On days of coadministration, an interval of 30 minutes is recommended between administration of venetoclax and other study treatment.

Azacitidine

Azacitidine is considered Standard of Care in the population enrolled in this study and it should be administered according to standard local clinical practice and local regulations. This may include administration by study site staff, or local administration at another hospital or through home administration by qualified site staff, or by trained non-study personnel. A standard dose of azacitidine (75 mg/m^2; body surface area (BSA) in m^2 = [height (cm) x weight (kg)/3600]$^{0.5}$) will be given subcutaneously or intravenously every day for seven consecutive days on days 1-7 out of a 28 days cycle (see local azacitidine package insert). In keeping with standard clinical practice, the alternative schedules 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, or of 75 mg/m^2 for six consecutive days on days 1-6, followed by a one day break, then one administration on day 8 will be permitted (alternative schedule).

[redacted]

Azacitidine regimen used in this protocol were selected because they are the most studied regimens and recommended by international treatment guidelines (NCCN, ESMO) (O'Donnell et al 2017, Fey et al 2013).

NOTE: On days of co-administration of venetoclax, azacitidine and MBG453, venetoclax should be administered first followed by azacitidine, and then MBG453. Further instructions on co-administration of study treatment are described in the pharmacy manual.

6.1.2 Additional study treatments

Not applicable

6.1.3 Treatment arms/group

6.1.4 Guidelines for continuation of treatment

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

For patients who achieve a CR and have received at least 18 cycles of study treatment, treatment with venetoclax and azacitidine may be discontinued at the discretion of the investigator, and the patient continued on study receiving only single agent MBG453.

6.1.5 Treatment duration

A subject may continue study treatment and follow the protocol-defined safety assessments as scheduled until:

- Disease progression (see Table 8-2)
- Relapse from CR, CRi
- Unacceptable toxicity
- Initiation of a treatment cycle is delayed due to toxicities by more than 42 consecutive days (measured from the intended start date of the new cycle (i.e. measured from Day 29 of the previous cycle) in absence of clinical benefit for the patient per investigator assessment.
- Subject is scheduled to receive HSCT or intensive chemotherapy at any time during the course of the study
- Withdrawal of consent
- Physician's decision
- Pregnancy
- Lost to follow-up
- Death
- Study termination by Novartis

6.1.5.1 Treatment beyond disease progression

Treatment beyond disease progression is not permitted.

[redacted]

6.2 Other treatment(s)

6.2.1 Concomitant therapy

For participants enrolled all medications, procedures, and significant non-drug therapies/procedures (including physical therapy) taken within 28 days of starting study treatment until 150 days after the last dose of MBG453 or 30 days after the last dose of venetoclax or azacitidine (whichever was later) or until start of a new antineoplastic therapy must be recorded in the appropriate Case Report Forms. Concomitant medication administered to treat AE/SAEs suspected to be related to study treatment will continue to be collected up to the end of the safety follow-up period.

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 treatment.

Subjects should not receive pre-medication to prevent infusion reaction before the first infusion of MBG453. If a subject experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a subject experiences a Grade ≥ 3 anaphylactic/anaphylactoid reaction, the subject will be discontinued from the study treatment (see Section 6.5.3 for guidance).

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

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

Blood transfusions received within 8 weeks before the first dose is administered, during the course of the study and until the end of post treatment follow-up, should be recorded in the appropriate Case Report Forms (see Table 8-1).

Intrathecal chemotherapy (e.g cytarabine) administered as CNS prophylaxis, at time of diagnostic lumbar puncture, is permitted. All other use of chemotherapy is prohibited (see Section 6.2.2).

Supportive therapy including prophylactic antibiotic and antifungal treatments, transfusions, growth factors (e.g. GCSF, ESA), etc. will be administered at the discretion of the investigators according to their local standard of care.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medications and local prescribing information of azacitidine (Vidaza® (Azacitidine) USPI 2008) and venetoclax (Venclexta® (Venetoclax) USPI 2018). If in doubt, the investigator should contact the Novartis medical monitor before a subject starts treatment or allowing a new

[redacted]

medication to be started. If the subject has already started treatment, contact Novartis medical monitor to determine if the subject should continue study treatment.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during study treatment in this study are listed below. Please also refer to Appendix 2 (see Section 16.2) for detailed guidance.

Strong or moderate CYP3A4 inhibitors and P-gp inhibitors: If, such therapy is necessary, it can be introduced, under the provision that the dose of venetoclax is reduced. Recommendation for venetoclax dose, when given in combination with strong CYP3A inhibitors (e.g., posaconazole, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, and voriconazole), moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, and verapamil) or P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, and ticagrelor) are provided in Table 6-3 below.

Table 6-3 Management of potential interactions of CYP3A and P-gp inhibitors with venetoclax

Co-administered Drug	Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase)
Posaconazole	Day 1 - 10 mg Day 2 - 20 mg Day 3 - 50 mg Day 4 - 70 mg	Reduce venetoclax dose to 70 mg
Other strong CYP3A inhibitor	Day 1 - 10 mg Day 2 - 20 mg Day 3 - 50 mg Day 4 - 100 mg	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor or P-gp inhibitor	Day 1 - 50 mg Day 2 - 100 mg Day 3 - 200 mg	Reduce venetoclax dose to 200 mg (at least 50% reduction)

The venetoclax dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor. Subjects should be instructed to avoid grapefruit products, Seville oranges, and starfruit during treatment with venetoclax as they contain inhibitors of CYP3A4.

Strong or Moderate CYP3A4 inducers: Concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St.John's wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered.

P-gp or BCRP substrates: Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran exetilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

[redacted]

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 closely. 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.

6.2.2 Prohibited medication

During the course of the study, subjects must not receive additional investigational drugs, devices, chemotherapy (with the exception of prophylactic intrathecal chemotherapy (see Section 6.2.1)), 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 treatment unless given for the management of immune toxicity.

The use of systemic steroid therapy and other immunosuppressive drugs is 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 (providing this is ≤ 10 mg/day prednisone or equivalent) 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 treatment 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 and 150 days after the last dose of MBG453. Inactivated vaccines, subunits recombinant, polysaccharide and conjugate vaccines and toxoid vaccines are allowed.

Vaccination against COVID-19, unless these are live vaccines, is allowed during the study but should not be administered on the same day of study treatment administration as recommended by the ASCO guidelines (Schneider et al 2021).

In addition, prohibited medication related to 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 for the subject, unless the subject is re-screened. The Subject No. consists of the Center Number (Center No.)

[redacted]

(as assigned by Novartis to the investigative site) with a sequential subject number 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 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

This study is open label and non-randomized.

Prior to dosing at Cycle 1 Day 1, subjects who fulfill all the inclusion/exclusion criteria will be enrolled via IRT and a treatment number will be provided for the study treatment MBG453 and (for all countries except the US) for study treatment venetoclax. Study treatment azacitidine will be sourced locally.

The Investigator (or delegate) will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria by completing the eligibility criteria checklist embedded in the system. The IRT will assign a unique medication number for the first package of study treatments to be dispensed to the subject.

6.4 Treatment blinding

The study is open-label with no blinding.

6.5 Dose escalation and dose modification

Two dose levels of MBG453, 400 mg Q4W and 800 mg Q4W will be evaluated. Intra-subject dose escalation is not permitted. Guidance for dose modifications is provided in Section 6.5.1.

6.5.1 Guidelines for assessing the risk of overdosing for the regimen in the safety run-in

6.5.1.1 MBG453 dose level and regimen

MBG453 will be given at 400 mg every 4 weeks in the first approximately 6 enrolled subjects (3 to 6 evaluable subjects) (1st cohort of the safety run-in). If this dose level is considered safe, MBG453 will be given at 800 mg every 4 weeks in the next approximately 12 subjects (at least 9 evaluable patients) (2nd cohort of the safety run-in).

In case the combination meets overdose criteria at whatever MBG453 dose tested in the safety run-in, the expansion phase will not be opened.

[redacted]

6.5.1.2 Guidelines for assessing tolerability

For the purpose of assessing the risk of overdosing (as defined by EWOC criterion, see details below) of MBG453 in combination with azacitidine and venetoclax, at each MBG453 dose level, after the required number of evaluable subjects, 3 to 6 subjects for cohort 1 and at least 9 subjects for cohort 2, have been included, and observed for at least 2 cycles, a safety review meeting will be conducted.Subject will be considered evaluable for DLT if:

- Subject has received 2 infusions of MBG453 at the assigned dose level in Q4W dosing regimen, and has taken at least 75 % of the planned dose of azacitidine and venetoclax (i.e. for 2 cycles: 11 doses of azacitidine out of the 14 doses planned and 42 doses of venetoclax out of the 56 doses planned with a successful ramp-up to full dose), and subject has had safety assessments for a minimum period of 2 cycles (from Cycle 1 Day 1 to the end of Cycle 2). Patients receiving a reduced dose of venetoclax due to co-administration of strong or moderate CYP3A4 inhibitors or P-gp inhibitors as described in Table 6-3, will be considered to have received the planned dose.

or

- Subject has experienced a DLT within the DLT observation period from first dose of MBG453 to the end of Cycle 2. Note that subjects who experience toxicity that meets the criteria for DLT but occurs prior to the first dose of MBG453 will be considered not evaluable.

At the Safety Review Meetings, Investigators and Novartis study personnel will review all relevant data available from the ongoing study including safety information, DLTs, time of occurrence of DLT, supported by all CTCAE v5.0 ≥ Grade 2 toxicity data during the first 2 cycles of the study treatment, and pharmacokinetic data from evaluable patients.

The decision will be guided by a simple Bayesian model with EWOC principle evaluating the probability of DLT. For each cohort of the safety run-in, the probability of excessive toxicity (i.e. DLT rate ≥ 33%) will be assessed after the required number of evaluable subjects have been treated and observed for 8 weeks (up to end of Cycle 2). If the EWOC criteria is satisfied (probability of excessive toxicity is lower than 25%), the Bayesian model will recommend to start enrollment to either cohort 2 or the expansion phase.

At the safety review meetings, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the time (days from start of therapy) of occurrence of DLT, the recommendations from the Bayesian analysis, and the available PK and pharmacodynamic information will all be evaluated by the Investigators and Novartis study personnel. Once the results of the safety review meeting are available, the investigator will receive written confirmation from Novartis indicating that the results of the safety run-in part were evaluated and that it is permissible to start enrollment to either cohort 2 or the expansion phase.

6.5.2 Definitions of dose limiting toxicities (DLTs)

Dose-limiting toxicities will be collected and evaluated in subjects enrolled to the safety run-in part. A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value considered by the Investigator to be at least possibly related to MBG453 as a single contributor or in combination with other component(s) of study treatment that occurs during the

[redacted]

DLT observation period and meets any of the criteria included in Table 6-4. The DLT observation period is Cycle 1 Day 8 (starting from the first infusion of MBG453) to the end of Cycle 2. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading.

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

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

Table 6-4 Criteria for defining dose-limiting toxicities during the safety run-in

Toxicity	DLT Criteria
Hematology	Because marrow aplasia is an expected consequence of AML and their therapy, for patients participating in this study, only persistent grade 4 neutropenia, thrombocytopenia and pancytopenia beyond Day 42 from the start of a study treatment cycle and is not related to leukemic infiltration will be considered to be a DLT (bone marrow evaluation may be required to determine if marrow aplasia is due to leukemia).
Vascular disorders	Hypertension CTCAE Grade 3 persisting for > 7 days after treatment is administered.
General disorders and administration site conditions	Infusion reaction CTCAE Grade 3 that does not resolve to Grade 1 within 72 hours or CTCAE Grade 4 of any duration.
Immune	Immune-related adverse events ≥ CTCAE Grade 3 persisting > 7 days after starting appropriate treatment* (e.g. with corticosteroids)
Ocular	Eye pain or reduction of visual acuity ≥ CTCAE Grade 2 that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of typical therapy OR requires systemic treatment
Pulmonary	Pneumonitis ≥ CTCAE Grade 2 persisting > 7 days despite treatment with corticosteroids
	Pneumonitis ≥ CTCAE Grade 3
Skin and subcutaneous tissue disorders	Photosensitivity ≥ CTCAE Grade 3 for > 7 days after treatment
	Rash ≥ CTCAE Grade 3 for > 7 days after treatment
	Rash CTCAE Grade 4
Gastrointestinal disorders	Diarrhea CTCAE Grade ≥ 3 ≥ 48 hrs., despite the use of anti-diarrhea therapy
	Nausea/ vomiting CTCAE Grade ≥ 3 ≥ 48 hrs., despite the use of anti-emetic therapy
	Pancreatitis CTCAE Grade ≥ 3
Investigations: Liver	Total blood bilirubin increase ≥ CTCAE Grade 2 with ≥ CTCAE Grade 2 ALT and/or AST
Other	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that

[redacted]

Toxicity	DLT Criteria
	lead to a dosing delay of > 7 days in cycle 1, or result in an inability to deliver ≥ 75% of the planned dose intensity for any of the study drugs in a cycle of treatment because of treatment-related toxicity.
	Any other unacceptable toxicity encountered by a subject as determined by the Investigators and Novartis.
Exceptions to DLT Criteria	
• Grade 3 fatigue, asthenia, fever, anorexia, or constipation • Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or prolonged hospitalization • Infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia • Grade 3 or 4 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage • Grade 3 or 4 isolated laboratory abnormalities that last ≤3 days	
* Unless otherwise specified for organ-specific immune-related DLTs Note: • CTCAE version 5.0 will be used for all grading. • Optimal therapy for vomiting, constipation, or diarrhea will be based upon institutional guidelines, avoiding the prohibited medications listed in this protocol.	

6.5.3 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions (for MBG453, azacitidine and venetoclax), and/or dose reductions (azacitidine and venetoclax only) are either recommended or mandated in order to allow subjects to continue the study treatment.

Guidelines for permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-5 and Table 6-6.

Dose interruption at the start of a new treatment cycle

In subjects who have achieved CR, CRi or MLFS and have Grade 4 neutropenia and/or Grade 4 thrombocytopenia lasting at least 7 days dosing of both venetoclax and azacitidine should be interrupted until resolution to ≤ Grade 2 or to a clinically significant threshold per investigator assessment (NCCN 2021). In case of a prolonged cytopenia, close blood monitoring is required, and the investigator should consider repeating bone marrow examination to determine if morphologic remission (CR, CRi, MLFS) is ongoing. Administer growth factors if indicated (NCCN 2021). MBG453 should not be administered during the dose interruption. After resolution, dosing of both azacitidine and venetoclax should be resumed on the same day with dose modification for venetoclax as specified in Table 6-6. The first day dosing is resumed will be considered as D1 of the new treatment cycle and MBG453 will be administered on Day 8 of the new cycle. In cases in which venetoclax and azacitidine have been permanently discontinued and the patient remains on MBG453, then in subjects who have achieved CR, CRi or MLFS and have Grade 4 neuttropenia and/or Grade 4 thrombocytopenia dosing of MBG453 should be interrupted until resolution to ≤ Grade 2. The first day dosing with MBG453 is resumed will be considered D8 of the new cycle.

[redacted]

Dose modifications for MBG453

Dose modifications for MBG453 will be done according to ASCO guidelines about management of immune-related AEs (Schneider et al 2021).

Additionally, the guidance indicated in Table 6-5 below, provides instructions for infusion reaction, immune-related adverse events not covered by ASCO guidelines and a general guideline for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgement and possibly attributable to the investigational drug. This general guideline will not apply in case of non-hematologic non-immune-related toxicities that are attributable to azacitidine, venetoclax and AML and its complications.

Deviations to dose interruptions, reductions and/or permanent discontinuations outlined in Table 6-5 are not allowed.

Administration of MBG453 may be delayed due to toxicities. A scheduled dose may be delayed within a cycle by up to 14 days. If a dose cannot be administered within the planned window within the cycle, then the dose should be skipped. Next scheduled dosing may resume once the adverse event has resolved to ≤ Grade 1 or baseline per the next planned treatment cycle. Dose reductions for MBG453 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 6-5) within 12 weeks after initiation of immunosuppressive therapy, MBG453 must be permanently discontinued.

Table 6-5 Criteria for dose interruption and re-initiation of study drug MBG453 for adverse drug reactions

Worst Toxicity Grade (CTCAE v5.0)	Recommended Dose Modifications
Infusion Reaction	
Grade 1	Decrease infusion rate until recovery
Grade 2	Stop infusion Before restarting - pre-medicate according to local institutional guidelines. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s).If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication*, then discontinue MBG453
Grade 3	Stop infusion If the AE resolves to ≤ Grade 1 within 72hrs: • At next scheduled treatment visit, pre-medicate according to local institutional guidelines. • Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour. • If the AE recurs despite slow rate of infusion and pre-medication*, then discontinue MBG453 If the AE does not resolve to ≤ Grade 1 within 72hrs: • Discontinue MBG453

[redacted]

Worst Toxicity Grade (CTCAE v5.0)	**Recommended Dose Modifications**
Grade 4	Discontinue MBG453
For adverse events thought to be immune-related AEs and not covered in the ASCO Guidelines for the management of immune-related adverse events in subjects treated with immune checkpoint inhibitor therapy (Schneider et al 2021)	
Grade 1	Continue treatment with MBG453
Grade 2 or Grade 3 ≤ 7 days	Delay treatment with MBG453 until resolved to ≤ Grade 1 or baseline
Grade 3 lasting > 7 days but < 21 days	1st and 2nd occurrence Delay study treatment until resolved to ≤ Grade 1 or baseline 3rd occurrence: Discontinue study treatment
Grade 3 lasting ≥ 21 days Or Grade 4	Discontinue study treatment
Dermatological toxicities	
Grade 1	Maintain MBG453. Use topical steroids, antihistamines, topical emollients.
Grade 2	Consider interrupting MBG453. Use topical or oral steroids, antihistamines. If MBG453 is interrupted and resolution to ≤ Grade 1, restart MBG453.
Grade 3 or 4	Interrupt MBG453. Manage per institutional practice. After resolution to ≤ Grade 1, consider restarting MBG453.
Bullous dermatitis	Grade 1, 2 and 3: Interrupt MBG453. Consult with dermatologist for appropriateness to restart MBG453. Grade 4: Permanently discontinue MBG453.
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue MBG453.
For non-hematological, non immune related toxicities clinically significant and possible attributable to the investigational drug (NCI CTCAE v5.0)** *(The guideline does not apply to for toxicities attributable to azacitidine or venetoclax or the underlying AML including its complications)*	
Grade 1 and Grade 2 tolerable	Continue treatment with MBG453
Grade 2 intolerable (includes all Grade 2 events defined as DLT in Table 6-4) and Grade 3	1st or 2nd occurrence: • Interrupt MBG453 until toxicity recovers to ≤ Grade 1 or baseline • Once recovered to ≤ Grade 1 or baseline restart MBG453 at the same dose level and schedule AE resolution to ≤ Grade 1 or baseline must occur within a maximum period of 56 days since interruption, otherwise MBG453 must be permanently discontinued. 3rd occurrence: • Permanently discontinue MBG453
Grade 4	Discontinue MBG453

[redacted]

Worst Toxicity Grade (CTCAE v5.0)	Recommended Dose Modifications
All dose modifications should be based on the available information and worst preceding toxicity *Prophylaxis regimens will include both paracetamol/acetaminophen and an antihistamine. **Per investigator judgement	

Dose modifications for azacitidine

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

Dose modifications for venetoclax

If venetoclax treatment is deemed by the investigator to possibly have contributed to an observed adverse event, the dose or duration of venetoclax treatment may be modified according to the following guidelines:

Table 6-6 Dose modifications for venetoclax

Event	Occurrence	Action
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Occurrence prior to achieving remission (CR, CRi, MLFS)	Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated.
	First occurrence after achieving remission (CR, CRi, MLFS) and lasting at least 7 days	Delay subsequent treatment and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose
	Subsequent occurrences in next treatment cycles after achieving remission (CR, CRi, MLFS) and lasting at least 7 days	Delay subsequent treatment and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose with a duration reduced by 7 days for each subsequent treatment cycle
Blood chemistry changes suggestive of TLS	-	Withhold treatment. If the event is resolved within 48 hours of last dose, treatment with venetoclax can be resumed at the same dose.

[redacted]

Event	Occurrence	Action
Events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve	-	Withhold treatment. Treatment should be resumed at a reduced dose (per the investigator discretion). When resuming treatment after interruption due to TLS, the instructions for prevention of TLS should be followed.
Grade 3 or 4 non-hematologic toxicities	First occurrence	Withhold treatment. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	Subsequent occurrences	Withhold treatment. Treatment should be resumed at a reduced dose (per the investigator discretion).

Permanent discontinuation of study treatment

If the study treatment (i.e. MBG453 + azacitidine + venetoclax) is interrupted for toxicities and the start of the subsequent study treatment cycle is delayed for more than 42 consecutive days (measured from the intended start date of the new cycle (Day 29 of the previous cycle) in absence of clinical benefit for the patient per investigator assessment, the subject should be discontinued from study treatment.

At any time during the study, patients unable to tolerate one or two of the study treatment drugs may continue study treatment with only the tolerated drug(s) provided the subject benefits per investigator's judgement.

These dose changes must be recorded on the appropriate CRF.

6.5.4 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 (including irAEs and SAEs) for 30 days following the last dose of venetoclax or azacitidine (whichever was later) and 150 days following the last dose of MBG453, whichever is later.

6.5.4.1 Follow-up for immune-related AEs

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

An irAE is any clinically significant AE affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic,

[redacted]

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 (Schneider et al 2021). See guidance in Table 6-5 for immune-related AEs not covered by ASCO guidelines.

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 cytokine assessments outlined in Table 8-1 must be performed.

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

6.5.4.2 Follow-up for Tumor Lysis Syndrome (TLS)

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 (Cairo and Bishop 2004, Coiffier et al 2008).

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, all subjects should receive allopurinol, or an alternative prophylaxis with anti-hyperuricemic agents, as well as adequate hydration (including instructing patients to drink 1.5 to 2.0 L of water daily, among other measures as clinically indicated), prior to study treatment. Events should be managed according to local guidelines. Also see Section 8.4.4 for considerations during the venetoclax ramp-up.

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

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

[redacted]

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

Laboratory tumor lysis syndrome

- Defined as two or more of the following values within three days before or in the days following initiation of a treatment cycle:
  - Uric acid ≥ 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 investigator's discretion.

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

Guidelines for follow-up on potential DILI cases are described in Table 6-7 and Table 6-8.

Table 6-7 Follow-up of abnormal liver chemistry results

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	Normal	None	• No change to study treatment
If elevated at baseline:			

[redacted]

ALT	TBL	Liver Symptoms	Action
ALT > 2 x baseline or > 200 U/L (whichever occurs first)	For patients with Gilbert's syndrome: No change in baseline TBL		• Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• Interrupt study drug • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			
If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			

[redacted]

Table 6-8 Action required for isolated total bilirubin elevation

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

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

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

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

6.5.4.4 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.

[redacted]

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time study treatment MBG453 is to be administered, IRT must be contacted to assign a medication (kit) number and (where applicable) for registration of the other study drugs dispensed to the subjects.

For study treatment taken at home (e.g. for tablets of venetoclax), the investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the subject. This information should be captured in the source document at each visit.

The date and time of all study treatment administrations (MBG453, venetoclax, and azacitidine) 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 parameters (measures of MBG453 and venetoclax) will be determined in all subjects treated with MBG453, as detailed in the pharmacokinetic section (Section 8.5.2).

Remote azacitidine administration compliance will be assessed by the off-site healthcare professional where permitted, and information provided to the Investigator and/or study personnel.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study treatment as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only.

All dosages for study treatment (MBG453, azacitidine and venetoclax) prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

MBG453

Each study site will be supplied by Novartis with the investigational drug MBG453 as global clinical open supply and will be packed and labelled under the responsibility of Novartis.

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

[redacted]

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

Azacitidine

Azacitidine may be administered i.v or subcutaneously. For details on preparation refer to the country-specific label instructions and/or azacitidine package insert.

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, azacitidine administration by a home nurse at a subject's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the subject is no longer appropriate or possible, and that it is in the interest of the subject's health to administer the study treatment even without performing an on-site visit.

Venetoclax

Patients will be provided with adequate supply of venetoclax (tablets for oral administration) for on site administration, if applicable, or for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Supply of venetoclax will either be global supply (supplied by Novartis and dispensed via IRT) or local supply depended on the country.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the 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. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

[redacted]

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

The study drug supply can be destroyed at the local Novartis facility or third party, as appropriate, or locally at site only if permitted by local regulations and authorized by Novartis.

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), IRB/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 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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and 21 CFR 50, privacy, data protection, local regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC. Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the 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. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

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.

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.

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

Subjects will be asked to complete an optional questionnaire to provide feedback on their clinical trial experience (Trial Feedback Questionnaire (TFQ) see Section 8.5.1.2) per the schedule indicated in Table 8-1.

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 may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

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

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).

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed for study procedures (including treatment administration). If MBG453 administration on Day 8 is delayed within a cycle due to toxicities, visit assessments for Day 8 should be shifted accordingly or occur on Day 22, in case of no administration. See Section 6.1 for details on study treatment. A window of +/- 8 days from the planned visit date is allowed for BMA procedures. Further, a maximum of 8 days is allowed between BMA efficacy, extramedullary disease assessment (if applicable) and hematology assessments of the same visit.

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

On PK collection days the windows are provided in Section 8.5.2. Subjects who discontinue the study treatment for any reason should be scheduled for an end of treatment (EOT) visit within

[redacted]

14 days from the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed.

Patient Reported Outcomes must be completed before any clinical assessments are performed at any given visit.

For post-treatment follow-up and survival information, please refer to Section 8.3.1, Section 9.1.

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, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ off-site healthcare professional(s) staff to the subject´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**																**End of Treatment**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7 (and subsequent cycles)**					
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Informed consent	X																				
IRT Registration	X	X																X			
Demography	X																				
Inclusion / Exclusion criteria	X																				
Medical history/current medical conditions	X																				
Disease History[1]	X																				
Prior antineoplastic therapies	X																				
Prior/concomitant medications, surgery and medical procedures (including blood transfusions requirement)[2]	X	Continuous																	X[4]	Only transfusions to be collected.[3]	
Adverse Events	X	Continuous																	X[4]		
Physical Examination	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S			

[redacted]

Period	**Screening**	**Treatment**																**End of Treatment**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7 (and subsequent cycles)**					
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Body Height	X																				
BSA (use height from screening)		X			X			X		X		X		X		X					
Body Weight	X	X			X			X		X		X		X		X		X			
ECOG PS	X	X			X			X		X		X		X		X		X			
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		every 12 weeks (aligned to time of response assessments) and if clinically indicated[5]	
Chemistry	X[6]	Pre-dose and at 7 hrs (+_1hr) post dose for each new dose during the venetoclax ramp-up and 24 hrs after reaching final dose (pre-dose of next dosing day), then on Day 1 of every subsequent Cycle, at EOT and unscheduled as clinically indicated																			
Coagulation	X	X			X			X		X		X		X		X		X			
Cytogenetics [7]	X																				
Urinalysis (dipstick)	S	If clinically indicated																			
Thyroid function[8]	X				X							X				at Cycle 8 Day 1 then every 3 cycles (Day 1) thereafter and as clinically indicated		X			

[redacted]

Period	**Screening**	**Treatment**																**End of Treatment**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7 (and subsequent cycles)**					
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Cytokines for safety (IFN-γ; IL-6, IL-1b,TNF-α)	X	Anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of AE																			
Virology hepatitis B and C	S	If clinically indicated																			
HIV serology (only if required per local regulation)	S																				
Additional hepatic tests in case of DILI[9]	X[10]	If clinically indicated																			
Serum Pregnancy test [11]	S	S[12]																S			
Urine Pregnancy Test OR Serum Pregnancy Test[11]					S			S		S		S		S		S			monthly[13]		
12-Lead ECG (triplicates)[14]	X	X	X						X									X			
IRT-Drug dispensation for MBG453			X			X			X		X		X		X		X				
IRT-Drug dispensation for venetoclax[15]		X			X			X		X		X		X		X					
MBG453 infusion			X			X			X		X		X		X		X				

[redacted]

Period	**Screening**	**Treatment**																**End of Treatment**	**Safety Follow-up**	**Post-Treatment Follow-up**	**Survival Follow-up**
Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7 (and subsequent cycles)**					
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D1**	**D8**	**D22**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Venetoclax administration		ramp-up (see Section 6.1.1) followed by daily administration																			
Azacitidine infusion		on Days 1- 7 of each Cycle OR on Days 1-6 and then on Day 8 of each cycle OR on Days 1-5 and then on Day 8 and Day 9 of each cycle																			
Efficacy - Bone marrow aspirate or biopsy	X				X							at C5D1, then every 3 cycles (D1) until CR, then every 6 cycles (D1) thereafter until disease progression, or start of new anti-neoplastic treatment (including HSCT), and as clinically indicated										
Efficacy - response assessment[16]					X							at C5D1, then every 3 cycles (D1) until CR, then every 6 cycles thereafter until disease progression, and as clinically indicated										
Efficacy - Imaging assessment for extramedullary disease	If extramedullary disease present: at screening, C2D1 and every 3 cycles thereafter until CR, then every 6 cycles thereafter until disease progression or start of new anti-neoplastic treatment (including HSCT), and as clinically indicated																				
PK sampling for MBG453[17]			X			X			X						X	at Day 8 of cycles 9,12,18,24		X	at 30 and 150 days (if visit is conducted at site)		
PK sampling for venetoclax[18]			X						X						X						
Immunogenicity (IG) sampling for MBG453[17]			X			X			X						X	at Day 8 of cycles 9,12,18,24		X	at 30 and 150 days (if visit is conducted at site)		
[redacted]																					

[redacted]

Period	Screening	Treatment																End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles)					
Days	-28 to -1	D1	D8	D22	D1	D8	D22	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	EOT	30, 90, 150 days	Every 12 weeks	Every 12 weeks
Biomarker - Bone marrow aspirate for MRD[20]	X				X							At C5D1, then every 3 cycles (D1) until CR, then every 6 cycles (D1) until disease progression, or start of new anti-neoplastic treatment (including HSCT), and as clinically indicated									

[redacted]

[redacted]

Period	Screening	Treatment																End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles)					
Days	-28 to -1	D1	D8	D22	D1	D8	D22	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	EOT	30, 90, 150 days	Every 12 weeks	Every 12 weeks
[redacted]																					
Trial Feedback Questionnaire[21]	X											X						X			
[redacted]																					
Antineoplastic therapies since discontinuation (including HSCT)																			X	X	X
Disposition	X																	X		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] The last assessment of bone marrow and/or peripheral blood counts should be used within 28 days prior to enrollment.
[2] Blood transfusions administered within 8 weeks prior to the first dose will be collected and recorded in the eCRF.
[3] Transfusions administered during post-treatment follow-up will be recorded in the CRF every 12 weeks (aligned with efficacy assessment visits).
[4] If the patient begins new antineoplastic medication before the end of the safety follow-up period, then only AEs/SAEs that are suspected to be related to study treatment (and concomitant medication used to treat suspected to be related AEs/SAEs) will continue to be collected. See Section 10.1.
[5] Starting from last on treatment efficacy assessment

[redacted]

Period	Screening	Treatment																End of Treatment	Safety Follow-up	Post-Treatment Follow-up	Survival Follow-up
Cycle		Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles)					
Days	-28 to -1	D1	D8	D22	D1	D8	D22	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	EOT	30, 90, 150 days	Every 12 weeks	Every 12 weeks

[6] Blood chemistry should be confirmed within 72 hours prior to planned first dose.
[7] Cytogenetics to be performed locally. If pre-existing cytogenetics result, since AML diagnosis, is available there is no need to repeat this assessment for screening. Assessment to be recorded in the clinical database (eCRF).
[8] Any deficiency should be corrected before the start of Study Treatment. Refer to Table 8-6 for details on analytes to be tested.
[9] Refer to Section 6.5.4.3 for DILI follow-up
[10] Only GLDH to be tested at baseline - see Table 8-7
[11] This test will be performed only for women of child bearing potential
[12] Does not need to be performed if it was done in screening within 72 hours before first dose
[13] Pregnancy testing for women of child bearing potential should be performed monthly during the safety follow-up period (urine or serum test may be performed, depending on local regulations).
[14] Refer to Section 8.4.2 for detailed guidance on timepoints
[15] Venetoclax (for all countries other than the US , which is using local supply) will be dispensed via IRT on Day 1 of each Cycle.
[16] See Section 8.3.1 for details on response assessments
[17] See Table 8-9 for detailed PK/IG sampling timepoints and schedule
[18] See Table 8-10 for detailed timepoints and collection schedule for venetoclax PK sampling.
[19] See Table 8-9 for detailed [redacted] sampling timepoints
[20] [redacted]
[21] TFQ is not considered study data and will be received electronically outside the clinical database

[redacted]

8.1 Screening

All subjects must provide signed ICFs prior to performing any study specific procedures. Screening assessments to confirm eligibility should be performed as per the schedule of assessments detailed in Table 8-1. Subjects will be evaluated against all study inclusion and exclusion criteria and safety assessments which must be completed within 28 days prior to the start of study treatment (C1D1), with the exception of the local serum pregnancy test (for women of child-bearing potential) which must be conducted and confirmed as negative within 72 hrs prior to the start of study treatment. Laboratory parameters may be retested within the 28-day screening period. If the repeat value remains outside of the specified ranges, the subject will be considered a screen failure.

An individual 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. Any re-screened subject should receive a new Subject No., and the original subject number must be noted on the Re-Screening CRF. All required screening activities must be performed when the subject is re-screened for participation in the study.

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 administration of study treatment (C1D1) will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form (CRF). The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure 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 Section 10.1.3 for reporting details). If the subject is screen failed or will not be treated, the IRT is to be notified as soon as possible that the subject was not enrolled.

8.2 Subject demographics/other baseline characteristics

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

- Disease history, including date of diagnosis, WHO sub-classification, prior antineoplastic therapies.
- Race/ethnicity (are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities)
- All prior and concomitant medications and medical procedure
- Blood transfusion **administered within 8 weeks** before the first dose is administered

[redacted]

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

Assessments to be performed at screening include:

- After all study ICFs are signed the subject will be registered with the IRT
- Inclusion/exclusion criteria
- Medical history/current medical conditions
- Disposition
- Physical examination
- ECOG Performance Status, body height, weight, vital signs (blood pressure (supine position preferred when ECGs are collected) and pulse, and body temperature).
- Laboratory - hematology, blood chemistry, coagulation, urinalysis, serum pregnancy test for women of child-bearing potential, thyroid function, cytogenetics, virology hepatitis B and C, HIV serology (only if required per local regulation)
- Triplicate 12-lead central ECG
- Bone marrow aspirate collection for MRD and other biomarkers
- Bone marrow biopsy / aspirate must be collected for efficacy assessment
- Imaging assessment if extramedullary disease is present or suspected
- [redacted]
- Blood sample for Cytokines
- Adverse events
- [redacted]

8.3 Efficacy

8.3.1 Efficacy assessments

Diagnosis at presentation according to WHO definition of AML will apply and be recorded in the eCRFs.

Response assessments (bone marrow aspirate (BMA)/bone marrow biopsies (BMB)), peripheral blood, hematology, transfusion independence, extramedullary disease assessments) will be performed locally, by the Investigator, according to the assessment schedule depicted in Table 8-1 for assessment of disease.

Bone marrow assessments will be performed at screening and pre-dose on C2D1 and C5D1 and every 3 cycles D1 thereafter until confirmed CR, and then every 6 cycles thereafter until progression, start of a new anti-neoplastic treatment (including HSCT), death, lost to follow-up or withdrawal of consent.

Hematology assessments will be performed at screening, and pre-dose on D1 and D8 of each cycle, on Day 22 of Cycle 1 and Cycle 2, at the end of treatment visit and every 12 weeks for subjects who enter post-treatment follow-up. In the absence of blood count recovery at C2D1 and beyond, complete blood count can be collected weekly for up to 2 weeks. Complete blood count results used for the response assessment will be derived from the best accompanying

[redacted]

laboratory hematology result within the time window from 1 week before and up to 2 weeks after the bone marrow assessment used to support the efficacy response assessment. All components (eg, platelets, absolute neutrophils) should come from the same test.

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

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

More frequent efficacy assessments may be performed at the Investigator's discretion, if medically indicated, and recorded on the Unscheduled Visit CRFs. All assessments will be analyzed.

Table 8-2 Response classification in AML at a given evaluation time (based on IWG Cheson et al 2003, ELN 2017 Döhner et al 2017)

Response Category	Definition[1]
Complete Remission	Bone marrow: • < 5% blasts • no blasts with Auer rods Peripheral blood: • neutrophils ≥ $1.0x10^9$/L • platelets ≥ $100x10^9$/L • no circulating blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement).
Complete remission with incomplete hematologic recovery (CRi)	Bone marrow: • < 5% blasts • no blasts with Auer rods Peripheral blood: • neutrophils < $1.0x10^9$/L or platelets < $100x10^9$/L

[redacted]

Response Category	Definition[1]
	• no circulating blasts No evidence of extramedullary disease (such as CNS or soft tissue involvement).
Morphologic leukemia free state (MLFS)	Bone marrow • < 5% blast • no blasts with Auer rods No evidence of extramedullary disease (such as CNS or soft tissue involvement)
Partial Remission (PR)	Bone marrow: • < 5% blasts AND presence of blasts with Auer rods **OR** • ≥ 50% decrease from baseline in blasts in bone marrow AND blast count in bone marrow is 5% to 25% Peripheral blood: • neutrophils ≥ 1.0 x 109/L • platelets ≥ 100 x 109/L • no blasts
Progressive Disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood • >50% increase in marrow blasts from maximum remission or baseline ,whatever is lower (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 X 10^9/L [500/µL], and/or platelet count to >50 X 10^9/L [50 000/µL] nontransfused); or • >50% increase in peripheral blasts (WBC X % blasts) to >5 X 10^9/L (>25 000/ µL) (in the absence of differentiation syndrome); or • New extramedullary disease
Stable disease	Absence of CR, CRi, PR, MLFS, and criteria for PD or relapse are not met
Relapse from CR or CRi	Only in patients with a CR or CRi. Any of the following: • Reappearance of blasts in peripheral blood **OR** • ≥ 5% blasts in bone marrow **OR** • (Re-)appearance of extramedullary disease
Unknown	In case the response assessment was not done or the assessment was incomplete
[1] If not defined otherwise, all of these criteria apply	

[redacted]

Evaluation of transfusion dependency

RBC and platelet transfusions will be assessed at baseline as well as during the course of the trial for all patients. Transfusion of blood products will be recorded in a separate module of the CRF. The type of transfusion, start and end date as well as the volume of blood product will be captured at each visit with hematologic assessment. A period of at least 8 weeks without any transfusion has been taken as a convention to define the status of transfusion independence.

Transfusion dependence and independence for RBC and/or platelets are defined below:

Transfusions for intercurrent diseases or events not due to AML (e.g. bleeding due to trauma, surgical procedures) should not be taken into account for the following:

Transfusion independence:

- Before first day of study treatment (C1D1): subjects having received no RBC or platelet transfusions within the 8 consecutive weeks prior to enrollment/first day of study treatment (C1D1)
- On or after first day of study treatment (C1D1) : absence of any RBC or platelet transfusion during any consecutive 8 weeks

Transfusion dependence:

- Transfusion dependence at baseline is defined as at least one RBC or platelet transfusion in the 8 weeks prior to C1D1

Extramedullary disease assessment

If clinical suspicion of extramedullary disease (EMD) exists or the subject has a clinical history of EMD, further evaluation using imaging assessments and other diagnostics (as clinically indicated) are required for subjects at screening. Presence or absence and physical location of EMD is to be captured in the CRF.

EMD is to be assessed via physical examination, cerebrospinal fluid (CSF) assessment in case of symptoms suggestive of meningeosis leukemia, and if clinically appropriate relevant imaging techniques.

In case of EMD at baseline or (re-) appearance during the study, the lesions should be considered for confirmation by imaging or biopsy if technically and/or clinically feasible. Imaging modalities and techniques should be performed as clinically indicated and per standard of care. Selected modalities should be used consistently for a given subject, if feasible.

If clinically indicated, post baseline imaging should only be performed in these anatomical regions that demonstrate possible disease.

EMD assessment, if applicable, will be performed at screening, C2D1 and every 3 cycles thereafter thereafter until confirmed CR, and then every 6 cycles thereafter until disease progression, start of a new anti-neoplastic treatment (including HSCT), death, lost to follow-up or withdrawal of consent.

[redacted]

Post-treatment efficacy follow-up

Subjects who discontinue treatment for reasons other than documented disease progression/ relapse from CR, start of a new anti-neoplastic treatment (including HSCT), death, lost to follow-up, or withdrawal of consent, will enter the post-treatment follow-up phase (Section 9.1.1.2). Hematology assessments must continue to be performed every 3 months, response should be assessed at least every 6 months, and bone marrow assessment should be done at least every 3 months until CR and every 6 months thereafter per Table 8-1, or as clinically indicated any time in case disease progression is suspected. Further information about blood transfusions will be continuously collected throughout the post treatment follow-up period.

The post-treatment follow-up period will last until patient's documented disease progression/relapse (per ELN criteria (Döhner et al 2017), see Table 8-2), death, lost to follow-up, or withdrawal of consent or the end of study whichever comes first. Post-treatment antineoplastic therapies including HSCT will continue to be captured during survival follow-up (see Section 9.1.1.3 and Table 8-1).

8.3.2 Efficacy assessment: MRD by MFC

Measurable residual disease (MRD) in bone marrow will be assessed by central multi-parameter flow cytometry (MFC). Assessments will be performed at baseline, and during the treatment period until disease progression as indicated in Table 8-3 below. The first volume aspirated from the bone marrow should be provided for this assessment, when possible.

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

Table 8-3 Collection of BMA for MRD by flow cytometry

Volume of BMA / visit	Visit	Time Point
4mL (First BMA draw should be provided for this assessment)	Screening	Anytime
	C2D1	Pre-study treatment dose
	C5D1	Pre-study treatment dose
	Every 3 cycles D1 after C5D1 until confirmed CR (e.g. C8D1, etc)	Pre-study treatment dose
	Every 6 cycles D1 after CR until disease progression or start of new antineoplastic treatment (including HSCT)	Pre-study treatment dose
	As clinically indicated (at same time of BM collection for efficacy)	Pre-study treatment dose
Note: BMA for this assessment should be collected at same time as BM collection of disease assessment/efficacy		

[redacted]

8.3.3 Appropriateness of efficacy assessments

The assessment of response to study treatment is based on standardized criteria as proposed by the European Leukemia Network (ELN) and the International Working Group (IWG) (Cheson et al 2003, Döhner et al 2017) in Table 8-2.

8.4 Safety

Safety assessments are specified in Table 8-4 below with the assessment schedule detailing when each assessment is to be performed.

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

Table 8-4 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination is required at D1 of each cycle. At D8 and D22, an abbreviated examination can be done at investigator's discretion. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate 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 in centimeters (cm) will be measured at Screening. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening and at subsequent timepoints as specified in Table 8-1.

Performance status:

ECOG Performance status scale will be used as described in Table 8-5.

Table 8-5 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

[redacted]

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 8-6) and the results will be collected in the eCRF.

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

A central laboratory will be used for the parameters listed in Table 8-7 and as per the schedule in Table 8-1.

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.

Table 8-6 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin (Hgb), white blood cells (WBC), differential (including basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands, metamyelocytes, myelocytes, promyelocytes, blasts), atypical cells (e.g. LUC, erythroblasts), platelets *(absolute value preferred, %s are acceptable)*
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Bicarbonate, Creatinine, Creatine kinase, Total Bilirubin, (Indirect Bilirubin, Direct Bilirubin)*, Total Cholesterol, Total Protein, Blood Urea Nitrogen (BUN) or Urea, 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)
Thyroid	At baseline: TSH, Free-T3 and Free-T4. During treatment: TSH at timepoints indicated in Table 8-1 and as clinically indicated. If TSH is abnormal, then test free-T3 and free-T4
Urinalysis** (dipstick)	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated.If urinalysis dipstick shows abnormalities, the site should perform a more detailed urinalysis follow-up as clinically indicated and per local practice.
Pregnancy Test**	Serum / Urine pregnancy test (refer to Section 8.4.3 'Pregnancy and assessments of fertility'
* Indirect and direct bilirubin only required if total bilirubin is abnormal ** Virology, urinalysis, and pregnancy test will only be reported in the source documentation ***If Troponin-T is not available, Troponin-I may be reported	

Table 8-7 Central clinical laboratory parameters collection plan

Test Category	Test Name
Cytokines	IFN-γ, IL-6, IL-1b, TNF-α
Chemistry for DILI[1]	Glutamate dehydrogenase (GLDH)
[1] at baseline and as clinically indicated for follow-up of DILI per Section 6.5.4.3	

[redacted]

8.4.2 Electrocardiogram (ECG)

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

The ECGs are to be collected with ECG machines supplied by the central ECG vendor at the timepoints indicated in the ECG collection plan (Table 8-8).

Table 8-8 ECG collection plan

Cycle	Day	Time point
Screening	Day -28 to Day -1	Anytime
Cycle 1	Day 1	Pre-dose[1]
	Day 8	Post-dose[2]
Cycle 3	Day 8	Post-dose[2]
EOT	N/A	Anytime
Unscheduled	Any	As clinically indicated
* all ECGs to be collected in 12-lead triplicate, at least 3 minutes apart [1] ECG collection prior to any study drug dosing [2] ECG collection at end of MBG453 infusion		

Clinically significant ECG abnormalities present at screening should be reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events. All ECGs must be recorded using the machines supported by the central ECG vendor and transmitted electronically to the central ECG vendor to be centrally reviewed by an independent reviewer. Any original ECG not transmitted electronically to the central laboratory should be forwarded for central review.

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

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated, and transmitted electronically to the central laboratory as unscheduled timepoints.

In case of QTcF prolongation, please refer to Section 6.5.4.4.

8.4.3 Pregnancy and assessments of fertility

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.

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

[redacted]

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

During the study, a urine/serum pregnancy test should be performed at Day 1 of each cycle (except Cycle 1 if a pregnancy test had been performed within 72 hours of the first dose) and a serum pregnancy test at EOT visit. Pregnancy testing (urine/serum) should occur at monthly intervals during the 150-day safety follow-up period. Refer to Table 8-1 for pregnancy testing schedule.

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 90 days after the last dose of azacitidine, 30 days after the last dose of venetoclax (or as per their respective local labels, whichever is longer) and 150 days after the last dose of MBG453. Highly effective contraception methods are defined in Section 5.2.

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

8.4.4 Additional safety monitoring and considerations during venetoclax ramp-up

The dose of venetoclax will be ramped up over 3 or 4 days to achieve the daily dose of 400 mg (see Table 6-2 for ramp-up procedure).

Blood chemistry should be taken pre-dose and at 7 hrs (+/- 1 hr) on during the ramp-up and approximately 24 hrs after reaching the final dose (pre-dose of the following dosing day, see Table 8-1).

Due to the known risk of TLS with venetoclax treatment, prior to first venetoclax dose on Cycle 1 Day 1, the subject should be provided with prophylactic measures including adequate hydration and anti-hyperuricemic agents and these measures should be continued during the ramp-up phase.

High risk patients may need additional measures like i.v. hydration and hospitalization, events should be managed per local guidelines.

Refer to Section 6.5.4.2 for guidance on minimising the risk of TLS and procedures to be followed before initiation of a treatment cycle and during the treatment cycle.

[redacted]

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

[redacted]

8.5.1.2 Trial Feedback Questionnaire (TFQ)

This trial will include an anonymized questionnaire, 'Trial Feedback Questionnaire' for subjects to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses would be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events and therefore would not be considered trial data and will be received electronically outside of the Clinical database.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

8.5.2 Pharmacokinetics

Pharmacokinetic (PK), Immunogenicity (IG) [redacted] samples will be obtained and evaluated in all subjects. Please refer to Table 8-9 and Table 8-10 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. The residual PK and immunogenicity plasma or serum samples may be used for [redacted]

[redacted]

8.5.2.1 Pharmacokinetic and Immunogenicity blood collection and handling

The MBG453 PK, [redacted] and IG blood sampling schedule is outlined in Table 8-9. A single blood sample of approximately 5 mL will be collected at each time point.

The venetoclax PK blood sampling schedule is outlined in Table 8-10. A single blood sample of approximately 3 mL will be collected at each time point.

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. When PK is collected at the same time point as ECG, the PK sample should be taken immediately after ECG.

The exact date and clock times of drug administration and blood draws for PK, IG [redacted] assessment will be recorded on the appropriate eCRF.

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

Detailed instructions for the collection procedures, handling, and shipment of MBG453 PK, IG [redacted] samples, and venetoclax PK samples will be provided in the [CMBG453C12201 Laboratory Manual].

Table 8-9 MBG453 PK, IG [redacted] blood collection log

Cycle	Day	Scheduled Time Point*	PK sample (MBG453)	IG sample	[redacted]
1	1	Pre-azacitidine dose			
	8	Pre-MBG453 infusion	X	X	
		End of MBG453 infusion (within 2 hours)	X		
2	8	Pre-MBG453 infusion	X	X	
3	8	Pre-MBG453 infusion	X	X	
		End of MBG453 infusion (within 2 hours)	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	
24	8	Pre-MBG453 infusion	X	X	
EOT[1]		Anytime	X	X	
30-Day Safety Follow-up		Anytime	X	X	
150-Day Safety Follow-up[2]		Anytime	X	X	

[redacted]

Cycle	Day	Scheduled Time Point*	PK sample (MBG453)	IG sample	[redacted]
Unscheduled[3]		Anytime	X	X	

*All pre-dose samples must be collected within 2 hours before start of infusion
[1] If EOT is due to reasons other than disease progression, an unscheduled PK and IG sample should also be collected at the time of confirmed disease progression.
[2] Samples at the 150 day safety follow-up visit can be collected at the Investigator's discretion if the follow-up visits are conducted at the site.
[3] Unscheduled PK and IG samples may be collected at any time if clinically indicated or at the Investigator's discretion

Table 8-10 Venetoclax PK blood collection log

Cycle	Day	Scheduled timepoint*	PK sample (venetoclax)
1	8	Pre-venetoclax dose	X
3	8	Pre-venetoclax dose	X
6	8	Pre-venetoclax dose	X

*All pre-dose samples must be collected within 30 min before dose administration

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 [CMBG453C12201 Laboratory Manual].
- Plasma concentrations of venetoclax will be determined using a validated LC-MS assay, with a current LLOQ of 10 ng/mL. The details of the assay will be documented in the [CMBG453C12201 Laboratory Manual].
- The assay to quantify and assess the IG against MBG453 will be a validated homogeneous bridging ELISA. The details of the assay will be documented in the [CMBG453C12201 Laboratory Manual].
- Bioanalysis for [redacted] will employ a validated ELISA. The details of the assay will be documented in the [CMBG453C12201 Laboratory Manual].

[redacted]

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

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

Study 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
- Any adverse events or laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Protocol-defined reasons for discontinuation (see Section 6.1.4 and Section 6.1.5)
- Termination of the study by Novartis

[redacted]

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' 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. 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 study treatment.

If discontinuation of study treatment occurs due to protocol defined reasons, subjects will be followed for efficacy, safety and survival as detailed in Section 9.1.1.1, Section 9.1.1.2 and Section 9.1.1.3.

9.1.1.1 Safety Follow-up

All patients must be followed for safety for 150 days after the last dose of MBG453 or 30 days after the last dose of azacitidine or venetoclax whichever is longer.

After the 30-Day on-site safety follow-up visit, patients will be followed via telephone call (or on-site visit if patient happens to be visiting the site) at 90 and 150 days after the last dose of MBG453. All safety assessments should be completed as per Table 8-1. However, if the patient begins new antineoplastic medication before the end of the safety follow-up period, the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected AEs and suspected SAEs will continue to be collected up to the end of the safety follow-up period. Patients continuing on MBG453 through an alternative setting (e.g. managed access program or a roll-over study) after the end of the study, should be followed for safety until the EOT visit. For female patients of child bearing potential, a pregnancy test will be performed at the timepoints listed in Table 8-1

9.1.1.2 Post-Treatment Follow-up

For subjects who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, efficacy assessments will continue to be performed as per the assessment schedule (Table 8-1) with hematological assessments every 12 weeks and bone marrow assessments every 12 weeks (for patients who achieve CR: every 24 weeks) (see Table 8-1) or as clinically indicated until documented disease progression/ relapse from CR, start of a new anti-neoplastic treatment (including HSCT), death, lost to follow-up, or withdrawal of consent.

[redacted]

9.1.1.3 Survival Follow-up

Patients will enter the survival follow-up period once they complete the safety follow-up period or have disease progression (whichever is later). Patients will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new anti-neoplastic therapy that has been started since the last contact date (including HSCT) and any SAEs related to study treatment, as well as information about the remission status and the date of progression/relapse from CR for patients who receive a HSCT will also be collected during these phone calls.

9.1.1.4 Replacement policy

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

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

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and 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
- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the subject, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

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/exercise privacy rights and record this information. The Investigator shall clearly document if the subject has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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/exercise privacy rights should be made as detailed in Table 8-1.

[redacted]

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

Further details on withdrawal of consent or the exercise of subjects' data privacy rights are included in the corresponding informed consent form.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other subjects' data privacy rights), 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 subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible to perform their End of Treatment Visit (EOT) and the assessments for EOT as described in Table 8-1. The subject will be treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

In the event that the study is terminated prematurely, e.g. based on recommendation of the steering committee (see also Section 10.2.2), patients still receiving study treatment and who, according to investigator assessment, continue to benefit from the treatment, will be offered to complete study treatment as per protocol or through an alternate setting see Section 9.2.

9.2 Study completion and post-study treatment

Following completion of the safety follow-up period and/or post-treatment follow-up period, all subjects will be followed for survival (see Section 9.1.1.3).

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.

The CR rate analysis will be conducted after the last patient enrolled has completed at least 12 cycles of treatment or discontinued earlier. Following the cut-off date for the analysis reported in the primary Clinical Study Report (CSR), the study will remain open and ongoing subjects will continue to receive study treatment and be followed per the schedule of assessments until discontinuation criteria is met per Section 9.1.1.

[redacted]

The end of study is defined as the earliest occurrence of one of the following:

- All subjects have been followed for at least 3 years have discontinued treatment or have died, been lost to follow-up or have withdrawn consent to further participation in the study.
- The last subject on treatment has been enrolled into a separate rollover study or another option of continued treatment with MBG453.

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

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

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a 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 AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

Adverse events will be assessed and graded according to:

1. 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

[redacted]

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 if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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

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

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

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

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

Adverse event monitoring should be continued for at least:

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

  OR
- until the start of a new post treatment antineoplastic medication if sooner than the 150 days mentioned above. If a patient starts post treatment antineoplastic medication, then only adverse events suspected to be related to study treatment should be collected, up to 150 days after discontinuation of MBG453.
- until the EOT visit for patients continuing on MBG453 through an alternative setting (e.g. managed access program or a roll-over study) after the end of the study.

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

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

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.

[redacted]

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

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

- fatal
- life-threatening

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

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

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

[redacted]

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 under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per ELN 2017 guidelines (Döhner et al 2017)), should not be reported as an SAE, except if the investigator considers that the progression of malignancy is related to study treatment.

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

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

10.1.3 SAE reporting

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

SAE reporting timeframes:

1. Screen Failures (e.g. a subject who is screened but is not treated or randomized): All 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. Treated Subjects (including randomized subjects in the Randomized Part): SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped azacitidine or venetoclax or 150 days after stopping MBG453, whichever is later. If a patient starts post treatment antineoplastic medication, then only SAEs suspected to be related to study treatment should be collected, up to 150 days or beyond after discontinuation of MBG453.
3. Patients continuing on MBG453 through an alternative setting (e.g. managed access program or a roll-over study) after the end of the study: SAEs should be collected until the EOT visit.

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, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or

[redacted]

otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

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

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy.

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

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

Pregnancy outcomes will not be collected for the female partners of any males who took study treatment in this study.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

[redacted]

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be required for this study considering that it is open-label single-arm study. However, close monitoring of safety is planned; specifically, Novartis and the study investigators involved in the safety run-in will conduct at least one safety review meeting for each cohort: once all evaluable subjects in that cohort are observed for at least 2 cycles of treatment or experienced a DLT, whichever occurs first, in order to review and discuss safety data, including adverse events, dose interruptions and dose modifications, as well as available pharmacokinetic data. At the planned safety review meeting, Novartis and the investigators must reach a consensus based on the available safety and clinical pharmacology data, to decide whether to continue with enrolment on the study.

10.2.2 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, i.e. not being Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will periodically review the study data and will make recommendations on the study conduct (including study termination). The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC 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 a Steering Committee charter.

[redacted]

11 Data Collection and Database management

11.1 Data collection

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

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

After final database lock, the investigator will receive copies of the 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 verificatio’’;fd n. **In addition to data entered into the eCRF , requisition forms may also need to be completed for (e.g. PK, [redacted] etc.) sample collection.**

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.

Kit numbers and data about MBG453 (and venetoclax for all countries other than the US) dispensed to the subject and all dose interruptions (for MBG453 only) 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. Azacitidine will not be tracked through IRT.

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

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

[redacted]

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period.

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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis or delegated CRO CRA organization. Additionally, a central analytics organization may analyze data, identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each 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 primary safety analysis (safety run-in part) will be conducted for each cohort when patients have received MBG453 + azacitidine + venetoclax for at least two cycles.

The primary efficacy analysis (CR rate analysis) will be performed on all subject data (from both safety run-in and expansion parts) at the time all subjects who are still receiving study treatment will have completed at least 12 cycles or discontinued earlier.

The long-term efficacy and safety analyses will be conducted on all subject data at the time all subjects will discontinue the study treatment or have been followed up for at least 3 years after the last patient enrolled whichever occurs first (see Section 9.2 for details). If required or requested by Health Authorities, updated analyses after the primary CR rate analysis may be conducted prior to the final analysis.

[redacted]

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented when applicable.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all subjects who received at least one dose of study treatment (i.e. at least one dose of MBG453 or at least one dose of azacitidine or at least one dose venetoclax). This will include patients in the safety run-in part and in the expansion part.

The Safety Set includes all subjects from the FAS.

The Dose-Determining Set (DDS) includes all subjects from the FAS enrolled the safety run-in part who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) between Cycle 1 Day 8 and the end of Cycle 2 of treatment. The definition for the minimum exposure criterion and the sufficient safety evaluations is detailed in Section 6.5.1.

The MBG453 and venetoclax pharmacokinetic analysis sets include all subjects from the Safety Set who provide at least one evaluable MBG453/venetoclax 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/venetoclax 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 listed and summarized descriptively for all subjects from 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 Safety set will be used for the analyses below.

The duration of exposure to MBG453 and to each study drug (azacitidine and venetoclax) as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by descriptive statistics.

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

[redacted]

The number of subjects with dose adjustments (reductions for azacitidine and venetoclax, interruptions, or permanent discontinuation) and the reasons will be summarized by study drug and all dosing data will be listed.

12.4 Analysis of the primary endpoint(s)

The primary objectives of the study are to determine whether MBG453 at the two tested dose levels is not meeting overdose criteria when added in combination with azacitidine and venetoclax (safety run-in part) and to assess the complete remission rate (CR) of MBG453, administered at 800 mg Q4W in combination with azacitidine and venetoclax (safety run-in and expansion part).

12.4.1 Definition of primary endpoint(s)

For the safety run-in part, the primary endpoint is the incidence of DLTs between Cycle 1 Day 8 and the end of Cycle 2 of treatment for subjects in each cohort and included in the DDS.

The primary endpoint of the study (combining data from the safety run-in part and the expansion part) is the proportion of patients treated with MBG453 800 mg Q4W achieving a complete remission (CR) as per investigator assessment (Cheson et al 2003, Döhner et al 2017 and Table 8-2).

A subject with CR is classified as a responder.

The following events that could occur after enrollment, may affect the interpretation of the results:

- **Stopping study treatment (including due to toxicities):** all CR will be taken into account regardless of any study treatment interruption or permanent discontinuation.
- **Start of further anti-neoplastic therapy:** A subject with a first CR after the time he/she receives any further anti-cancer therapy would not be considered responder.
- **Hematopoetic stem cell transplantation (HSCT):** A subject with a first CR after the time he/she receives a SCT would not be considered responder.

12.4.2 Statistical model, hypothesis, and method of analysis

DLT analysis (safety run-in part)

Assessing whether MBG453 at the two tested dose levels is not meeting overdose criteria when added to azacitidine and venetoclax will be based on the estimation of the probability of DLT within the DLT observation period (Cycle 1 Day 8 to the end of Cycle 2) for patients in the DDS.

The assessment in safety run-in part will be guided by a Bayesian analysis of DLT data for MBG453 with azacitidine and venetoclax within the DLT observation period (Cycle 1 Day 8 to the end of Cycle 2) of treatment. The probability of DLT is modeled using a Bayesian approach detailed in Section 16.1.

After each cohort of the safety run-in part, posterior distributions for the risk of DLT will be summarized to provide the posterior probability that the risk of excessive toxicity (DLT rate >33%) is less than 25% (EWOC principle, Babb et al 1998).

[redacted]

CR analysis (safety run-in and expansion parts)

A Bayesian design will be used in order to estimate the CR rate in patients from the FAS treated with MBG453 800 mg Q4W and to provide inferential summaries (e.g., mean, median, standard deviation, 95% credible intervals, and interval probabilities) based on Bayesian posterior distribution of the CR rate. Assuming a uniform informative prior distribution (Beta(1,1)), the distribution of the CR rate will be updated with all available data from the patients included in the FAS and treated with MBG453 800 mg Q4W. This dual-criterion design will allow to base trial success not only on the statistical significance for superiority against the control (CR exceeds the null-value) but also by considering a minimum clinically estimated effect size (CR exceeds the decision value).

The decision criteria for trial success are the following:

1. Statistical significance: the posterior probability that CR rate is > 50% (null value) is at least 97.5%
2. Clinical relevance: the posterior median of CR rate is ≥ 61% (decision value).

The posterior distribution will be used to derive the probability that the true CR rate is superior to 50%. Based on preliminary efficacy data observed with the combination azacitidine + venetoclax, a 50% CR rate is a reasonable threshold to be considered in this specific setting (Daniel A. et al 2018).

The results will be also presented with a frequentist formulation. The CR rate and the exact 95% confidence interval (CI) (Clopper and Pearson 1934), as well as the 1-sided p-value will be provided in patients from the FAS treated with MBG453 800 mg Q4W. The test will be performed using an overall one-sided 2.5% level of significance. Thus, the null hypothesis (H_0:CR ≤ 50%) will be rejected if the lower bound of the two-sided 95% exact CI is >50%.

The analysis will be performed using data up to the analysis data cut-off date, which will be at the time all subjects who are still receiving study treatment will have completed at least 12 cycles or discontinued earlier.

12.4.3 Handling of missing values/censoring/discontinuations

For the determination of CR, only assessments after first dose of study treatment and prior start of any other anti-neoplastic therapy or HSCT are considered. An adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses (if appropriate) will be described in the Statistical Analysis Plan.

12.5 Analysis of secondary endpoints

The secondary objectives in this study are to assess the effect of MBG453 in combination with azacitidine and venetoclax on duration of response (CR, CR/CRi and CR/CRh), Event-Free Survival (EFS), Overall Survival (OS), CR/CRi rate, CR/CRh rate, MRD negativity rate, pharmacokinetic, immunogenicity, transfusion independency, as well as on safety and tolerability.

[redacted]

12.5.1 Efficacy endpoint(s)

Efficacy endpoints will be analyzed and summarized for the FAS and by dose level of MBG453.

Time-to-event endpoints will be analyzed using Kaplan-Meier method: the Kaplan-Meier curves, medians and 95% CI of the medians will be presented.

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

Of note, all response assessments used for efficacy analysis below will be based on investigator assessment (Cheson et al 2003, Döhner et al 2017 and Table 8-2), unless otherwise stated.

Duration of response: duration of complete remission (CR), duration of complete remission/complete remission with incomplete blood count recovery (CR/CRi), duration of complete remission/complete remission with partial hematological recovery (CR/CRh)

The duration of CR will be assessed in patients with CR as per investigator assessment, defined as the time from achievement of CR to the first documented relapse or progressive disease or death due to any cause, whichever occurs first. For subject without event, duration of CR is censored at the date of last adequate response assessment.

The duration of CR/CRi will be assessed in patients with CR or CRi as per investigator assessment, defined as the time from achievement of CR or CRi to the first documented relapse or progressive disease or death due to any cause, whichever occurs first. Same censoring rule as duration of CR will be applied.

Similarly, the duration of CR/CRh will be assessed in patients with CR or CRh as per derivation (Döhner et al 2022), defined as the time from achievement of CR or CRh to the first relapse or progressive disease or death due to any cause, whichever occurs first. Same censoring rule as duration of CR will be applied.

Besides, CRh will be derived by Novartis following the below criteria (Döhner et al 2022): neutrophils $\geq 0.5 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L and otherwise all other CR criteria met (see Table 8-2).

Event-Free Survival (EFS)

Event-free survival (EFS) is the time from date of start of treatment until date of death due to any cause, relapse from CR, or treatment failure, whichever occurs first. Treatment failure is defined as lack of reaching CR until C8D1 or earlier permanent discontinuation (set to Day 1). A subject without EFS event will have their EFS censored at the time of the last adequate assessment performed on or before the cut-off date.

Overall Survival (OS)

OS is defined as the time from start date of treatment 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 whenever the death occurred, i.e. even after new anti-neoplastic therapy, HSCT, interruptions, or discontinuation of study treatment due to any reason.

[redacted]

CR/CRi rate

CR/CRi rate is defined as the proportion of subjects with best overall response of either complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) as per investigator assessment (Table 8-2). CR/CRi rate will be provided with exact 95% confidence interval (Clopper and Pearson 1934).

CR/CRh rate

CR/CRh rate is defined as the proportion of subjects with best overall response of either complete remission (CR) or complete remission with partial hematologic recovery (CRh) as per derivation (Döhner et al 2022). CR/CRh rate will be provided with exact 95% confidence interval (Clopper and Pearson 1934).

MRD negativity rate

MRD negativity is defined as a MRD negative sample (frequency of LAIP below 0.1%, as determined by MFC-MRD at Central Lab) and bone marrow remission (below 5%). The subject had to achieve an MRD-negative response at or after morphological remission. MRD negativity rate is defined as the proportion of subject with MRD negativity. Best MRD status will be summarized descriptively with 95% exact confidence intervals in full population (i.e. FAS), and/or any subgroup of interest (CR, CR/CRi, CR/CRh, etc.)

Red blood cells (RBC)/Platelets transfusion independence

Red blood cells (RBC)/Platelets transfusion independence RBC/Platelets transfusion independence rate is defined as the proportion of subjects having received no RBC/Platelets transfusions during at least 8 consecutive weeks (see Section 8.3.1 for details). The number and percentage of subjects will be shown for the overall FAS and then also in only those with transfusion dependence at baseline (i.e $\geq$ 1 RBC or platelet transfusion in 8 consecutive weeks prior to start of treatment). Percentages will be provided with exact 95% confidence intervals (Clopper and Pearson 1934). For subjects with at least one period of transfusion independence, the total duration of all transfusion independence periods will be also summarized. The duration of the transfusion independence is defined from the end date of the last transfusion received until the date transfusions are given again or last treatment in case transfusions had not (re-)started during treatment.

12.5.2 Safety endpoints

Safety analyses will be summarized for the safety set and by dose level of MBG453.

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

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

[redacted]

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

An overall safety period will be defined from date of first administration of study treatment to 150 days after the last dose of MBG453.

Adverse events

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

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

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

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

Vital signs

All vital signs abnormalities will be summarized by visit.

12-lead ECG

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

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.

[redacted]

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.

12.5.3 Pharmacokinetics

The respective PAS for MBG453 and venetoclax will be used in all pharmacokinetic data analysis.

MBG453 and venetoclax drug concentrations

MBG453 and venetoclax concentration data will be listed by subject, and visit/sampling time point. Descriptive summary statistics for MBG453 and venetoclax concentrations will be provided by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum, as well as the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as zero. Values below the LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%. PK parameters (the minimum observed plasma or serum drug concentration (Cmin or Ctrough) and the maximum (peak) observed plasma or serum drug concentration (Cmax)) will be estimated and reported. Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

All concentration data for MBG453 and venetoclax vs. time profiles will be displayed graphically. The concentrations collected before dose administration on Day 8 of Cycle 3 and beyond are Ctrough for MBG453.

As the half life of venetoclax is approximately 26 hours, the sample collected at Cycle 1 Day 8 will be considered as the baseline venetoclax concentration at steady state before any dose administration of MBG453. The impact of MBG453 on the venetoclax concentrations may be assessed by comparing concentrations before and after MBG453.

Population pharmacokinetic analysis

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

[redacted]

Immunogenicity analysis

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

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

No formal interim analysis is planned for this trial.

However, safety review meetings will be conducted after patients included in the first cohort (treated with MBG453 at the 400 mg Q4W) have completed 2 cycles of treatment, and assuming the 400mg Q4W dose is considered safe, after patients included in the second cohort (treated with MBG453 at 800 mg Q4W) have completed 2 cycles of treatment and prior starting the expansion part. The decision to escalated to the 800 mg Q4W dose and to continue with the MBG453 dose of 800 mg Q4W will be guided by a Bayesian analysis based on the incidence of dose limiting toxicity (DLT) data.

The primary analysis on CR rate will be performed after all subjects have completed 12 cycles of treatment with MBG453 + azacitidine + venetoclax or discontinued earlier. A final analysis will be performed after all subjects have completed the study which is planned 3 years after the last patient enrolled. Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis. If required or requested by Health Authorities, updated analyses after the primary CR rate analysis may be conducted prior to the final analysis.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

DLT analysis:

No formal statistical power calculations to determine sample size were performed for this part of the study. In the case that the MBG453 administered at 400 mg Q4W with the fixed dose combination of azacitidine plus venetoclax is confirmed to be safe and tolerated in the first 3 to 6 patients, an additional cohort of 9 to 12 patients treated with MBG453 administered at 800 mg Q4W will be enrolled.

CR analysis:

The sample size calculation is based on the Complete Remission (CR) rate (primary efficacy endpoint) observed in patients treated with MBG453 at 800 mg Q4W (from both safety run-in

[redacted]

and expansion parts). The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

Based on available data (Daniel A. et al 2018), the CR rate with the combination azacitidine+venetoclax is expected to be around 50%. The first criteria to declare the trial successful is to test if the CR with MBG453 in combination with azacitidine and venetoclax is superior to 50% (statistical significance). The second criteria is to obtain a minimum estimated effect size of at least 61% for the CR (clinical relevance).

The Bayesian formulation of this dual criterion design can be expressed as below:

- Bayesian statistical significance: probability for a positive treatment effect (i.e. CR rate ≥ 50% | data) ≥ 0.975
- Clinical relevance: posterior median of CR rate ≥ 61%

With two criteria stated above the minimally required sample (n_{min}) size is 76 and the final sample size was set to 80. For 80 patients, the table below shows data scenarios (number of responders) with respective inferential results and decisions. The minimum number of responders to declare this trial successful (both statistical significance and clinical relevance met) is 49 out of 80 patients (61%). Based on simulations (Table 12-2), a total of 49 responders out of 80 results in a posterior median CR rate of 61.1% and a posterior probability for a positive effect (CR>50%) of 0.978. If the number of responders is less than 49, both criteria are missed (NO-GO). A uniform informative Beta (1,1) prior with mean 50% has been used in these calculations.

Table 12-1 Data scenarios, inferential results and decisions (n=80)

True CR rate	Posterior median CR	Posterior probability for a positive effect (CR>50%)	Decision for trial success
44/80 (55.0%)	54.9%	0.813	Failed
45/80 (56.3%)	56.1%	0.867	Failed
46/80 (57.5%)	57.4%	0.909	Failed
47/80 (58.8%)	58.6%	0.940	Failed
48/80 (60.0%)	59.8%	0.962	Failed
49/80 (61.3%)	61.1%	0.978	Successful
50/80 (62.5%)	62.3%	0.987	Successful

Operating characteristics for various true CR rates are presented in the table below. The type-I error under the null value (CR rate = 50%) is 2.8% and power is 79.5% assuming a true CR of 65%.

Table 12-2 Operating characteristics for various true CR rate (n=80)

True CR rate	Probability of success (Go)	Probability of failure (No-Go)
40/80 (50.0%)*	0.028	0.972
44/80 (55.0%)	0.156	0.844
46/80 (57.5%)	0.287	0.713
48/80 (60.0%)	0.458	0.542
49/80 (61.3%)	0.549	0.451
50/80 (62.5%)	0.639	0.361

[redacted]

True CR rate	Probability of success (Go)	Probability of failure (No-Go)
52/80 (65.0%)**	0.795	0.205
54/80 (67.5%)	0.904	0.096
56/80 (70.0%)	0.964	0.036
*For a true CR rate of 50% (null value), the probability for a trial success is 2.8% (*type-I error)*. **For a true CR rate of 65%, the probability for a trial success is 79.5% (*power*).		

These calculations were made using the software R (version 3.4.3) using the RBesT package.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local law and regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS).

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, protocol amendments, written informed consent form, consent form updates, Investigator's Brochure, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to subjects.

The Investigator will be responsible for the following:

- Signing 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.
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

[redacted]

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Directive 2001/20/EC or European regulation 536/2014 for clinical studies, and all other applicable local regulations
- 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 or Clinical Trials Information System (CTIS) public website. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT or CTIS public website etc.).

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

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Patient Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

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.

[redacted]

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16 Appendices

16.1 Appendix 1: Statistical Details for Safety Run-in Part: Bayesian model: prior and design properties for hypothetical data scenarios

This appendix provides details of the statistical model, the dosing decisions for some hypothetical data scenarios and the operating characteristics.

16.1.1 Statistical Models

The safety run-in part of this study to confirm that the combination is safe will be guided by a Bayesian analysis of dose limiting toxicity (DLT) data. The Bayesian analysis will be based on a standard logistic regression model to assess the integrated toxicity risk of the combination MBG453 with azacitidine and venetoclax. We assume that the triple combination has some background toxicity with what we have already observed with the combination MBG453 and azacitidine for the following reasons: 1/ azacitidine and venetoclax will be administered at fixed doses during the study; 2/ no DLT was observed for the combination azacitidine and venetoclax (study conducted by AbbVie and published in February 2018 (Lancet 2018)); 3/ a clinically relevant drug-drug interaction effect is considered unlikely; 4/ no dose-safety relationship was observed so far in clinical studies in patients treated with MBG453 and azacitidine. Thus, we decided to use only one model to assess the toxicity risk of this triple combination rather then quantifying the contribution of each of the three compounds.

Let $\pi(d)$ be the risk of DLT for the combination MBG453+azacitidine+venetoclax given at dose d every 4 weeks (Q4W) for MBG453 (all other doses, for azacitidine and venetoclax, being fixed). This dose-DLT model is logistic:

$\text{logit}(\pi(d))=\log(\alpha)+\beta \log(d/d^*)$ where d^*= MBG453 800 mg Q4W (scaling dose)

Hence, α (>0) are the odd of a DLT at MBG453 800 mg Q4W in combination with azacitidine and venetoclax and β (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose of MBG453.

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the logistic model parameters for the triple combination. The aim of the MAP approach is to derive a prior distribution for the logistic parameters $(\log(\alpha^*),\log(\beta^*))$ of the new trial using DLT data from historical studies. To make the prior more robust, an additional mixture component corresponding to high toxicity was introduced.

Description of the meta-analytic-predictive (MAP) approach

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s (s=1,…,S). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$r_{ds}|\pi_{ds} \sim \text{Bin}(\pi_{ds},n_{ds})$

$\text{logit}(\pi_{ds})=\log(\alpha_s)+\beta_s \log(d/d^*)$

$(\log(\alpha_s),\log(\beta_s))|\ \mu,\psi \sim \text{BVN}(\mu,\psi)$, s=1,…,S

[redacted]

$(\log(\alpha^*),\log(\beta^*)) \mid \mu,\psi \sim BVN(\mu,\psi)$

The parameters $\mu = (\mu_1,\mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation ρ. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for ρ

The MAP prior for model parameters in the new trial, $(\log(\alpha^*),\log(\beta^*))$, is the predictive distribution:

$(\log(\alpha^*), \log(\beta^*)) \mid (r_{ds}, n_{ds}$ □ $s=1,\ldots,S)$

Since the predictive distribution is not available analytically, Markov chain Monte Carlo (MCMC) is used to simulate values from this distribution. This is implemented using JAGS version 3.12. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

Prior specifications for the MAP components

Firstly, weakly informative priors are assumed for log(α) and log(β), with mean (μ_1) equal to logit (0.10) corresponding to the anticipated DLT rate at the reference dose (MBG453 800 mg Q4W) and with mean (μ_2) equal to -2 corresponding to a slope parameter closed to 0 resulting from the absence of dose-safety relationship observed so far with MBG453 in combination with decitabine or azacitidine. Priors for τ1 and τ2 are assigned such that (1) their medians correspond to substantial between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between trial standard deviations (Neuenschwander 2014). The prior distributions for the model used for deriving the MAP priors are specified in Table 16-1.

Table 16-1 Prior distributions for the parameters of the MAP model used to derive the prior for the logistic model parameters

Parameter	Prior distribution
μ_1	N(mean = logit(0.10), sd = 2)
μ_2	N(mean = -2, sd=1)
τ_1	log-normal(mean = 0.25, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.125, sd = log(2)/1.96)
ρ	uniform(-1,1)

The prior described above was then updated by using the dose-DLT data from a Novartis study [MBG453X2105] in patients treated with MBG453 (single therapy or in combination with decitabine or azacitidine) (5.6%, 1 DLT out of 18 newly diagnosed AML patients). Historical data are presented in Table 16-2 and Table 16-3.

[redacted]

Table 16-2 Historical data from [MBG453X2105] for MBG453 administered every 2 weeks in combination with decitabine or azacitidine

MBG453 dose level (mg)	Number of evaluable patients	Number of patients treated with decitabine D or azacitidine A	Number of patients with a DLT defined as:
240 mg Q2W	2	D:2, A:0	1
400 mg Q2W	10	D:5, A:5	0

Table 16-3 Historical data from [MBG453X2105] for MBG453 administered every 4 weeks in combination with decitabine or azacitidine

MBG453 dose level (mg)	Number of evaluable patients	Number of patients treated with decitabine D or azacitidine A	Number of patients with a DLT defined as:
800 mg Q4W	6	D:6, A:0	0

Prior specifications for the robustification component

To take into account the potential situation that MBG453+(decitabine or azacitidine) in combination with venetoclax could be substantially more toxic than when administered in combination with decitabine or azacitidine, a second prior component with vague bivariate normal distribution centered around a higher toxicity is added to improve the robustness of the final prior. The prior distributions for this robustness component are described below:

- The mean (log(α) and log(β)) = (logit(0.33), -2), i.e. the median DLT rate at the reference dose (800 mg Q4W) was assumed to be 0.33 and the slope parameter was assumed to be closed to 0 resulting from the absence of dose-safety relationship observed so far with MBG453 in combination with decitabine or azacitidine.
- To complete the specification, the prior standard deviation, sd(log(α) and log(β)), was set equal to (2,1), which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation, corr(log(α) and log(β)) was set equal to 0.

Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 16-4.

The prior summaries for DLT rates are summarized in Table 16-5.

Table 16-4 Prior distribution (BVN Mixture (log(α, β))

Parameter	Mean	Standard deviations	correlation	weight
Component 1 (MAP prior)	(-2.682 ; -2.077)	(0.779 ; 0.971)	0.013	0.710
Component 2 (MAP prior)	(-4.090 ; -2.024)	(0.939 ; 0.967)	0.040	0.190
Component 3 (high toxicity)	(-0.708 ; -2.000)	(2 ; 1)	0	0.10

[redacted]

Table 16-5 Summary of prior distribution of DLT rates

	Prior probabilities that P(DLT) is in the interval :			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
MBG453 400 mg Q4W	0.883	0.068	0.049	0.092	0.142	0.005	0.050	0.617
MBG453 800 mg Q4W	0.863	0.084	0.054	0.101	0.148	0.006	0.057	0.649

16.1.2 Hypothetical on-study scenarios

To illustrate the performance of the Bayesian model used to guide the tolerability assessment in the safety run-in part for MBG453 in combination with venetoclax plus azacitidine, hypothetical data scenarios are displayed in Table 16-6 and Table 16-7 below. Decision might be based on additional safety, PK or PD information.

The study will continue if probability of excessive toxicity (i.e. DLT rate ≥ 33% i.e. excessive toxicity) is less than 0.25, satisfying the EWOC criteria.

Table 16-6 Probability of excessive toxicity estimated by the Bayesian model after the first cohort

Scenario	MBG453 regimen in the 1st cohort	Number of patients in the 1st cohort	Number of DLTs in the 1st cohort	DLT rate in the 1st cohort (%)	Probability of excessive toxicity
1	400 mg Q4W	3	0	0	0.005
2	400 mg Q4W	3	1	33.3	0.079
3	400 mg Q4W	3	2	66.7	**0.474**
4	400 mg Q4W	4	2	50.0	**0.292**
5	400 mg Q4W	4	3	75.0	**0.787**
6	400 mg Q4W	5	2	40.0	0.181
7	400 mg Q4W	5	3	60.0	**0.612**
8	400 mg Q4W	6	2	33.3	0.113
9	400 mg Q4W	6	3	50.0	**0.450**
Note that the EWOC (escalation with overdose control) criterion is defined as P (excessive toxicity) < 0.25.					

If ≤ 1 DLTs out of 3 or 4 patients or ≤ 2 DLTs out of 5 or 6 patients are observed in the first cohort, the probability of excessive toxicity (i.e. DLT rate of ≥ 33%) with dosing regimen of MBG453 400 mg Q4W is < 25%, satisfying the EWOC criteria. In this case, it would be recommended to start the second cohort treated with MBG453 800 mg Q4W.

If ≥ 2 DLTs out of 3 or 4 patients or ≥ 3 DLTs out of 5 or 6 patients are observed in this first cohort, the probability of excessive toxicity with dosing regimen of MBG453 400 mg Q4W does not satisfy the EWOC criteria. In this case, it would be recommended to stop the trial.

[redacted]

Table 16-7 Probability of excessive toxicity estimated by the Bayesian model after the second cohort

Scenario	MBG453 regimen in the 2nd cohort	Number of DLT/patients in the 1st cohort	Number of patients in the 2nd cohort	Number of DLTs in the 2nd cohort	DLT rate in both cohorts (%)	Probability of excessive toxicity
1	800 mg Q4W	0/3	9	0	0	<0.001
2	800 mg Q4W	0/3	9	1	8.3	0.002
3	800 mg Q4W	0/3	9	2	16.7	0.011
4	800 mg Q4W	0/3	9	3	25.0	0.058
5	800 mg Q4W	0/3	9	4	33.3	0.188
6	800 mg Q4W	0/3	9	5	41.7	**0.452**
7	800 mg Q4W	1/3	9	3	33.3	0.188
8	800 mg Q4W	1/3	9	4	41.7	**0.436**
9	800 mg Q4W	2/4	9	2	30.8	0.134
10	800 mg Q4W	2/4	9	3	38.5	**0.348**
11	800 mg Q4W	2/5	9	2	28.6	0.103
12	800 mg Q4W	2/5	9	3	35.7	**0.278**
13	800 mg Q4W	2/5	9	4	42.9	**0.539**
14	800 mg Q4W	2/6	9	2	26.7	0.084
15	800 mg Q4W	2/6	9	3	33.3	0.223
16	800 mg Q4W	2/6	9	4	40.0	**0.459**
Note that the EWOC (escalation with overdose control) criterion is defined as P (excessive toxicity) < 0.25.						

In case of no DLT observed in the first cohort:

If ≤ 4 DLTs out of 9 patients are observed in the second cohort, the probability of excessive toxicity (i.e. DLT rate of ≥ 33%) with dosing regimen of MBG453 800 mg Q4W is < 25%, satisfying the EWOC criteria. In this case, it would be recommended to start the expansion part.

If 5 or more DLTs out of 9 patients are observed in this second cohort, the probability of excessive toxicity with dosing regimen of MBG453 800 mg Q4W does not satisfy the EWOC criteria. In this case, it would be recommended to stop the trial.

In case of 1 or 2 DLT observed in the first cohort:

If ≤ 4 DLTs out of 12, 13 or 14 patients or ≤ 5 DLTs out of 15 patients are observed in both cohorts, the probability of excessive toxicity (i.e. DLT rate of ≥ 33%) with dosing regimen of MBG453 800 mg Q4W is < 25%, satisfying the EWOC criteria. In this case, it would be recommended to start the expansion part.

If ≥ 5 DLTs out of 12, 13 or 14 patients or ≥ 6 DLTs out of 15 patients are observed in both cohorts, the probability of excessive toxicity with dosing regimen of MBG453 800 mg Q4W does not satisfy the EWOC criteria. In this case, it would be recommended to stop the trial.

[redacted]

16.1.3 Operating characteristics

Table 16-8 presents the probability to declare an excessive toxicity (i.e. the number of simulations for which the probability that the true DLT rate is ≥ 33% is equal or higher than 25%) for different scenarios:

- Scenario 1 (Prior Toxicity): the true DLT rate in both cohorts (MBG453 400 mg and 800 mg Q4W) are similar to prior information; the combination of MBG453 with azacitidine and venetoclax is safe whatever the dose of MBG453 tested.
- Scenario 2 (Low Toxicity with dose-DLT slope): the true DLT rate in the first cohort is equal to 10% (defined as safe) and the true DLT rate in the second cohort is equal to 20% (defined as safe).
- Scenario 3 (Threshold Toxicity): the true DLT rate in both cohorts are equal to 33% (threshold to declare an excessive toxicity) without a dose-DLT relationship.
- Scenario 4 (High Toxicity without dose-DLT slope): the true DLT rate in both cohorts are equal to 40% (defined as an excessive toxicity) without a dose-DLT relationship.
- Scenario 5 (High Toxicity with dose-DLT slope): the true DLT rate in the first cohort is equal to 20% (defined as safe) and the true DLT rate in the second cohort is equal to 40% (defined as an excessive toxicity).
- Scenario 6 (Very High Toxicity with dose-DLT slope): the true DLT rate in the first cohort is equal to 25% (defined as safe) and the true DLT rate in the second cohort is equal to 50% (defined as an excessive toxicity).

Table 16-8 Operating characteristics for different true values of DLT rate

Scenario	True DLT rate in the first cohort	True DLT rate in the second cohort	Probability to declare an excessive toxicity after the first cohort[a]	Probability to declare an excessive toxicity after the second cohort[b]	Probability to declare an excessive toxicity for at least one cohort	Mean number of patients enrolled in the safety run-in
1 (Prior Toxicity)	5.0%	5.7%	0.005	0	0.005	15.0
2 (Low Toxicity with dose-DLT slope)	10%	20%	0.023	0.039	0.061	14.7
3 (Threshold Toxicity)	33%	33%	0.269	0.316	0.500	12.2
4 (High Toxicity without dose-DLT slope)	40%	40%	0.427	0.494	0.710	10.5
5 (High Toxicity with dose-DLT slope)	20%	40%	0.117	0.428	0.495	13.8

[redacted]

Scenario	True DLT rate in the first cohort	True DLT rate in the second cohort	Probability to declare an excessive toxicity after the first cohort[a]	Probability to declare an excessive toxicity after the second cohort[b]	Probability to declare an excessive toxicity for at least one cohort	Mean number of patients enrolled in the safety run-in
6 (Very High Toxicity with dose-DLT slope)	25%	50%	0.175	0.674	0.731	13.2

Note: Simulations are performed in R3.4.3 with number of simulations = 1000 and randomization seed =12345;

[a]: probability to declare an excessive toxicity after the first cohort (cohort size of 3, 4, 5 or 6 patients) out of 1000 simulated trials;

[b]: probability to declare an excessive toxicity after the second cohort (cohort size of 9, 10, 11 or 12 patients) given that over toxicity was not declared after the first cohort (conditional probability).

16.1.4 References

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16.2 Appendix 2: Concomitant medications to be used with caution and/or requiring action

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Novartis Internal Oncology Clinical Pharmacology Guidance, Drug-Drug Interaction and Co-Medication Considerations (v05, release date: 2015), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (medicine.iupui.edu/clinpharm/ddis/main- table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies –Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (druginteractioninfo.org/).

Please refer to Section 6.2.1.1 for actions that need to be taken when using these concomitant medications. Please contact the Novartis medical monitor with any questions.

Table 16-9 List of medications to be used with caution and/or requiring action during study drug treatment

Strong inhibitors of CYP3A	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice[1], conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[1], imatinib, isavuconazole, netupitant, nilotinib, tofisopam, *Schisandra sphenanthera* (nan wu wei zi), asafoetida resin (*Ferula asafoetida*), verapamil
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)
Moderate inducers of CYP3A	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat, thioridazine
Inhibitors of P-gp	alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, clarithromycin, clopidrogel, conivaptan, cremophor EL and RH40, curcumin, daclatasvir, diltiazem, dronedarone, eliglustat, erythromycin, felodipine, fluvoxamine, fostamatinib, ginkgo (Ginkgo biloba), green tea, indinavir, isavuconazole, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir, mibefradil, milk thistle (silymarin, silibinin), mirabegron, nelfinavir, nifedipine, nitrendipine, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), paroxetine, propafenone, quercetin, quinidine, quinine, ranolazine, rifampicin, ritonavir, rolapitant, saquinavir, Schisandra chinensis extract (wuweizi), simeprevir, St. John's wort extract (Hypericum perforatum) , survorexant, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, vandetanib, velpatasvir, verapamil, voclosporin, vorapaxar
NTI substrates of P-gp	cyclosporine, digoxin, fentanyl, paclitaxel, phenytoin, quinidine, sirolimus, tacrolimus
Substrates of P-gp (≥2X AUC change)	aliskiren, ambrisentan, atorvastatin, azithromycin, colchicine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, fentanyl, fexofenadine, lapatinib, linezolid, loperamide, maraviroc, nadolol, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, topotecan

Substrates of P-gp mentioned in USPI	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
Substrates of BCRP	Atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
[1] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent.	

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