NOVARTIS

Clinical Development

MBG453

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

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
15-Jun-2020	FPFV	Creation of version 1.0	N/A - First version (based on protocol incl. amendment 1 from 10-Feb-2020 and amendment 2 from 19-May-2020)	N/A
31-Oct-2024	Prior to final analysis DBL	Creation of version 2.0	Amendment 1 (based on protocols incl. amendment 3 from 08-Apr-2021 and amendment 4 from 22-Dec-2021 and amendment 5 from 08-Dec-2022)	• Typos corrections and clarifications • Naming change of study drug to investigational drug, study treatment or study treatment component, as needed. • Based on Novartis' decision to terminate the program, the team was aligned to skip primary analysis and have a single final CSR, update the wording in *section 1*, *1.1*, *2.1* and *2.2*. • Update to align with the protocol amendment 4: - *Sections 2.2* and *2.5.1*, update DLT criteria and response criteria • Update to align with the protocol amendment 5 and simplify analysis for leaning purpose: - Update timing for primary endpoint across the entire document: all subjects should complete at least 12 cycles of treatment or discontinued treatment earlier, as compared to 7 cycles in original protocol. - *Sections 1.2*, *2.6.1* and *2.9.3*: 1) 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"; 2) add CR/CRh rate, duration

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				of CR/CRh and MRD negativity rate in subjects with CR/CRh as secondary endpoints; 3) Modify MRD negativity definition to request MRD-negative response (observed LAIP<0.1% via MRD samples) to be observed at or after morphological remission (bone marrow blast <5%) and update MRD analyses; [redacted] • *Section 2.2:* move IG analysis set from *Section 2.8.3* • *Section 2.3.1* add analysis on COVID-19 related protocol deviation as per new template. • *Section 2.4.1* remove analysis on cycle delayed and add analysis on cycle length by cycle. • *Section 2.4.2* remove the table for prior surgery and radiotherapies which will listed only. Update analysis on transfusion: analyze only AML-related transfusions. • *Section 2.5.2* added to display via boxplot all assessments for disease response (incl. bone marrow, peripheral blood and extramedullary disease) and list some efficacy endpoints by subject (incl. BOR, OS, duration of response) • *Section 2.6* update to restrict the analysis of time-to-event secondary endpoints on MBG453 800mg Q4W dose level only. • *Section 2.6.1* add definitions of transfusion independence and dependence. • *Section 2.6.3* delete the rule of "two or more missing assessments" for all time-to-event endpoint analyses. • *Section 2.7.3* remove the shift tables for laboratory tests where grades are not defined by CTCAE v5.0. • *Section 2.7.4* add notable PR and QRS criteria in Table 2-4; Update vital signs

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				section to state that all patients will be analyzed regardless of their baseline value. • *Section 2.8* specify the analysis of PK endpoints by dose level of MBG453. Remove analysis for PK parameters and DDI. • [redacted] • [redacted] • [redacted] • [redacted] • *Appendix* - Update derivation of date of last exposure to investigational drug (MBG453), azacitidine, venetoclax and study treatment - Add the derivations of cumulative dose, dose intensity and relative dose intensity of venetoclax - Add the derivations of start/end date of a treatment cycle and cycle length - [redacted] - Add the rules of derivation on last contact date - Add ELN risk stratification categories (both 2017 and 2022) and the derivation algorithms - Add ELN 2022 response categories in AML patients and its detailed derivation rules used for CRh-involved endpoints and analyses

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AML	Acute myloeid leukemia
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
BMA	Bone marrow aspirate
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CI	Confidence interval
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery
CSR	Clinical study report
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DDS	Dose-determining set
DLT	Dose limiting toxicity
DMS	Document Management System
eCRF	Electronic case report form
eCRS	Electronic case retrieval strategy
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EFS	Event free survival
ELN	European Leukemia Net
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire
EOT	End of treatment
EQ-5D-5L	EuroQol Group - standardized measure of health status questionnaire
FAS	Full analysis set
HSCT	Hemapoietic stem cell transplantation
IG	Immunogenicity
LLOQ	Limit of quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MFC	Multiparameter Flow Cytometry
MLFS	Morphologic leukemia free state
MRD	Measurable residual disease
NGS	Next Generation Sequencing
OS	Overall survival

PD	Progressive disease
PFS	Progression-free survival
PGI	Patient global impression
PK	Pharmacokinetics
PR	Partial remission
PRO	Patient-reported outcomes
PT	Preferred term
QoL	Quality of life
Q4W	Every 4 weeks
RAP	Report and analysis process
RBC	Red blood cells
RFS	Relapse free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SMQ	Standardized MedDRA queries
SOC	System organ class
TFLs	Tables, figures, listings
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) describes the planned analyses for the final Clinical Study Report (CSR) of the study CMBG453C12201, a phase II, open-label, single-arm, multi-center study of MBG453 in combination with azacitidine and venetoclax in adult subjects with newly diagnosed AML, who are not suitable for intensive chemotherapy and not planned for hematopoietic stem cell transplantation (HSCT).

As specified in the Section 12.7 of the study protocol, safety meetings were conducted during the safety run-in part of the study to assess the tolerability of MBG453 at two different doses (400 mg and 800 mg administered every 4 weeks) when given together with azacitidine + venetoclax before enrolling subject in the expansion part of the study. This SAP served as the basis for those analyses as well; however, a separate selection of tables, figures and listings (TFL) was done. In the meetings (one held on 22-Mar-2021, another on 26-Oct-2021), steering committee members agreed that there is no safety concern identified with the combination of MBG453 (400 mg or 800mg) with azacitidine and venetoclax, then MBG453 800 mg expansion cohort was opened and a total of 85 patients were enrolled and treated at 800 mg MBG453 (including those in safety run-in part).

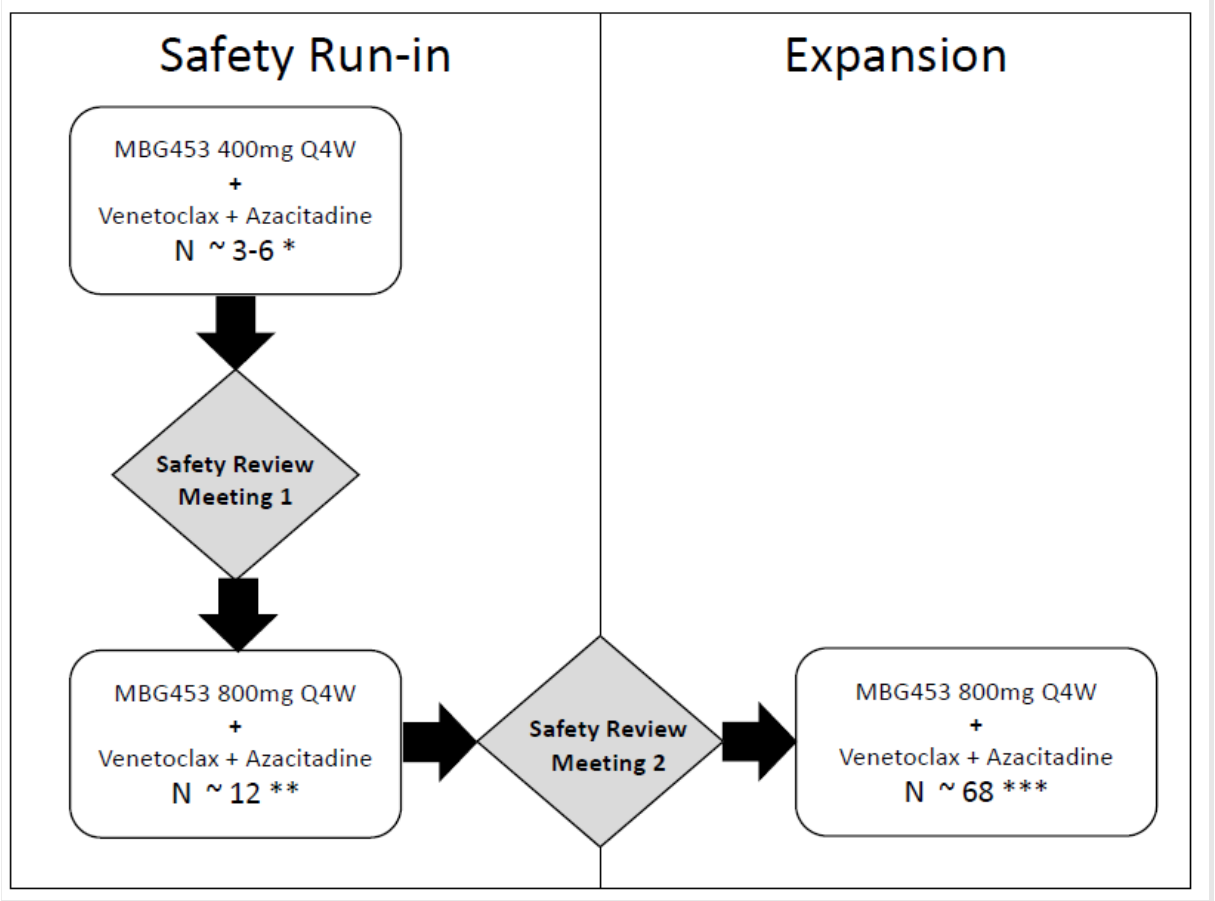
The content of this SAP is based on the CMBG453C12201 protocol, Amendment 5 (08-Dec-2022). All decisions regarding the analysis, as defined in the SAP document, have been made prior to database lock.

However, Novartis made the decision in December 2023 to early terminate the sabatolimab (MBG453) clinical development program following the results of the primary analyses of phase II STIMULUS MDS1 and Phase III STIMULUS MDS2 studies – both studies failed to meet their primary objectives. As a consequence, this study was decided to be early terminated and the investigator letter about this decision was sent on 11-Jan-2024. Based on this decision, the primary analysis of CR rate after 12 cycles will be skipped, and the study data will be analyzed and reported based on all data up to final database lock (DBL) in the final CSR. This also meets the regulatory requirements.

1.1 Study design

CMBG453C12201 is a 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. The study consists of 2 parts: Part 1 is a Safety Run-in (including two cohorts tested sequentially) to assess whether MBG453 is safe when given in combination with azacitidine and venetoclax; Part 2 is the expansion phase to assess the efficacy of MBG453 when given in combination with azacitidine and venetoclax. Approximately 6 subjects will be enrolled at the starting dose level, 400 mg Q4W. Provided the starting dose level is determined to be safe, approximately 12 subjects will be enrolled at the second dose level (800 mg Q4W). If no safety concerns are identified at either dose level in the Safety Run-in part, approximately additional 68 subjects treated with MBG453 at 800 mg Q4W will be enrolled in the Expansion part. A total of approximately 80 subjects treated with MBG453 at the 800mg Q4W dose level (including those in the safety run-in) is planned. The number of subjects included in each study part/cohort is presented in Figure 1-1.

Figure 1-1 Study Design



* The safety run-in cohort MBG453 400mg Q4W requires 3 evaluable subjects (approximately 6 enrolled subjects) to have been observed for at least 2 cycles.
** The safety run-in cohort MBG453 800mg 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 800mg Q4W dose level.

Study treatment consists of cycles of MBG453 (400 mg or 800 mg) administered on Day 8 of each cycle in combination with azacitidine administered intravenous or subcutaneous at 75 mg/m2 daily during 7 days at the beginning of each cycle (between Day 1 to Day 9 with 3 different regimens possible), and venetoclax administered orally at 400 mg daily or below when administered concomitantly with CYP3A4 inhibitors or P-gp inhibitors (following ramp up starting on Day 1). The planned duration of a cycle is 28 days. Crossover between the different MBG453 doses (400 mg and 800 mg Q4W) is not permitted at any time during the study: subjects included in the first cohort of the safety run-in part will be treated with MBG453 at the 400 mg Q4W dose level during the whole study participation and subjects included in the second cohort of the safety run-in part and in the expansion phase will be treated with MBG453 at the 800 mg Q4W dose level during the whole study participation. Study treatment may continue until the subject experiences disease progression (as defined by ELN 2017 Döhner et al 2017) or unacceptable toxicity.

The first safety review meeting to assess whether MBG453 400 mg Q4W is not meeting overdose criteria (i.e. an excessive incidence of Dose Limiting Toxicities (DLT)) when added

in combination with azacitidine and venetoclax (first cohort of the safety run-in part) will take place after the first 6 subjects treated with MBG453 400 mg Q4W have completed 2 cycles of treatment. If no safety concerned are observed at this dose level, a second safety review meeting to assess whether MBG453 800 mg Q4W is not meeting overdose criteria when added in combination with azacitidine and venetoclax (second cohort of the safety run-in part) will take place after the first 12 subjects treated with MBG453 800 mg Q4W have completed 2 cycles of treatment. Details on the definition of dose limiting toxicities (DLT) are presented in Table 2-2.

The efficacy of MBG453 when given in combination with azacitidine and venetoclax will be assessed after all subjects have completed 12 cycles of treatment (primary analysis). Subjects will be followed thereafter for at least 3 years after the last subject had been enrolled (or earlier if all subjects had discontinued or moved to a rollover protocol or other option of continued treatment with MBG453). Based on this data, the final CSR will be written (final analysis). However, the primary analysis will be skipped as Novartis decided to early terminate this study, and all the analyses (except some exploratory analyses) will be performed and reported in the final CSR.

No randomization and no interim analysis are planned for this Phase II study.

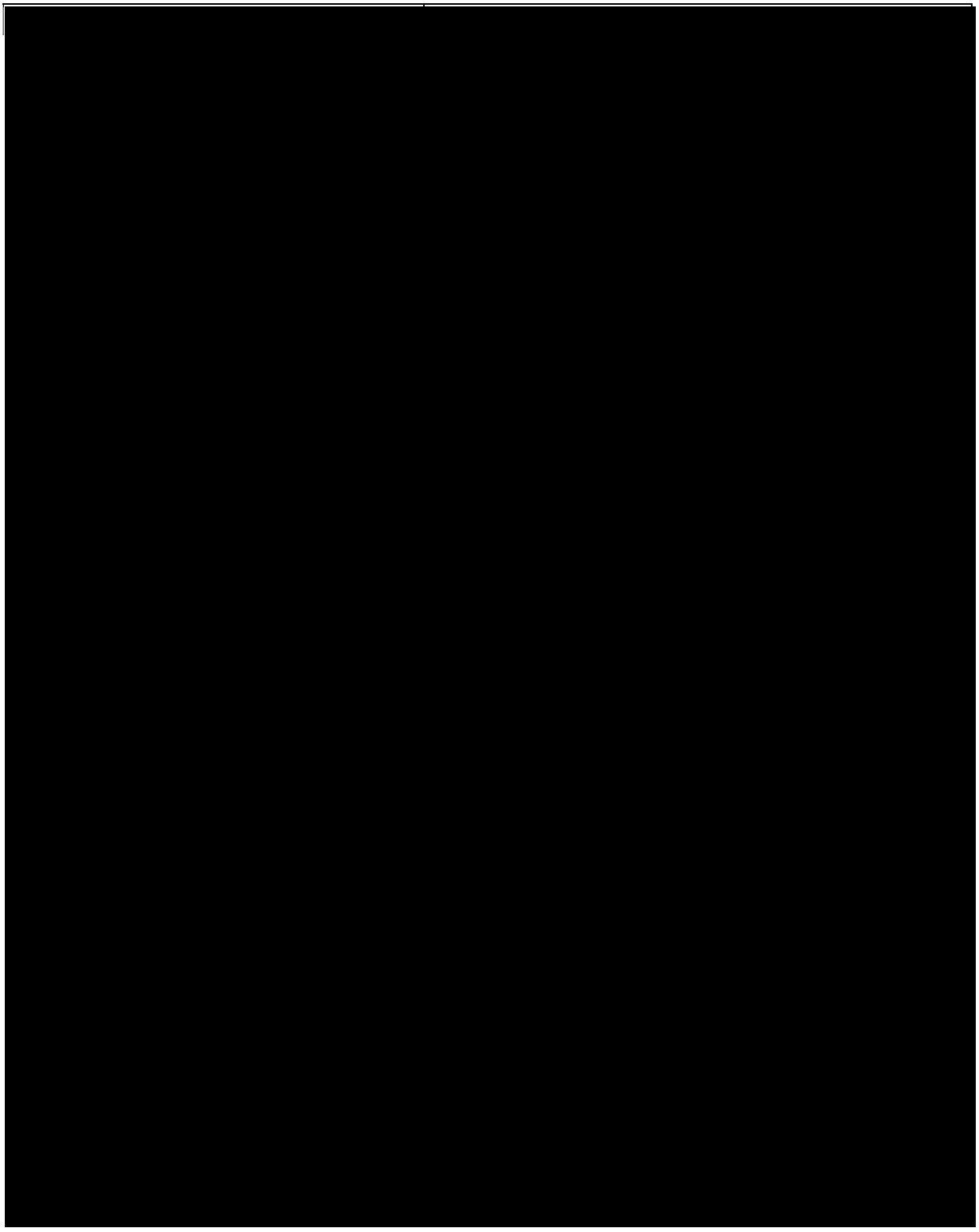
1.2 Study objectives and endpoints

Table 1-1 (which is a copy of the Table 2-1 from the study protocol) outlines the primary, secondary and [redacted] objectives and belonging endpoints. Further details are given in the statistical methods section of this SAP.

Table 1-1 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 tested dose levels is not meeting overdose criteria when added to azacitidine + venetoclax in subjects with AML not suitable for chemotherapy.	• Incidence of dose limiting toxicities (DLT) between Cycle 1 Day 8 and end of cycle 2.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the measurable residual disease (MRD) negativity rate	• Proportion of subjects with MRD negativity (a MRD negative sample determined by Multiparameter Flow Cytometry (MFC)-MRD and a bone marrow remission) in the full population and/or any subgroup of interest (CR, CR/CRi, CR/CRh)

Objective(s)	Endpoint(s)
• To assess the CR/CRi rate and the duration of CR/CRi	• Proportion of subjects achieving a complete remission (CR) or complete remission with incomplete hematologic recovery (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 complete remission with partial hematologic recovery (CRh), as per derivation (Döhner et al 2022) • 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, or relapse from CR, or treatment failure defined as failure to reach CR by Cycle 8 Day 1, whichever occurs first, as per investigator assessment (Cheson et al 2003, Döhner et al 2017)
• 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]



2. Statistical methods

2.1 Data analysis general information

The final analysis, as well as the analyses that were used for the safety review meetings of the safety run-in part of the study will be performed by Novartis.

SAS or R will be used to perform all data analyses and to generate tables, figures and listings.

As Novartis decided to early terminate the study, the study data will be analyzed and reported based on all data up to final DBL in the final CSR.

Data included in the analysis / data cut-off handling

For each of the safety review meetings a data cut-off date was established after the targeted number of subjects had completed 2 cycles of treatment. All safety data (including duration of exposure to study treatment, dose interruptions/reductions, study treatment discontinuation, etc.), demographics, disease history (including cytogenetics, risk category, de novo vs secondary, etc.), hematology data, blast counts from bone marrow and PK data with an assessment date or event start date (e.g. laboratory assessment date or start date of an adverse event) prior to or on the cut-off date was included in the analysis. The list of analyses to be presented at the time of the safety review meetings are provided in Section 2.10.

For the final CSR, all data collected prior to final DBL will be included in the analysis.

General analysis conventions

Qualitative data (e.g., gender, race) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight) will be summarized by appropriate descriptive statistics (e.g. mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum).

General definitions

"Investigational drug" refers to MBG453.

"*Study treatment"* will refer to the combination of MBG453 with azacitidine and venetoclax.

"Study treatment component" refers to MBG453, azacitidine or venetoclax

Other general definitions are detailed in Appendix Section 5.1.

2.2 Analysis sets

For the safety review meetings, the analysis sets defined below were restricted to the population enrolled in the safety run-in part and subjects were analyzed according to the dose regimen they have been assigned to: MBG453 400 mg Q4W for the first cohort and MBG453 800 mg Q4W for the second cohort. At the time of the second Safety Review meeting to assess the overtoxicity risk for the second cohort (800 mg Q4W dose level), the available data from the first cohort (400 mg Q4W dose level) were also displayed.

For the final analysis, the analysis sets defined below will include subjects from both the safety run-in and the expansion parts. Subjects will be analyzed according to the dose regimen they have been assigned to (MBG453 400 mg Q4W or MBG453 800 mg Q4W columns) and overall ("All subjects" column), unless otherwise specified.

Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects who received at least one dose of any component of the study treatment (i.e. at least one dose of MBG453 or at least one dose of azacitidine or at least one dose of venetoclax).

Safety Set

The Safety Set includes all subjects from the FAS.

Dose-Determining Set

The Dose-Determining Set (DDS) includes all subjects from the FAS enrolled in the safety run-in part who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) starting from Cycle 1 Day 8 to the end of Cycle 2. Details on the definition of dose limiting toxicities (DLT) are presented in Table 2-2. A 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 where full dose is equal to 400 mg or less when administered concomitantly with CYP3A4 inhibitors or P-gp inhibitors), and subject has had safety assessments for a minimum period of 2 cycles (from Cycle 1 Day 1 to the end of Cycle 2), 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.

Note: A subject who leaves the study before receiving any dose of MBG453 will not be included in the DDS.

Note: For a subject with a grade 4 neutropenia, thrombocytopenia and pancytopenia (hematological toxicity that could be qualified as a DLT) occurred during the DLT evaluation period (from Cycle 1 Day 8 to the end of Cycle 2), a sufficient follow-up time will be considered to determine if the adverse event has to be qualified as a DLT. As per protocol, 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). Thus, in such a situation, the cut-off date for the safety review meeting could be delayed to enable to qualify or not this hematological toxicity as a DLT.

Note: The period from Cycle 1 Day 8 to the day before Cycle 3 Day 1 corresponds to the period from the first dose of MBG453 in Cycle 1 to the day before the first dose of azacitidine in Cycle 3. In case of Cycle 3 is not initiated, the period to consider for the DLT evaluation will be the period from the first dose of MBG453 in Cycle 1 to the maximum date between the last day of study treatment administration (azacitidine or venetoclax) in Cycle 2 and the theoretical last day of Cycle 2 (Cycle 2 Day 28).

Pharmacokinetic Analysis Sets

The MBG453 and venetoclax pharmacokinetic analysis sets include all subjects from the Safety Set who provide at least one evaluable MBG453 PK concentration or one evaluable venetoclax PK concentration respectively for the two populations.

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 or venetoclax respectively must be taken prior to sampling
- For pre-dose samples: the sample is collected before the next dose administration

Immunogenicity (IG) Analysis Sets

The Immunogenicity prevalence set includes all subjects in the Safety Set with a non-missing baseline IG sample or at least one non-missing post-baseline IG sample.

The Immunogenicity incidence set includes all subjects in the Immunogenicity prevalence set with a non-missing baseline IG sample and at least one non-missing post-baseline IG sample.

A non-missing IG sample indicates a sample that is evaluable and analyzed. Baseline IG sample is the IG sample that was taken before the first administration of MBG453.

Subject Classification

Subjects may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-1.

Table 2-1 Subject classification based on protocol deviations and non protocol deviations criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent for participation in the study	No dose of any component of study treatment
Safety Set	No written informed consent for participation in the study	No dose of any component of study treatment
DDS	No written informed consent for participation in the study	Not enrolled in safety run-in part or not met the minimum exposure criterion or no sufficient safety evaluations in the absence of DLT during the DLT evaluation period

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
PK analysis set	No written informed consent for participation in the study	See definition of PK analysis sets
IG analysis set	No written informed consent for participation in the study	See definition of IG analysis sets

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the study will not be included in the analyses. But samples collected before the subject withdrawal of consent sent but that have not yet been analyzed at the time of the subject withdrawal may still be used for further testing / analysis in accordance with the protocol and the informed consent form. The date on which a subject withdraws consent is recorded in the eCRF.

Additional data for which there is a separate informed consent, e.g., biological sample etc., collected in the clinical database without having obtained that consent or after withdrawal of consent will not be included in the analyses.

2.2.1 Subgroup of interest

No specific subgroups of interest will be considered to support efficacy and safety analyses. Exploratory subgroups analyses for either efficacy or safety may be added later and/or handled in separate planning documents (e.g. TFLs).

2.3 Patient disposition, demographics, and other baseline characteristics

The FAS will be used for the analyses below. Patient disposition, demographics and other baseline characteristics will be summarized by dose level of MBG453 (400 mg Q4W, 800 mg Q4W) and for all subjects (“All subjects” column).

2.3.1 Patient disposition

Number (%) of subjects screened and enrolled will be summarized by country and center. For subjects who are screen failures, the reasons for not completing screening will be summarized based on “Screening Phase Disposition” eCRF.

The number (%) of subjects in the FAS who started treatment, are still on treatment, who entered and discontinued post-treatment follow-up and who discontinued the study after survival follow-up will be summarized together with the respective reasons for treatment/post-treatment follow-up/end of study discontinuation (which corresponds to end of survival follow-up). All disposition information will be listed.

The number (%) of subjects in the FAS with any protocol deviation (PD) will be tabulated by deviation category. COVID-19 related PD will be tabulated separately. All protocol deviations will be listed, together with their relationship to COVID-19 pandemic.

Protocol deviations leading to exclusion from analysis sets will be tabulated separately and the number (%) of subjects in each analysis set will be summarized.

2.3.2 Demographic and other baseline characteristics

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

BMI (kg/m2) at baseline will be calculated as weight[kg] / (height[m]²) using weight at baseline and height at screening. Body Surface Area (BSA) is based on the Mosteller formula described in Section 2.4.1.

Details on AML diagnosis (initial diagnosis, ELN 2017 risk classification (Döhner et al 2017), current disease status (de novo or secondary) and cytogenetic abnormalities will be tabulated and time since diagnosis will be summarized.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable outputs. Comorbidities at baseline that exclude subjects from receiving intensive chemotherapy (presence of specific cardiac, pulmonary, hepatic or renal comorbidities) will be summarized by age category (<75 years old and ≥ 75 years old).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The Safety set will be used for the analyses below and summary tables will be presented by dose level of MBG453 (400 mg Q4W, 800 mg Q4W) and for all subjects ("All subjects" column).

2.4.1 Study treatment / compliance

The duration of exposure to study treatment and to each study treatment component (MBG453, azacitidine and venetoclax) as well as the actual dose intensity, relative dose intensity, doses changes and cycle lengths will be summarized by descriptive statistics.

Duration of exposure

The duration of exposure (in months) will be summarized for study treatment (combination) and for each study treatment component individually (MBG453, azacitidine and venetoclax) based on summary statistics and categorical analyses (e.g. exposure <1 month, at least 1 month, at least 2 months etc.). Details on start and end dates used for derivations are outlined in Appendix Section 5.1.

Cumulative dose

For MBG453, the actual cumulative dose in mg is the sum of "dose administered" from the eCRF of all cycles during the exposure to MBG453.

For azacitidine, the actual dose in mg/m^2 in each cycle is the "dose administered" in mg during that cycle divided by the body surface area (BSA) at the beginning of the cycle using the weight measured before the infusion at that cycle. If the weight is not collected at the beginning of the cycle, the weight from the previous visit will be considered. The actual cumulative dose in mg/m^2 is then the sum of all cycles. The following formula is used for BSA:

$$\text{BSA } (m^2) = \sqrt{\text{Weight (kg)} * \text{Height at screening (cm)}/3600} \text{ (Mosteller formula)}$$

For venetoclax, the actual cumulative dose in mg is the sum of "dose administered" from the eCRF of all cycles during the exposure of venetoclax.

Dose intensity and relative dose intensity

Dose intensity is defined for subjects with non-zero duration of exposure. For subjects who did not take the drug, the dose intensity is by definition equal to zero. The actual dose intensity (computed as the ratio of actual cumulative dose received and duration in days from first to last cycle initiated) and the relative dose intensity (computed as the ratio of actual dose intensity and planned dose intensity) will be summarized for each study treatment component by descriptive statistics. The planned dose intensity for each of the study treatment components is the ratio of planned cumulative dose and duration in days from first to last cycle initiated:

- For MBG453, the planned dose intensity is 400 mg/28 days or 800 mg/28 days,
- For azacitidine, the planned dose intensity is 75 mg/m²/day which is equivalent to 525 mg/m²/28 days,
- For venetoclax, the planned dose intensity is 400 mg/day which is equivalent to 11200 mg/28 days when the recommended full daily dose of Venetoclax is 400 mg and without the ramp-up period.

The relative dose intensity is then computed as the ratio of actual dose intensity and planned dose intensity. As example, if a subject received MBG453 at 600 mg Q4W on average throughout the study (instead of the 800 mg Q4W as planned per protocol), the relative dose intensity for this subject is 0.75.

Details on the duration in days from the first to last cycle initiated for the derivation of the dose intensity and the relative dose intensity are provided in Appendix Section 5.1.

Details on the derivation of cumulative dose, dose intensity and relative dose intensity of venetoclax are provided in Appendix Section 5.1.

Dose reduction, dose interruption and permanent discontinuations

The number (%) of subjects with any dose changes (incl. reductions, interruptions, or permanent discontinuations) and the reasons (e.g. AE, dosing error, dispensing error) will be taken from the 'Study Treatment eCRF' and summarized by study treatment component. The total duration of interruptions by subject will be summarized for the study population by time intervals, e.g., <1week, ≥1-<2 weeks, ≥2-<3 week etc. (these time intervals may be adjusted depending on the observed data).

Cycle initiated and cycle length

The number of cycles initiated by subject will be summarized. The cycle length (i.e., duration of cycle) by subject will also be summarized by cycle based on summary statistics and categorical analyses (e.g., cycle length <35 days, ≥35-<42 days, ≥42-<56 days, ≥56-<70 days, ≥70 days etc.). Details on derivation are provided in Appendix Section 5.1.

2.4.2 Prior, concomitant and post therapies

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

Prior anti-neoplastic medications will be summarized using the FAS. Medications will be summarized by ATC class and preferred terms. Prior surgery and radiotherapy treatments will be listed only.Anti-neoplastic medications after discontinuation of study treatment during follow-up within the study will be summarized by ATC class and preferred term. HSCTs will be also summarized with the source, the type of transplant and the allogeneic donor type. Both analyses will be using the FAS.

All transfusions of blood products (incl. those not related to AML) prior and after start of study treatment will be listed and only AML-related transfusions will be summarized using the FAS. For that, the number of transfusion units will be normalized by time (e.g., fixed 8-weekly interval, mentioned below as episode) prior to and on-treatment (overall and by reason due to study indication (no/yes)). The number of subjects with at least one transfusion episode and the number of units per episode will also be described. Further analyses to summarize transfusion independence and dependence are described in the efficacy section.

2.5 Analysis of the primary objective

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

2.5.1 Primary endpoint

DLT analysis (safety run-in part)

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

Details on the definition of DLT which are to be captured in the Adverse Event eCRF were defined in Table 6-4 of the protocol that was copied into Table 2-2 below.

Table 2-2 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 treatment 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	Total blood bilirubin increase ≥ CTCAE Grade 2 with ≥ Grade 2 ALT/AST
Other	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that 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.

Toxicity	DLT Criteria
	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	

CR analysis (safety run-in and expansion parts)

For the CR analysis, the primary endpoint is the proportion of subjects included in the FAS and assigned to MBG453 at the 800 mg Q4W dose level (in both safety run-in and expansion parts) who achieved a complete remission (CR) as per investigator assessment.

Details on the definition of response categories which are to be captured in the eCRF by the investigator were defined in Table 8-2 of the protocol that was copied into Table 2-3 below.

Table 2-3 Response classification in AML at a given evaluation time (based on IWG Cheson et al 2003, ELN 2017 Döhner et al 2017)

Response Category	Definition[1]
Complete Remission	Bone marrow: • < 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 • no circulating blasts

Response Category	Definition[1]
	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 >25 X 10^9/L (>25 000/ µL) (in the absence of differentiation syndrome); or • New extramedullary disease
Stable disease (SD)	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

The investigator does not determine best overall response, he/she is assessing only the response based on the given bone marrow and peripheral blood data, as well as on the presence or absence of extramedullary disease. The best overall response is the best disease response recorded from the start of the treatment until the first occurrence of relapse or death. Best response will be derived by Novartis for each subject as one of the following: CR, CRi, MLFS, PR, SD, PD, and unknown for all other cases.

The primary estimand related to CR rate is described by the following attributes:

1. Population: subjects with newly-diagnosed acute myeloid leukemia (AML) who are not suitable for intensive induction chemotherapy as defined by inclusion/exclusion criteria and who are assigned to the MBG453 800 mg Q4W dose level.
2. Primary variable: percentage of subjects achieving a complete remission (CR) as per investigator assessment.
3. Treatment of interest: the investigational treatment MBG453 at the 800 mg Q4W dose level combined with azacitidine and venetoclax; the treatment of interest can be also a monotherapy or a combination of two of the three drugs because subjects unable to tolerate one or two of the study treatment drugs may continue study treatment with only the tolerated drug(s) as long as the subject benefits as per investigator's judgement.

Handling of intercurrent events:

- Failure to receive any component of the assigned treatment strategy due to any reason will be handled using treatment policy strategy because the nature of the treatment strategies includes the possibility that MBG453 or azacitidine or venetoclax is discontinued while the other treatment component is continued as long as the subject benefits. Thus, all CR will be taken into account regardless of any study treatment interruption or permanent discontinuation.
- Start of new anti-neoplastic therapy before observing a CR will be handled using the hypothetical strategy because the new anti-neoplastic therapy has the potential to confound the interpretation of effect of the treatment strategy. Thus, a subject with a first CR after the time he/she receives any further neoplastic therapy will not be considered with a CR.
- Hematopoietic stem cell transplantation (HSCT) is a rare opportunity for subjects in remission and thus, an outcome of the treatment. Therefore, the effect of interest integrates the outcome HSCT. A subject with a first CR after the time he/she receives HSCT will not be considered with a CR.

2.5.2 Statistical hypothesis, model, and method of analysis

DLT analysis (safety run-in part)

A Bayesian model will be used to assess whether MBG453 at the two tested dose levels is not meeting overdose criteria when added to azacitidine and venetoclax in subjects from the DDS. The relationship between dose and the probability of DLT is modeled using a logistic regression detailed in Appendix Section 16.1 of the protocol.

A summary of the characteristics of this Bayesian model is presented below:

- A single logistic model will assess the toxicity risk of this triple combination rather than quantifying the contribution of each of the three compounds and their interactions.
- Prior information consists of historical data for 90% and a robustification component for 10%.
- The prior risk of excessive toxicity (i.e. risk of DLT within [33%-100%]) is 4.9% for the MBG453 400 mg Q4W and 5.4% for the MBG453 800 mg Q4W.
- Decisions to start the second cohort and the expansion part are guided by the escalation with overdose control (EWOC) principle (Babb et al 1998): it will be recommended to newly enrolled subjects (in the second cohort or in the expansion part) if the risk of excessive toxicity is less than 25%.

After each cohort in the safety run-in part, the posterior distribution for the risk of DLT for new subjects at the dose level of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT for each dose level of MBG453 lies within the interval [33%, 100%] (i.e. excessive toxicity).

CR analysis (safety run-in and expansion parts)

A Bayesian design will be used to estimate the CR rate in subjects from the FAS assigned to the MBG453 800 mg Q4W dose level 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 subjects included in the FAS and assigned to the MBG453 800 mg Q4W dose level. 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%. 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 via exact Fisher test will be provided in subjects from the FAS assigned to the MBG453 800 mg Q4W dose level. 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%.

2.5.3 Handling of missing values/censoring/discontinuations

CR analysis (safety run-in and expansion parts)

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". Evaluation of response during study treatment relies on bone marrow and peripheral blood assessment, as well as on the presence or absence of extramedullary disease. A subject will be considered in complete remission if an adequate response assessment of CR is observed after first dose of study treatment and even if one or several inadequate response assessments ("unknown" or "not done") have been documented prior of CR determination.

2.5.4 Sensitivity and Supportive analyses

CR analysis (safety run-in and expansion parts)

The complete response (CR) rate with the exact 95% confidence interval will be presented for subjects assigned to the MBG453 400 mg Q4W dose level, as well as for all subjects from the FAS.

A listing of all derived efficacy endpoints by subject will also be provided including BOR, OS time, OS end date and duration of response. In addition, for some selected laboratory parameters and for bone marrow blasts percentage, trends over time (baseline and on-treatment timepoints during the first 12 cycles of treatment) will be displayed via boxplots and corresponding tables displaying the summary statistics for these selected timepoints be produced.

2.6 Analysis of secondary efficacy objective(s)

Secondary efficacy endpoints will be analyzed and summarized for the FAS and by dose level of MBG453 (400 mg Q4W, 800 mg Q4W) and for all subjects ("All subjects" column), except those time-to-event endpoints (i.e., duration of response, EFS and OS).

The time-to-event endpoints will be analyzed and summarized for all subjects from FAS assigned to the MBG453 800 mg Q4W dose level only.

2.6.1 Secondary endpoints

Of note, all response assessments used for secondary efficacy endpoints/analyses will be based on investigators' assessments (Cheson et al 2003, Döhner et al 2017 and Table 2-3), unless otherwise stated.

Duration of response

The duration of complete remission (CR) will be assessed in subjects with best overall response of CR as per investigator assessment, defined as the time from achievement of CR as per investigator assessment (prior to any new antineoplastic therapy, including HSCT) to the first documented relapse from CR (including progression after CR) or death due to any cause, whichever occurs first. For subject without an event, duration of CR is censored at the date of last adequate response assessment.

Similarly, the duration of complete remission/complete remission with incomplete blood count recovery (CR/CRi) will be also assessed for subjects with best overall response of CR or CRi as per investigator assessment by considering the start date as the first documented CR or CRi (prior to any new antineoplastic therapy, including HSCT) whatever occurs first; and the duration of complete remission/complete remission with partial hematological recovery

(CR/CRh) will be assessed in subjects with best overall response of CR or CRh as per derivation (Döhner et al 2022) by considering the start date as the first achievement of CR or CRh (prior to any new antineoplastic therapy, including HSCT) whatever occurs first. Same censoring rule as duration of CR will be applied.

CRh will be assessed following the below criteria (Döhner et al 2022): neutrophil $\geq 0.5x10^9$/L and platelets $\geq 50x10^9$/L and otherwise all other CR criteria met. And note that all response categories and their occurrence dates used for derivation of duration of CR/CRh will be based on Novartis' derivation per Döhner et al 2022. See Appendix 5.2.2 for details.

The following events could occur after reaching response (CR, CRi or CRh) and may affect the interpretation of the results:

- Start of further anti-neoplastic therapy: For subject without an event before the time he/she receives any further anti-cancer therapy, duration of response would be censored at the date of the last adequate assessment prior to start of further anti-neoplastic therapy.
- Hematopoietic Stem cell transplantation (HSCT): For subject without an event before the time he/she receives an HSCT, duration of response would be censored at the date of the last adequate assessment prior to start an HSCT.
- Stopping study treatment (including due to toxicities): All events will be taken into account when they occur, regardless of any study treatment interruption or permanent discontinuation.
- Discontinuation from study due to lost to follow-up or withdrawal of consent: For subject without an event prior to discontinuation due to lost to follow-up or withdrawal of consent, duration of response will be censored at the last adequate assessment date.

The duration of response censoring reason will be summarized as:

1. Ongoing without event
2. New anti-neoplastic therapy
3. HSCT
4. Withdrew consent
5. Lost to follow-up
6. Discontinuation due to subject/physician/guardian's decision

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 CRi (including progression after CR or CRi), or treatment failure, whichever occurs first. Treatment failure is defined as lack of reaching CR until C8D1 or earlier permanent discontinuation from study without reaching CR (set to Day 1). As many cycles are delayed, the C8D1 time window for treatment failure is defined as the maximum of 7 cycles (including C8D1 assessment) or the first 7 months after start of treatment. 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.

The following events could occur after start of treatment and may affect the interpretation of the results:

- Start of further anti-neoplastic therapy: For subject without an event before the time he/she receives any further anti-cancer therapy, EFS would be censored at the date of the last adequate assessment prior to start of further anti-neoplastic therapy.
- Hematopoietic Stem cell transplantation (HSCT): For subject without an event before the time he/she receives an HSCT, EFS would be censored at the date of the last adequate assessment prior to start an HSCT.
- Stopping study treatment (including due to toxicities): All events will be taken into account when they occur, regardless of any study treatment interruption or permanent discontinuation.
- Discontinuation from study due to lost to follow-up or withdrawal of consent: For subject without an event prior to discontinuation due to lost to follow-up or withdrawal of consent, EFS will be censored at the last adequate assessment date.

The EFS censoring reason will be summarized as:

1. Ongoing without event
2. New anti-neoplastic therapy
3. HSCT
4. Withdrew consent
5. Lost to follow-up
6. Discontinuation due to subject/physician/guardian's decision

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.

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 (see Table 2-3). 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 as per derivation (Döhner et al 2022). CR/CRh rate will be provided with exact 95% confidence interval (Clopper and Pearson 1934). Here, both CR and CRh will be based on Novartis' derived responses per Döhner et al 2022. See Appendix 5.2.2 for details.

MRD negativity rate

MRD negativity rate is defined as the proportion of subjects with MRD negativity, which is defined as an MRD negative sample (frequency of LAIP below 0.1%, as determined by MFC-MRD at Central Lab) in subject with remission (bone marrow blast <5%, considering CR and/or CRi as per investigator assessment (see Table 2-3), and/or CR/CRh as per derivation (Döhner et al 2022)). MRD-negative response should be observed at or after morphological remission, and prior to relapse or disease progression.

MRD data will be summarized descriptively at each scheduled timepoint post-baseline to assess number (%) of subjects with MRD-negative status.

MRD negativity rate by time points (incl. until Cycle 2 Day 1, until Cycle 5 Day 1, until Cycle 8 Day 1, and until Cycle 11 Day 1) and overall will be summarized descriptively with 95% exact confidence intervals (Clopper and Pearson 1934), in FAS, and in subgroups of interest (e.g., in subjects with overall response of CR/CRi as per investigator assessment (see Table 2-3), and CR/CRh as per derivation (Döhner et al 2022), and in subjects who are evaluable for MRD).

Red blood cells (RBC)/Platelets transfusion independence

Red blood cells (RBC)/Platelets transfusion independence rate is defined as the proportion of subjects having received no RBC/Platelets transfusions during at least 8 consecutive weeks after start of treatment until end of treatment. 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. ≥ 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). Shift tables will be provided to describe the transfusion status at baseline versus the best transfusion status post-baseline. Transfusion status for RBC/platelets are defined as follows:

- Transfusion independence:
  - At baseline: subjects having received 0 units within the 8 consecutive weeks prior to baseline.
  - Post-baseline: subjects having received 0 units of transfusion within any 8 consecutive weeks during the study.
- Transfusion dependence:
  - At baseline: subjects having received ≥ 1 unit within the 8 consecutive weeks prior to baseline.
  - Post-baseline: subjects having received ≥ 1 unit of transfusion within any 8 consecutive weeks during the study.

Note, only AML-related transfusion would be counted. That is, transfusions for intercurrent disease or events not due to AML (e.g., bleeding due to trauma, surgical procedure) would not be taken into account.

For subjects with at least one period of transfusion independence post-baseline, 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. The total duration of all transfusion independence periods is the sum of each period of the transfusion independence.

2.6.2 Statistical hypothesis, model, and method of analysis

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

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.

2.6.3 Handling of missing values/censoring/discontinuations

The censoring rules for time to event endpoints are described in the definitions above.

2.7 Safety analyses

Safety analyses will be summarized for the safety set and by dose level of MBG453 (400 mg Q4W, 800 mg Q4W) and for all subjects ("All subjects" column).

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

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

1. Pre-treatment period: from day of 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.

2.7.1 Adverse events (AEs)

Summary tables for adverse events (AEs) will include all AEs that started or worsened during the on-treatment period. When specified, some AEs summaries will include all AEs occurring during the overall safety period.

The number (and percentage) of subjects with treatment emergent adverse events will be summarized by primary system organ class (SOC), preferred term (PT) and maximum severity. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

In the AE summaries, the primary SOC will be presented alphabetically, and the PT will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the "overall" column (combining the two dose levels of MBG453). The summaries will show 'All grades' (including AEs with missing grade) and 'Grades ≥ 3'.

The following adverse event summaries will be produced selecting all or a subset of AEs depending on seriousness, relationship to study treatment, outcome or action taken:

- AEs (by SOC and by PT) and separately those considered related to study treatment
- SAEs and separately those considered related to study treatment
- SAEs with number of occurrences (an occurrence is defined as >1 day between start and prior end date of record of same PT)
- Non-SAEs
- SAEs with fatal outcome and separately those considered related to study treatment
- AEs leading to permanent study treatment discontinuation by study treatment component (AEs leading to MBG453 permanent discontinuation, AEs leading to azacitidine permanent discontinuation, AEs leading to venetoclax permanent discontinuation and AEs leading to permanent discontinuation of any of the 3 study treatment components)
- AEs leading to dose adjustment/interruption
- AEs requiring additional therapy
- COVID-19 related adverse events by MedDRA COVID-19 (SMQ) terms.

In addition, all AEs and SAE by SOC and PT will be also provided on the overall safety period. All reported AEs will be listed and those that started during the pre-treatment, on-treatment and post-treatment period will be flagged.

2.7.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound MBG453. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. These searches will be defined in the eCRS (electronic Case Retrieval Strategy) in the DMS (Document Management System) and a listing of search terms will be provided in the CSR.

For each specified AESI, the number (%) of subjects with at least one event of the AESI occurring during on treatment period will be summarized together with the individual preferred terms in that grouping. In addition, number (%) of subjects with at least one AESIs by maximum CTC grade, related AESIs, serious AESIs as well as action taken and outcome of the respective AESI will be summarized.

2.7.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment deaths not in the AE CRF but in the survival CRF) will be produced showing deaths reasons by primary reason and PT. All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.7.3 Laboratory data

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

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

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

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

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

Liver function parameters of interest are total bilirubin, ALT, AST and alkaline phosphatase. The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

For hematology parameters, trends over time (baseline and on-treatment timepoints) will be displayed via boxplots and corresponding tables displaying the summary statistics will be produced.

All CTCAE Grade 3 or 4 laboratory toxicities will be listed.

2.7.4 Other safety data

Safety data listed in this section will be analyzed and summarized for the safety set and presented by dose level of MBG453 (400 mg Q4W, 800 mg Q4W) and for all subjects (“All subjects” column), and by visit/sampling timepoint.

2.7.4.1 ECG and cardiac imaging data

ECG are collected as 12-lead triplicate using the ECG machines supplied by the central laboratory and then transmitted electronically to the central laboratory for central review by an independent reviewer. These central ECGs are done at screening, C1D1 pre-dose, C1D8 post-dose, C3D8 post-dose and at end of treatment; however, additional ECGs can be done if clinically indicated.

Notable ECG values during on-treatment period in subjects with normal values at baseline (for the respective QTc value) will be summarized using the following criteria:

Table 2-4 Notable ECG values

ECG parameter (unit)	Clinically notable criteria
QTcF (ms)	Increase >30 and <=60 ms Increase >60 ms New >450 to <=480 ms New >480 to <=500 ms New >500 ms
QT (ms)	Increase >30 to <=60 ms Increase >60 ms New >450 to <=480 ms New >480 to <=500 ms New >500 ms
HR (bpm)	Increase >25% and HR >100 bpm Decrease >25% and HR<50 bpm
PR (ms)	Increase from baseline >25% and to a value > 200 ms New value of > 200 ms
QRS (ms)	Increase from baseline >25% and to a value > 120 ms New values of QRS > 120 ms

In addition, local ECGs are performed but not used for summary of QTc values. If abnormalities are observed based on these local ECGs, these abnormalities are to be reported and thus summarized as AEs.

2.7.4.2 Vital signs

Notable vital sign values during on-treatment period will be summarized using the following criteria:

Table 2-5 Notable vital sign values

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Weight (kg)	Increase >=10% from baseline	Decrease >= 10% from baseline
Body temperature (°C)	>= 39.1	-

2.8 Pharmacokinetic endpoints

Pharmacokinetic endpoints will be analyzed and summarized by dose level of MBG453 (400 mg Q4W, 800 mg Q4W).

2.8.1 MBG453 and venetoclax drug concentrations

Pharmacokinetic analyses will be summarized for the MBG453 or venetoclax pharmacokinetic analysis set. MBG453 and venetoclax concentration data will be listed by dose level, subject, and visit/sampling time point. Descriptive summary statistics for MBG453 and venetoclax concentrations will be provided by dose level, visit/sampling time point, excluding concentrations at EOT, 30-day follow-up, 150-day follow-up visit and unscheduled visit. 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%. MBG453 and venetoclax concentration data obtained from samples collected outside of PK sample collection window as defined per protocol will be flagged and excluded for the summary statistics.

All concentration data for MBG453 vs. time profiles with arithmetic mean (+/- SD) and geo-mean will be displayed graphically, excluding concentrations at EOT, 30-day follow-up, 150-day follow-up visit and unscheduled visit.

[redacted]

2.8.3 Immunogenicity analysis

Immunogenicity will be characterized descriptively by tabulating ADA prevalence based on the Immunogenicity prevalence set and ADA incidence on-treatment based on the Immunogenicity incidence set.

Any IG sample collected after 150 days of the last dose of MBG453 will not be used for summaries or derivations.

ADA prevalence (i.e., ADA-positive samples) will be calculated as the number of ADA-positive samples among the number of subjects with a non-missing sample.

ADA incidence (i.e., ADA-positive subjects) will be calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive subjects among the number of subjects in the Immunogenicity incidence set. Subject ADA status accounted for the ADA incidence are defined as follow:

- Treatment-induced ADA-positive subject: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample (i.e. ADA-positive sample post-baseline with ADA-negative sample at baseline).
- Treatment-boosted ADA-positive subject: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample (i.e. ADA-positive sample post-baseline with titer that is at least the fold titer change greater than the ADA-positive baseline titer).

  Further details on the immunogenicity analyses will be provided in separate document at compound level as required.

[redacted]

[redacted]

[redacted]

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

[redacted]:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]

2.10 Interim analysis

No formal interim analysis is planned for this trial.

However, two safety review meetings were conducted:

- One meeting after subjects included in the first cohort (treated with MBG453 at the 400 mg Q4W) have completed 2 cycles of treatment,
- A second meeting after subjects included in the second cohort (treated with MBG453 at 800 mg Q4W) have completed 2 cycles of treatment.

The decision to start enrollment in the second cohort and to continue with the MBG453 dose of 800 mg Q4W in the expansion phase will be guided by a Bayesian analysis based on the incidence of dose limiting toxicity (DLT) data.

For each cohort (MBG453 400 mg and 800 mg Q4W) of the safety run-in part, the following information (summaries and/or listings) will be provided:

- Number (%) of subjects treated and included in the analysis sets
- Basic demographic and background data
- Disease characteristics (including ELN risk category)
- Medical history
- Concomitant medications
- Patient disposition

- Protocol deviations
- Duration of exposure to study treatment
- Dose intensity and relative dose intensity
- Number (%) of subjects with any dose changes (incl. reductions, interruptions, or permanent discontinuations) and the reasons
- DLTs, AEs, treatment related AEs, SAEs, on-treatment deaths reported during the DLT evaluation period, as well as DLTs, AEs, treatment related AEs, SAEs, on-treatment deaths reported up to the data cut-off date
- AESI overview (if AESI definition is available at time of the safety review meetings)
- Posterior distribution for the risk of DLT for new subjects at the dose level tested (see Section 2.5)
- Laboratory data and vital signs abnormalities
- Blast counts from bone marrow, extramedullary disease assessment and investigator's response assessment
- MBG453 concentrations (what is available)
- ADA concentrations (what is available)

For the regular safety review meetings conducted after the safety run-in part, the same information as listed above will be provided except the investigator's response assessment.

The exact list of tables, listings and figures prepared for those safety review meetings will be defined in a separate planning document (e.g. TFL).

3. Sample size calculation

DLT analysis (safety run-in part):

No formal statistical power calculations to determine sample size were performed for this part of the study. In the case that 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 subjects, an additional cohort of 9 to 12 subjects treated with MBG453 administered at 800 mg Q4W will be enrolled.

CR analysis (safety run-in and expansion parts):

The sample size calculation is based on the Complete Remission (CR) rate (primary efficacy endpoint) observed in subjects treated with MBG453 at 800 mg Q4W (from both safety run-in and expansion parts). The hypotheses to be tested and details of the testing strategy are described in Section 2.5.2.

Based on available data (Pollyea D. 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 subjects, 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 subjects (61%). Based on simulations (Table 3-1), 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 3-1 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 3-2 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
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.

4. Change to protocol specified analyses

Not applicable.

5. Appendix

5.1 General definitions

Date of first administration of study treatment component (MBG453 or azacitidine or venetoclax)

The date of first administration of a study treatment component (MBG453 or azacitidine or venetoclax) is defined as the first date when a non-zero dose of the respective study treatment component is administered and recorded on the study treatment eCRF page.

Date of last administration of study treatment component (MBG453 or azacitidine or venetoclax)

The date of last administration of a study treatment component (MBG453 or azacitidine or venetoclax) is defined as the last date when a non-zero dose of the respective study treatment component is administered and recorded on the study treatment eCRF page. So both, first and last date of study treatment component, are derived separately for each drug which is part of the study treatment.

Date of first administration of study treatment (combination)

The date of first administration of study treatment (or start date of study treatment) is defined as the first date when a non-zero dose of any component of the study treatment (MBG453, azacitidine or venetoclax) is administered.

Date of last administration of study treatment (combination)

The date of last administration of study treatment (or start date of study treatment) is defined as the last date when the last non-zero dose of any last component of the study treatment (MBG453, azacitdine or venetoclax) is administered.

Date of last exposure to study treatment component (MBG453 or azacitidine or venetoclax)

One planned cycle length is 28 days and the start date of a cycle is defined as the first administration of azacitidine within a cycle. Azacitidine is planned to be administered daily every cycle during 7 days at the beginning of each cycle (between Day 1 to Day 9). MGB453 is administered every 4 weeks (Q4W), on Day 8 of each cycle, unless there was a toxicity leading to a dosing interval increase. Venetoclax is planned to be administered on each day of the 28-day cycle.

The date of last exposure to MBG453 is therefore calculated as:

- Minimum (last date of administration of MBG453 + 27 days, date of death, last contact date in case subject is lost to follow-up, analysis cut-off date), as MBG453 injections are given Q4W.

The date of last exposure to azacitidine is calculated as:

- Minimum (last date of administration of azacitidine + 20 days, date of death, last contact date in case subject is lost to follow-up, analysis cut-off date) as the 7 doses of azacitidine are given in the beginning of each cycle.

The date of last exposure to venetoclax is calculated as:

- Minimum (the date of last administration of a non-zero dose of venetoclax, date of death, last contact date in case subject is lost to follow-up, analysis cut-off date), as venetoclax is given in a daily administration (in case of regimen change to "three weeks on, one week off", the cycle would end after 7 days; in case of regimen change to "two weeks on, two week off", the cycle would end after 14 days; in case of regimen change to "one week on, three week off", the cycle would end after 21 days).

End date of the last cycle initiated

The end date of the last cycle initiated is the maximum date between:

- The planned end date (Day 28) of the last cycle initiated when the last non-zero dose of any last component of the study treatment (MBG453 or azacitidine or venetoclax) is administered,
- The actual date of the last administration of a non-zero dose of any last component of the study treatment.

The end date of the last cycle initiated (Day 28 or beyond) will be applicable even if this date goes beyond the data cut-off date (i.e., it should not be truncated to the date of data cut-off).

Date of last exposure and duration of exposure to study treatment (combination)

For the calculation of the duration of exposure to study treatment (combination), the date of last exposure to study treatment (combination) will be derived as the minimum date between:

- The latest of last date of exposure to MBG453, azacitidine and venetoclax = maximum (date of last exposure to MBG453, date of last exposure to azacitidine, date of last exposure to venetoclax),
- Date of death,
- Last contact date in case subject is lost to follow-up,
- Analysis cut-off date

The duration of exposure to study treatment (combination) will be calculated as follow: date of last exposure to study treatment (combination) - date of first administration of study treatment (combination) + 1.

Duration from first to last cycle initiated to calculate dose intensity and the relative dose intensity

For the calculation of the dose intensity and relative dose intensity, the duration in days from first to last cycle initiated will be calculated as follow: end date of the last cycle initiated - date of first administration of study treatment (combination) + 1.

Thus, this derivation will be irrespective of date of death or last contact date (i.e., it should not be truncated to the date of death or date of last contact date).

Cumulative dose, dose intensity and relative dose intensity of venetoclax

For venetoclax, as per protocol, the full dose will be adjusted due to the concomitant administration of CYP3A inhibitors or P-gp inhibitors. By this adjustment, the intended exposure to venetoclax is assumed to remain unchanged from clinical perspective (equivalent to full daily dose 400 mg). To this end,

- Cumulative dose will be calculated by two methods. The first one is actual cumulative dose which uses the "dose administered" in Study Treatment - Venetoclax eCRF (unadjusted method), and the second one is cumulative dose which uses the adjusted "dose administered" (400 mg/day), if administered with the concomitant CYP3A inhibitors or P-gp inhibitors (adjusted method). The first is to reflect the actual amount of venetoclax a patient receives, and the second is to reflect the actual exposure to venetoclax.
- Similarly, dose intensity will also be calculated by two methods: unadjusted and adjusted methods.
- Of note, planned dose intensity of venetoclax will only be calculated by the adjusted method and will be averaged in case the full dose changed during the ramp-up period.

For example, if a subject received a full dose of venetoclax at 400 mg during the first 2 cycles (including the ramp-up period), the dose interrupted in the next 14 days and then resumed to receive full dose of venetoclax at 200 mg with the concomitant CYP3A4 inhibitors or P-gp inhibitors during the subsequent 42 days (until the end of Cycle 4). So for this subject, his venetoclax dose/exposure can be summarized as follows:

	Unadjusted method	Adjusted method
Cumulative dose	(100+200+300)+ 400 × 25 days + 400 × 28 days + 0 × 14 days + 200 × 42 days = 30200 mg	(100+200+300)+ 400 × 25 days + 400 × 28 days + 0 × 14 days + 400 × 42 days = 38600 mg
Dose intensity	30200/(28 days × 4) × 28 days = 7550 mg per 28 days	38600/(28 days × 4) × 28 days = 9650 mg per 28 days
Planned dose intensity	-	[(100+200+300) + 400 × 25 days+ 400 × 28 days + 400 × 14 days + 400 × 42 days] / (28 days × 4) × 28 days = 11050 mg per 28 days
Relative dose intensity	-	9650/11050 = 87.33%

End date of a treatment cycle and cycle length

The cycle length (days), i.e., duration of a treatment cycle, will be calculated as follows: for each cycle, cycle length = the end date of cycle – the start of cycle + 1.

The start date of a treatment cycle is defined as the first azacitidine administration within the cycle, if azacitidine is administered within the cycle (in case azacitidine is not administered within the cycle, a cycle starts at 7 days before the date of MBG453 administration within the cycle; in case neither azacitidine or MBG453 is administered within the cycle, a cycle starts at the date of first venetoclax administration within the cycle as per 28-day/cycle).

The end date of a treatment cycle = the start date of next treatment cycle – 1. If it is the last cycle, the end date of last cycle is the end date of last initiated, which is calculated as above.

Study day

The study day describes the day of the event or assessment date, relative to the reference start date (start date of study treatment).

The study day is calculated as follows:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory or ECG assessment, vital sign measurement etc.) is the start of study treatment. The same reference start date will be used for efficacy (e.g. response assessment, time-to-event endpoints) and patient-reported outcomes (PRO).

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations and PROs, the last non-missing assessment, including unscheduled assessments on or before the date of start of study treatment is taken as “baseline” value or “baseline” assessment.

For safety evaluations, the last available assessment including unscheduled assessments on or before the date of start of study treatment is taken as “baseline” assessment.

If subjects have no value as defined above, the baseline result will be missing.

Last contact date

The last contact date will be used for censoring of subjects in the analysis of overall survival.

The last contact date is defined as the latest complete date from the below list on or before the data cut-off date (Table 5-1). The cut-off date will not be used for last contact date, unless the subject was seen or contacted on that date. No date post cut-off date will be used.

Completely imputed dates (e.g., the analysis cut-off date programmatically imputed to replace the missing end date of a dose record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring only if coming from the 'Survival' eCRF.

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the last complete date among the following:

Table 5-1 Last contact date data sources

Source data	Conditions
Date of Randomization	No condition
Last date subject was known to be alive from Survival Follow-up page	Subject status is reported to be alive or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose
Response assessment date	Response marked as 'done'
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
ECOG performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

5.2 Statistical models

5.2.1 ELN risk stratification categories

Sub-classification of AML subjects will be categorized by using the ELN 2017 risk stratification (Döhner et al 2017) and ELN 2022 risk stratification (Döhner et al 2022).

ELN risks will be derived based on the following rules: for each subject,

1) If he/she has any favorable genetic abnormality (cytogenetic or molecular genetic), a "Favorable" risk will be assigned. That is, Favorable genetic abnormalities always took precedence.
2) Then, if he/she has any adverse genetic abnormality (cytogenetic or molecular genetic), an "Adverse" risk will be assigned.

3) Then, if he/she has any intermediate genetic abnormality (cytogenetic or molecular genetic), an “Intermediate” risk will be assigned.

4) Then, if he/she has no cytogenetic and molecular genetic assessments, a “Missing” risk will be assigned; Otherwise, an “Intermediate” risk will be assigned.

Table 5-2 2017 ELN risk stratification by genetics[a]

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] • Biallelic mutated *CEBPA*
Intermediate	• Mutated NPM1 and FLT3-ITD[high(c)] • Wild type NPM1 without FLT3-ITD or with FLT3-ITDlow(c) (w/o adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3); MLLT3-KMT2A[d] • Cytogenetic abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1); DEK-NUP214 • t(v;11q23.3); KMT2A rearranged • t(9;22)(q34.1;q11.2); BCR-ABL1 • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype[e], monosomal karyotype[f] • Wild type NPM1 and FLT3-ITD[high(c)] • Mutated RUNX1[g] • Mutated ASXL1[g] • Mutated TP53[h]

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

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

c. Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semi-quantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve (AUC) "*FLT3*-ITD" divided by AUC "*FLT3*-wild type"; recent studies indicate that acute myeloid leukemia with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic hematopoietic-cell transplantation.

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

e. Three or more unrelated chromosome abnormalities in the absence of one of the World Health Organization-designated recurring translocations or inversions, i.e., t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

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

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

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

Table 5-3 2022 ELN risk stratification by genetics at initial diagnosis[a]

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/RUNX1::RUNX1T1[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11[b,c] • Mutated NPM1[b,d] without FLT3-ITD • bZIP in-frame mutated CEBPA[e]
Intermediate	• Mutated NPM1b,d with FLT3-ITD • Wild-type NPM1 with FLT3-ITD • t(9;11)(p21.3;q23.3)/MLLT3::KMT2A[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/DEK::NUP214 • t(v;11q23.3)/KMT2A-rearranged[g] • t(9;22)(q34.1;q11.2)/BCR::ABL1 • t(8;16)(p11;p13)/KAT6A::CREBBP • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1) • t(3q26.2;v)/MECOM(EVI1)-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2[j] • Mutated TP53[k]

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

b. Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.

c. Concurrent of KIT and/or FLT3 gene mutation does not alter risk categorization.

d. AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.

e. Only in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.

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

g. Excluding KMT2A partial tandem duplication (PTD).

h. Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.

i. Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding corebinding factor AML).

j. For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

k. TP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Of note, two “Adverse” genetic abnormalities in ELN 2022 risk stratification, t(8;16)(p11;p13)/KAT6A::CREBBP and t(3q26.2;v)/MECOM(EVI1)-rearranged, were not collected in this study at the planning of the study design.

5.2.2 ELN 2022 response categories in AML patients

All response categories for AML patients (based on ELN 2022 (Döhner et al 2022)), including CR, CRh, CRi, MLFS, PR, No response, Non-evaluable for response, Relapsed disease (after CR, CRh or CRi), and their occurrence dates will be derived by Novartis. For more details, please refer to another document "CMBG453C12201-AML-responses-criteria.docx", under NCV:

https://novartis-clinical.veevavault.com/ui/#permalink=V0X0000000BL001

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