NOVARTIS

Clinical Development

MBG453/Sabatolimab

CMBG453B12201 / NCT03946670

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

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
13-Aug-19	FPFV	Creation of version 1.0	N/A - First version (based on protocol incl. amendment 1 from 10-Apr-19)	N/A
13-Aug-2020	Prior to CR rate analysis DBL and unblinding	Creation of version 2.0	Amendment 1 (based on protocol incl. amendment 3 from 6-May-2020)	- Typos corrections and clarifications. - Table 1.1 and section 2.6 secondary efficacy endpoints: update of the objectives and endpoints according to protocol amendment 3; main updates addition of EFS and HI. - Table 2.2 Modified response classification: update of the responses according to protocol amendment 3; main updates addition of HI and modification of the definition of transfusion independence/dependence. - Section 2.2 Analysis Set: update of the safety set definition for subjects who will never receive MBG453/Placebo. [redacted] - Section 2.5.1 Complete remission rate: update of the definition according to protocol amendment 3[redacted] - Section 2.6.2 Safety: changes in the AE summaries, [redacted] deletion of shift table for laboratory tests where grades are not defined by CTCAE v5.0 - Section 2.6.3 Pharmacokinetics: clarifications [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14-Apr-2021	Prior to CR rate analysis DBL and unblinding	Creation of version 3.0	Amendment 2 (based on protocol incl. amendment 3 from 6-May-2020 and Type C FDA meeting)	- Typos corrections and clarifications. - Section 2.4.2 Clarifications added for transfusion analyses and for prior anti-neoplastic therapies - Section 2.5.3: • Listing added for bone marrow blasts percentage. • Graph added for bone marrow blasts percentage. • Plots for some selected hematology parameters were moved to the efficacy section 2.5.3 instead of the safety section 2.6.2. [redacted] - Section 2.6.3: • Additional AE tables, especially one for COVID-19 related AEs and one for AEs for safety follow up period (day 31-150 after last dose of study drug) • Table 2.4 updated with all ECG parameters • [redacted] • Addition of listings for sample ADA status and subject ADA status. • [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				[redacted].
9-Dec-2021	Prior to PFS interim analysis DBL and unblinding	Creation of version 4.0	Amendment 3 (based on protocol amendment 4 from 2-Sep-2021)	- Typos corrections and clarifications - Naming change of study drug to investigational drug - Section 2.3.2 addition of a rationale for collecting race - Section 2.5.2 Censoring reasons updated to take into account discontinuation from follow-up/study due to subject/guardian/physician decision - Section 2.6.1 addition of mCR with HI as a response rate category and clarification of the responses rates which will be summarized. [redacted] - Section 2.6.3 PK addition of C2h in the table as a synonyme of Cmax - Sections 2.8 and 2.9 and in others SAP sections: modifications as per protocol amendment 4. The main purpose of this amendment was to clarify that long-term safety and efficacy data is collected until 4 years after last subject was randomized, which is the time of the end of study and the data cut-off date for the final overall survival (OS) analysis. Further, based on the observed pooled Progression Free Survival (PFS) events, the pooled rate of discontinuations without PFS event, the limited number of subjects that are still at risk to have a PFS event and the predictions of future PFS events, the target number of PFS events for the final PFS analysis might not be reached at all or within a reasonable time frame. Thus, the final PFS analysis (FA) data cut-off date is now planned to be approximately 4 months after the interim PFS analysis (IA) data cut-off date (or after approximately 108 PFS events are observed if this is earlier) if PFS is not

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				already significant at IA. The final PFS analysis if applicable, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date. Based on FDA's recommendation, the alpha spending function for PFS and OS analyses were modified to use O'Brien and Fleming boundaries.

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List of abbreviations

ADA	Anti-drug Antibody
AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quantitation
BM	Bone marrow
BMI	Body mass index
BOR	Best Overall Response
BP	Blood pressure
BSA	Body surface area
CI	Confidence interval
CHM	Cochran-Mantel-Haenszel
CR	Complete Remission
CRO	Contract research organization
CSR	Clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DMS	Document Management System
DOR	Duration of response
eCRF	Electronic Case Report/Record Form
[redacted]	[redacted]
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
[redacted]	
EOT	End of treatment
[redacted]	
FAS	Full Analysis Set
Hgb	Hemoglobin
HLT	High level terms
HMA	Hypomethylating agent
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IV	Intravenous
IA	Interim Analysis
IG	Immunogenecity
IPSS-R	International Prognostic Scoring System

IRT	Interactive Response Technology
IWG	International Working Group
LPLV	Last Patient Last Visit
mCR	marrow Complete Remission
MDS	Myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
[redacted]	[redacted]
NCI	National Cancer Institute
NMQ	Novartis MedDRA queries
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PFS	Progression free survival
[redacted]	
PK	pharmacokinetic(s)
PR	Partial remission
[redacted]	
PS	Performance status
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
[redacted]	
RBC	red blood cell(s)
SAE	serious adverse event
SAP	Statistical analysis plan
SD	Stable Disease
SMQ	standardized MedDRA queries
SOC	Standard of Care
[redacted]	
TFL	Tables Figures Listings
[redacted]	
[redacted]	[redacted]
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the primary Clinical Study Report (CSR) of the study CMBG453B12201, a randomized, double-blind, placebo-controlled, phase II study evaluating the efficacy and safety of MBG453 in combination with hypomethylating agents in subjects with IPSS-R intermediate, high or very high-risk myelodysplastic syndrome (MDS).

As specified in the study protocol amendment 4, the CR rate analysis was performed approximately 7 months after the last subject has been randomized in the study. The CR rate analysis was performed in May 2021 and the DMC recommended to continue the study blinded without changes.

In case the PFS is declared statistically significant at the PFS IA, this analysis will constitute the basis for the primary CSR. Otherwise, the final PFS analysis , will be considered as the primary analysis and will constitute the basis of the primary CSR. Updated analyses after the primary CSR will be conducted and reported as needed. This SAP will serve as the basis for those analyses as well, however, a separate selection of tables, figures and listings (TFL) might be done.

The content of this SAP is based on the CMBG453B12201 protocol including amendment 4 (2-Sep-2021). All decisions regarding the analysis, as defined in the SAP document, have been made prior to database lock and unblinding of the study data. The SAP is written using the future tense, as the first version was approved at the start of the study.

1.1 Study design

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

Subjects will be randomized in a 1:1 ratio as described in Figure 1.1 to one of the following:

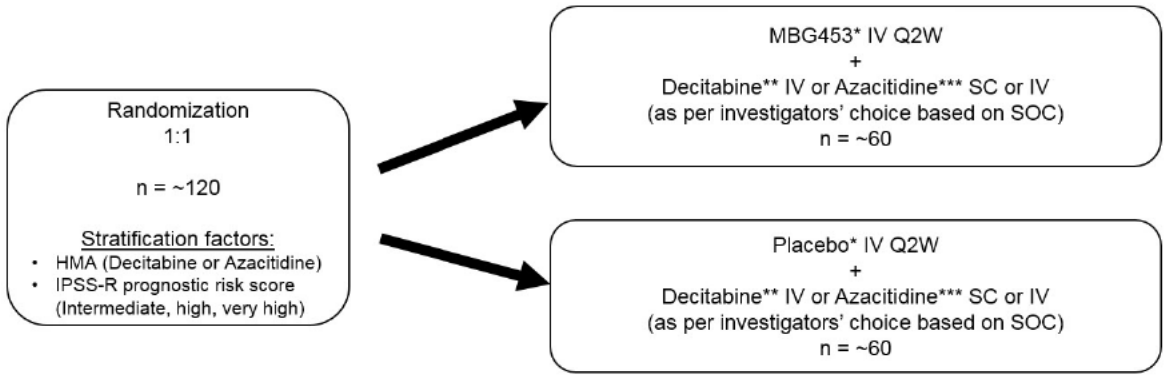
- MBG453 + HMA (decitabine or azacitidine) or
- Placebo + HMA (decitabine or azacitidine)

The randomization will be stratified by two stratification factors:

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

The study treatment consists of cycles of MBG453 or placebo in combination with HMA administered to the subjects until treatment discontinuation as described in the protocol. The planned duration of a cycle is 28 days. Crossover between treatment arms is not permitted at any time during the study.

Figure 1-1 Study design



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

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

Data Monitoring Committee (DMC)

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical study, including the site investigators participating in the study. The DMC will regularly assess safety data and recommend to the sponsor whether to continue, modify, or terminate the study. The DMC will review also efficacy at the time of the CR rate analysis and subsequent PFS analyses if CR rate analysis is not statistically significant.

[redacted] the DMC analyses will use this SAP as basis with regard to definition of endpoints, analyses and statistical testing plan.

1.2 Study objectives and endpoints

The following Table 1-1 (which is a copy of the Table 2-1 from the study protocol) outlines the primary, secondary [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)**
• To determine if MBG453 combined with standard HMA therapy improves complete remission in subjects with intermediate, high, or very high risk MDS	• Complete remission(CR) rate according to International Working Group (IWG) for MDS as per investigator assessment
• To determine if MBG453 combined with standard HMA therapy improves PFS in subjects with intermediate, high or very high risk MDS	• PFS is defined as time from randomization to disease progression (including transformation to acute leukemia per WHO 2016 classification), relapse from CR according to IWG-MDS or death due to any cause, whichever occurs first, as per investigator assessment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess Overall Survival in each treatment arm	• Time from randomization to death due to any cause
• To assess EFS in each treatment arm	• EFS is defined as time from randomization to lack of reaching CR within the first 6 months, relapse from CR or death due to any cause, whichever occurs first. CR and relapse from CR are defined according to International Working Group (IWG) for MDS (Section 2.5) as per investigator assessment.
• To assess Leukemia-free survival in each treatment	• Time from randomization to ≥ 20% blasts in bone-marrow/peripheral blood (per WHO 2016 classification) or diagnosis of extramedullary acute leukemia or death due to any cause
• To assess responses rate in each treatment arm	• Percentage of CR/mCR/PR according to IWG-MDS as per investigator assessment and HI according to IWG-MDS
• To assess duration of complete remission in each treatment arm	• Time from the date of the first documented CR to the date of first documented relapse from CR or death due to any cause, whichever occurs first
• To assess time to complete remission in each treatment arm	• Time from randomization to the first documented CR
• To assess the improvement in RBC/platelets transfusion independence in each treatment arm.	• Number and percent of subjects who are RBC/platelets transfusion independent and duration of transfusion independence (Section 2.5) after randomization as per IWG-MDS
• To assess the safety profile of MBG453 when given in combination with HMA	• Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs, incidence of notable ECG abnormalities
• To characterize the pharmacokinetics of MBG453 when given in combination with HMA	• Serum concentrations and pharmacokinetic parameters for MBG453

Objective(s)	Endpoint(s)
• To evaluate immunogenicity of MBG453 when given in combination of HMA	• Anti-drug Antibody (ADA) prevalence at baseline and ADA incidence on-treatment

[redacted]

2 Statistical methods

2.1 Data analysis

The primary analysis will be performed by Novartis. However, the DMC analyses will be performed by an Independent Statistician and Independent Programmer at a CRO. [redacted]

SAS version 9.4 or later R 3.4.3 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis / data cut-off handling

For each of the analyses a data cut-off date will be defined.

The CR rate analysis will be done when all randomized subjects have completed 6 cycles of treatment or have discontinued the study. In order to allow for confirmation of response at least 4 weeks after the initial response, the cut-off date will be set to 7 months after the last patient is randomized (or earlier depending on when the last patient had achieved CR).

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

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

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

For each of the analyses, all statistical analyses will be performed using all data collected in the database up to the data cut-off date. All 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 will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

General analysis conventions

Data will be summarized by treatment arm: demographics and other baseline characteristics as well as efficacy data and anti-neoplastic therapies / HSCT for the Full Analysis Set, safety and any other data (unless specified otherwise) for the Safety Set.

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, 25^{th} and 75^{th} percentiles, minimum, and maximum).

Study treatment and investigational drug

MBG453 matching placebo refers to as “placebo” and azacitidine and decitabine as “HMA” throughout this document and in the analyses. The treatment arms are MBG453 + HMA and placebo + HMA.

Study treatment refers to the combination of MBG453 or placebo with HMA.

Investigational drug refers to the individual components: MBG453 or placebo.

2.2 Analysis sets

Full Analysis Set

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

Safety Set

The Safety Set includes all subjects who received at least 1 dose of any component of the study treatment (MBG453 + HMA or placebo + HMA). Subjects will be analyzed according to the study treatment they received, either MBG453 + HMA or placebo + HMA. If the subject never received the investigational drug (i.e. MBG453 or placebo) and took at least 1 dose of HMA, subjects will be analyzed in the placebo + HMA treatment arm.

Pharmacokinetic Analysis Set

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

For a concentration to be evaluable:

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

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	None
Safety Set	No written informed consent	No dose of any component of study treatment
PAS	No written informed consent	See definition of PAS

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. 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

The main subgroups of interest are the stratification factors for which the primary efficacy endpoints will be analyzed:

- IPSS-R risk categories (very high vs. high vs. intermediate) as per randomization
- Hypomethylating agents (azacitidine vs. decitabine) as per randomization, if enough subjects in the decitabine arm.

[redacted]

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

Number (%) of subjects screened will be summarized by country and center. In addition, the number (%) of subjects randomized will be summarized by country, center and treatment arm.

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

All disposition information will be listed.

Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category. All protocol deviations will be listed.

Analysis sets

The number (%) of subjects in each analysis set will be summarized by treatment arm and randomization stratum for the FAS. A listing will be provided displaying all subjects excluded from analysis sets.

2.3.2 Demographic and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively using the FAS and listed.

MBG453 is a novel compound (tested in a novel combination) and the collection of race is required to perform subgroup analysis. The aim is to detect potential signal in safety and efficacy.

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 MDS diagnosis (initial diagnosis, WHO classification, current disease status (de novo or secondary) and cytogenetic abnormalities) will be tabulated and time since diagnosis summarized.

Data from the IRT system at randomization will be summarized also: HMA selected (azacitidine or decitabine), IPSS-R risk category including the components (blasts in BM, number of cytopenias and cytogenetic abnormalities).

Medical history

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.

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

2.4.1 Study treatment / compliance

Duration of exposure

The duration of exposure (in months) will be summarized for study treatment and for each investigational drug individually (MBG453 and placebo) and for HMA (azacitidine or decitabine) based on summary statistics and categorical analyses (e.g. exposure <1 month, at least 1 month, at least 2 months etc.). [redacted]

Dose intensity

The actual dose intensity (computed as the ratio of actual cumulative dose received and duration in days with at least one component of the combination) 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.

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

For HMA (azacitidine and decitabine), 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. The actual cumulative dose in mg/m^2 is then the sum of all cycles. The following formula is used for BSA:

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

The duration considered for the derivation of the dose intensity and the relative dose intensity will be derived from the start date of study treatment to the end of the last cycle initiated irrespective of date of death, last contact date for withdraw consent and cut-off date:

the last exposure to study treatment (combination) will be the planned end date (Day 28) of the last cycle initiated with MBG453 and/or HMA, whichever is the latest. [redacted]

The relative dose intensity is then comparing the actual dose intensity during subjects' exposure with the protocol planned dose of 400 mg Q2W for MBG453/placebo and 20 mg/m^2 for decitabine and 75 mg/m^2 for azacitidine, e.g. if a subject received 300 mg Q2W on average throughout the study, the relative dose intensity for this subject is 0.75.

Dose reductions, interruptions or 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, physician decision) will be taken from the 'Study Treatment eCRF' and summarized by investigational drug and by HMA. 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).

2.4.2 Concomitant and post-treatment therapies / HSCT

Prior and concomitant medications/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 therapies

Prior anti-neoplastic medications will be summarized using the FAS. Medications will be summarized by ATC class and preferred term.Radiotherapies and surgeries will be listed using the FAS.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD).

Transfusions

All transfusions of blood products (incl. those not related to MDS) prior and after start of study treatment will be listed. Only MDS related transfusions (e.g. bleeding, surgical procedure, hemolysis, infections) of platelet and red blood cells will be summarized using the FAS. For that, the number of transfusion units will be normalized by time (fixed 8-weekly interval, mentioned below as episode) prior to and on-treatment. 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.

Post treatment anti-neoplastic therapies and HSCT

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.

2.5 Analysis of the primary endpoint(s)

The 2 primary objectives of the study are to compare complete remission (CR) rate and progression-free survival (PFS) as per investigator assessment between the two treatment arms. The primary endpoints are CR rate and PFS as per the International Working Group (IWG) criteria for MDS (see Table 2-2 and further details in sections 2.5.1 and 2.5.2 of this analysis plan).

To conclude for efficacy, the treatment effect needs to be demonstrated in any (or both) of the primary endpoints CR rate and/or PFS. The type I error control for this primary endpoint family is described in Section 2.8.

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 2-2 below.

Table 2-2 Modified response classification per IWG criteria in MDS (Platzbecker et al 2018, Cheson et al 2006, Cheson et al 2000)

Response category	Definition#
Complete remission (CR)	**Bone marrow:** ≤ 5% blasts with normal maturation of all cell lineages. (Note: Persistence of dysplasia will be noted but does not preclude achievement of complete remission [CR]) **Peripheral blood:** • Hgb ≥ 10 g/dL AND • Platelets ≥ $100*10^9$/L AND • Neutrophils ≥ $1.0*10^9$/L AND • Blasts 0% *(Note: the subject must not receive RBC or platelet transfusions, myeloid growth factor within 2 weeks before this disease assessment)*
marrow Complete remission (mCR)	**Bone marrow:** ≤ 5% blasts and blast count decrease by ≥ 50% compared to baseline **Peripheral blood/transfusion:** Marrow CR may be achieved with or without improved blood counts or with or without transfusions
Partial remission (PR)	All CR criteria except **Bone marrow:** ≥ 50% decrease from baseline in blasts in bone marrow AND blast count in bone marrow > 5%
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Relapse from CR	Only in subjects with a CR: **At least 1 of the following criteria is met:**

Response category	Definition[#]
	[in absence of another explanation not due to MDS, such as acute infection, bleeding, hemolysis, etc. Note that observation of peripheral blasts is not a sufficient criterion for relapse. However in that case, a bone marrow examination should be made to determine whether relapse has occurred] • Return to baseline bone marrow blast percentage • Decrease of ≥ 50% from maximum remission/response*** levels in neutrophils *AND neutrophils <1.0*10^9/L. Note: neutrophils counts during periods of active infection will not be considered in determining the maximum* • Decrease of ≥ 50% from maximum remission/response*** levels in platelets *AND platelets < 100*10^9/L* • Decrease *from maximum remission/response*** levels* in Hgb concentration by ≥ 1.5g/dL *AND Hgb < 10 g/dL* • Becoming transfusion dependent**
Disease progression	**At least 1 of the following criteria is met:** [in absence of another explanation not due to MDS, such as acute infection, bleeding, hemolysis, etc. Note that observation of peripheral blasts is not a sufficient criterion for progression. However in that case, a bone marrow examination should be made to determine whether relapse has occurred] **Bone marrow** according to the number of blasts of the subject at baseline: • Less than 5% blasts at baseline: ≥ 50% increase in blasts *over baseline* to > 5% blasts • 5%-<10% blasts at baseline: ≥ 50% increase *over baseline* to > 10% blasts • 10%-<20% blasts at baseline: ≥ 50% increase *over baseline* to > 20% blasts. Subjects with more than 20% of blasts will be considered to have transformation to acute leukemia per 2016 WHO classification (Arber et al 2016) **Peripheral blood:** • Decrease of ≥50% from maximum remission/response*** levels in neutrophils *AND neutrophils < 1.0*10^9/L. Note: neutrophils counts during periods of active infection will not be considered in determining the maximum* • Decrease of ≥ 50% from maximum remission/response*** levels in platelets *AND platelets < 100*10^9/L* • Reduction from baseline in Hgb by ≥ 2g/dL *AND Hgb < 10g/dL* **Becoming transfusion dependent**** ***Occurrence of acute leukemia or extramedullary leukemia per investigator's judgement***
Modified Hematological Improvement per IWG-MDS criteria in MDS (Cheson et al 2006)	
HI category	**Definition[#] (HI must last at least 8 weeks)**
Erythroid response (HI-E) (pretreatment*, <11 g/dL)	1. Hgb increase from baseline by ≥ 1.5 g/dL, in at least 2 consecutive Hgb measurements and maintained over at least 8 weeks

Response category	Definition[#]
	2. Relevant reduction from baseline of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of < 9 g/dL pre-treatment will count in the RBC transfusion response evaluation.
Platelet response (HI-P) (pretreatment*, <100 x 10^9/L)	1. Absolute increase from baseline of ≥ 30 x 10^9/L for subjects starting with > 20 x 10^9/L platelets 2. Increase from baseline from < 20 x10^9/L to > 20 x10^9/L and by at least 100% for subjects starting with < 20 x 10^9/L platelets
Neutrophil response (HI-N) (pretreatment*, <1.0 x 10^9/L)	At least 100% increase and an absolute increase from baseline of > 0.5 x 10^9/L

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

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

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

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

Transfusions Status Definitions for RBC/platelets

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

Transfusion dependence:

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

Transfusion independence:

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

•

2.5.1 Complete remission rate

The primary endpoint CR rate is the percentage of subjects with best overall response of complete remission (CR) as per the International Working Group (IWG) criteria for MDS per investigator assessment (Cheson et al 2006, Platzbecker et al 2018; Table 2-2). Any CR is considered which is observed and confirmed by the time of the CR rate analysis data cut-off, including CRs observed after cycle 7 in subjects who had been followed for longer period already.

[redacted]

2.5.2 Progression Free Survival (PFS)

PFS is defined as the time from the date of randomization to the date of the first documented progression/relapse from CR per investigator assessment or death due to any cause. Progression includes acute leukemia transformation as per WHO 2016 classification. Relapse after CR and progression will be assessed by the investigator (Table 2-2). A subject without PFS event will have their PFS censored at the time of the last adequate assessment performed on or before the cut-off date.

[redacted]

For subjects without PFS event, PFS is censored at last adequate assessment. This is the last response assessment conducted that is not considered as unknown.

For PFS, an event occurring after two or more consecutive missing response assessments (not done or unknown) is censored in the analysis of PFS at the last adequate response assessment before the event date and reason for censoring then summarized as 'Event documented after two or more missing response assessments'.

[redacted]

The PFS censoring reason will be summarized as:

1. Ongoing without event
2. New anti-neoplastic therapy
3. Withdrew consent
4. Lost to follow-up
5. Event documented after two or more missing response assessments
6. Discontinuation due to subject/physician/guardian's decision

2.5.3 Statistical hypothesis, model, and method of analysis

[redacted]

Complete remission rate

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

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

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

CR rate will be provided for each treatment arm with exact two-sided 95% confidence intervals (CI) (Clopper and Pearson 1934). The BOR (and with that the CR rate) will be calculated using all available data up to the analysis data cut-off date, which will be 7 months after the last subject is randomized.

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

Progression Free Survival

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

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

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

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

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

A listing of all responses assessments by subject will be provided including BOR, PFS time, PFS event (yes/no), OS time, death date and duration of CR. Bone marrow blasts percentage will also be listed. In addition for some selected laboratory parameters and for bone marrow blasts percentage, trends over time (baseline and on-treatment timepoints during the first 6 cycles of treatment) will be displayed via boxplots and corresponding tables displaying the summary statistics for these selected timepoints be produced.

2.5.4 Handling of missing values/censoring/discontinuations

[redacted]

[redacted]

A subject whose disease has not progressed or died by the date of the analysis cut-off will have their PFS censored at the time of the last adequate tumor evaluation performed on or before the cut-off date. Clinical deterioration will not be considered as documented disease progression.

Further details were already described in Section 2.5.1 (Complete remission rate) and Section 2.5.2. (PFS).

2.5.5 Sensitivity analyses

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

- If disease progression/relapse from CR or death is documented after two or more missing response assessments, the subject will be considered with an event at the documented event date rather than censoring PFS at the last adequate assessment prior to that event.

2.5.6 Supportive analyses

Subgroup analyses for CR rate and PFS

If the primary endpoint analyses for CR rate and/or PFS are statistically significant, homogeneity of the treatment effect across randomization stratification factors will be assessed for the following subgroups:

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

No formal statistical test of hypotheses will be performed. The CR rate together with exact 95% CI will be summarized for each subgroup. For CR, the difference together with the with the associated 95% CI (Clopper and Pearson 1934) will be presented for each subgroup in a forest plot. For PFS, the HR together with the associated 95% CI obtained using the unstratified Cox regression model will be presented for each subgroup in a forest plot.

2.6 Analysis of secondary endpoints

2.6.1 Efficacy

Efficacy endpoints will be calculated and summarized for the FAS.

Time-to-event endpoints will be analyzed using Kaplan-Meier method as described above. Hazard ratio and 95% CIs from the stratified Cox-model will be provided. The overall survival will be tested [redacted] only, if the primary endpoint CR is statistically significant and if, and when the primary endpoint PFS is statistically significant at either IA or final PFS analysis. The final PFS analysis if PFS is not already significant at IA, and the interim OS analysis will be performed approximately 4 months after the PFS IA data

cut-off date. The final OS analysis data cut-off date will be defined as 4 years after last subject randomized.

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

[redacted]

Overall Survival (OS)

OS is defined as the time from date of randomization to date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

[redacted]

The OS censoring reason will be summarized as 'Alive' or 'Lost to follow-up' by treatment arm. Subjects not known to have died will have the censoring reason 'Lost to follow-up' if the reason for discontinuation from study is 'Lost to follow-up' or 'Withdrawal of consent'. Otherwise, subjects will have the censoring reason 'Alive'.

Event Free Survival (EFS)

EFS is defined as time from randomization to lack of reaching CR within the first 6 months, relapse from CR (including progression after CR) or death due to any cause, whichever occurs first. CR and relapse from CR are defined according to International Working Group (IWG) for MDS (Section 2.5) as per investigator assessment. A subject without EFS event will have their EFS censored at the time of the last adequate response assessment performed on or before the cut-off date. For subject without reaching CR within the first 6 months, an EFS event at day 1 will be considered.

Leukemia-free survival (LFS)

Leukemia-free survival is defined as the time from date of randomization to $\geq$ 20% blast in bone-marrow/peripheral blood as per WHO 2016 classification or diagnosis of extramedullary acute leukemia or death to any cause. For subject without event, the time is censored at the

latest date the subject was known to be alive and without leukemia (last adequate assessment (bone marrow and/or hematology assessment) on or before the cut-off date).

Response rate (CR/mCR/mCR with HI/PR/HI)

Response rate is defined as the proportion of subjects with best overall response of either complete remission (CR)/marrow remission (mCR)/partial remission (PR)/hematologic improvement (HI) as per investigator assessment according to modified MDS-IWG at any time during the study (on or before cut-off date) (Table 2-2). The rates of mCR, SD and UNK with HI will be also summarized. Rates of each BOR category and the sum of CR/mCR/PR, CR/mCR/PR/HI and CR/PR/HI will be provided with exact 95% confidence intervals (Clopper and Pearson 1934). Stable Disease (SD) rate is defined as the proportion of subjects with best overall response of SD per investigator assessment. Any hematologic improvement rate, based on Table 2-2, will be reported separately with exact 95% confidence intervals (Clopper and Pearson 1934). [redacted]

Duration of CR

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

[redacted]

Time to CR

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

Red blood cells (RBC) / Platelet transfusion independence

RBC/Platelets transfusion independence rate is defined as the proportion of subjects having received no RBC/Platelets transfusions during at least 8 consecutive weeks after randomization (Table 2-2). The number and percentage of subjects will be shown for the FAS and then also in only those with transfusion dependence at baseline as defined in Table 2-2. 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.

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

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

2.6.2 Safety

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

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. laboratory shift tables). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with start date during the on-treatment period (treatment-emergent AEs).

All safety analyses will be using the Safety Set. When specified, some analyses will be performed not only by treatment arm but also by HMA treatment (azacitidine vs. decitabine), provided enough subjects in each treatment arm had received decitabine.

On-treatment period for safety analyses

The following section streamlines the on-treatment period definition for safety analyses compared to the protocol section 12.5.2. For safety reporting, the overall observation period will be divided into three mutually exclusive segments:

1. **Pre-treatment period**: from day of subject's informed consent to the day before first administration of study treatment
2. **On-treatment period**: from day of first administration of study treatment to 30 days after last administration of study treatment (MBG453, placebo or HMA).
3. **Post-treatment period**: starting at day 31 after after last administration of study treatment (MBG453, placebo or HMA).

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

Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period (until 30 days after last administration of study treatment). When specified, some AEs summaries will include all AEs occurring during the overall safety period.

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

All AEs reported in the AE eCRF page will be listed along with the information collected on those AEs, e.g. toxicity grade, relationship to study treatment, outcome, action taken etc. AEs that started during the pre-treatment, post-treatment and after the overall safety period will be flagged.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT). 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 preferred term 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 system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the MBG453 + HMA arm. 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 (all AEs (by SOC and by PT) and separately those considered related to study treatment and all AEs by HMA
- 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 preferred term).
- Non-SAEs
- SAEs with fatal outcome and separately those considered related to study treatment
- AEs leading to study treatment or MBG453/Placebo discontinuation and by HMA
- Related to study treatment AEs leading to study treatment discontinuation
- AEs leading to dose adjustment/interruption for (MBG453/Placebo), HMA and study treatment
- 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.

Adverse events for safety follow up period (day 31-150 after last dose of investigational drug) will be described by system organ class and preferred term.

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 SOC and preferred term. All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment, post-treatment and overall safety period will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

Vital signs

Notable vital sign values during on-treatment period in subjects with non-notable values at baseline (e.g. systolic BP >90 and <180 mmHg for analysis of systolic BP) will be summarized using the following criteria:

Table 2-3 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	-

ECG

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 C1D1 pre-dose, C1D8 post-dose and C3D8 pre-dose, 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
QT or QTcF (ms)	Increase >30 and <=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.

Clinical laboratory evaluations

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

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

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

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

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

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.

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

ECOG Performance status

ECOG PS categorical data will be summarized by timepoint (with visit windows as defined in Table 4.1).

2.6.3 Pharmacokinetics

Pharmacokinetic (PK) data analysis will be performed for MBG453 only. The PAS will be used for all pharmacokinetic data analyses.

Descriptive statistics (n, m (number of non-zero concentrations), mean, coefficient of variation (CV%), standard deviation, median, geometric mean, geometric CV%, minimum and maximum) for MBG453 will be presented at each scheduled timepoint. PK parameters such as those listed in Table 2-5 will be estimated and reported. Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst and will be displayed in the listing of all PK concentrations as zero and flagged. However, BLQ values will be treated as missing for the calculation of the geometric means and geometric CV% but included as zero in the other summary statistics. Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

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

The concentrations collected before dose administration on Day 8 of Cycle 3 (and later cycles) are considered steady-state concentrations for MBG453.

Table 2-5 Non-compartmental pharmacokinetic parameters

Cmin* or Ctrough*	The minimum observed plasma or serum drug concentration (mass x volume-1)
Cmax* or C2h*	The maximum (peak) observed plasma or serum drug concentration (mass x volume-1)

Population pharmacokinetic (PopPK) analysis

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

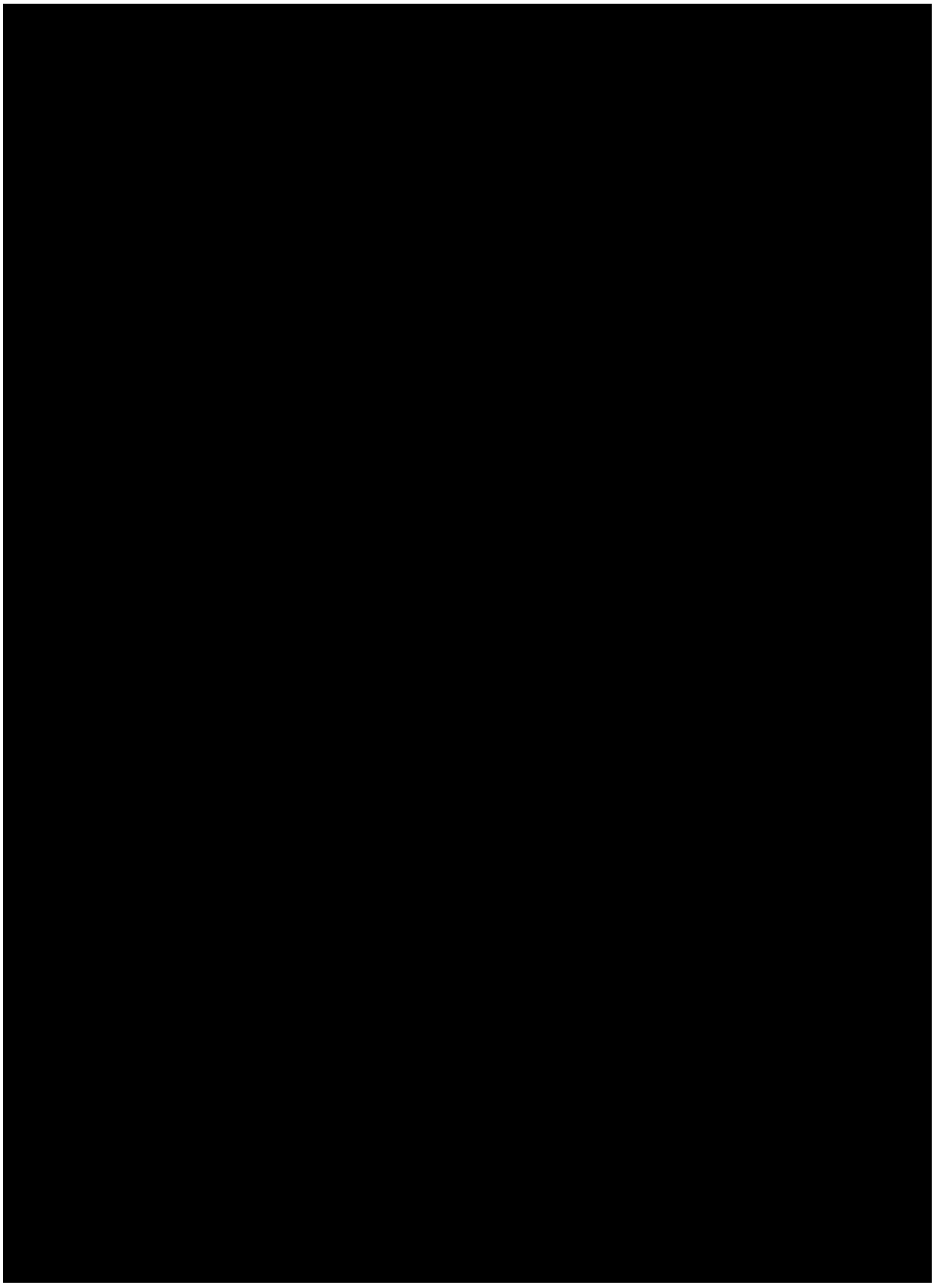
Immunogenicity (IG) / anti-drug antibody (ADA)

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

ADA incidence (i.e. ADA-positive subjects) will be calculated as the number of subjects with at least one on-treatment ADA-positive sample divided by the number of subjects with a determinant baseline IG sample and at least one determinant post-baseline IG sample.

Listings will be provided of sample ADA status (including titer for positive samples) and subject ADA status.

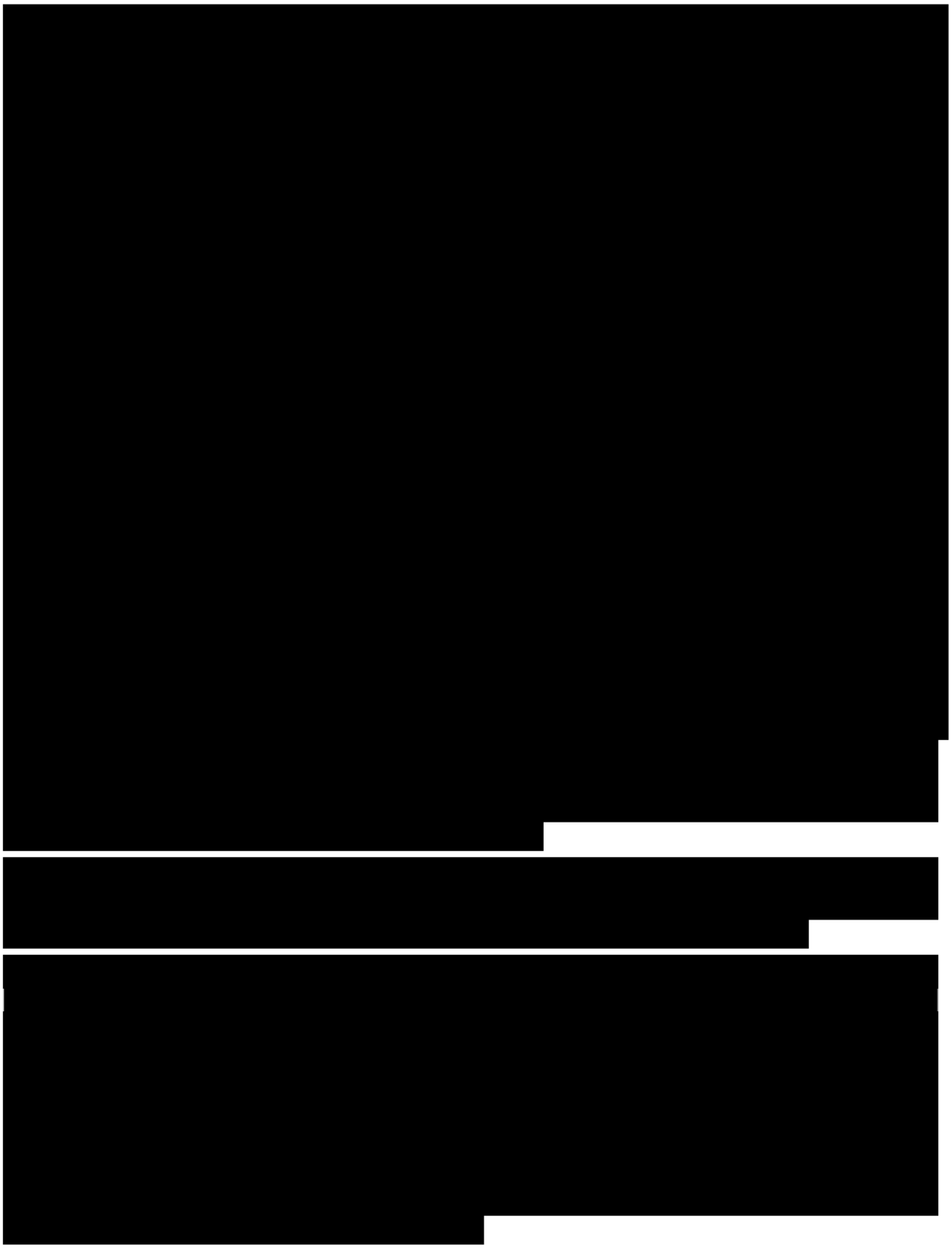
[redacted]



2.8 Interim analysis

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

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



The secondary endpoint OS will be tested only, if the primary endpoint CR is statistically significant and if, and when the primary endpoint PFS is statistically significant at either IA or

final PFS analysis. The final PFS analysis if PFS is not already significant at IA, and the interim OS analysis will be performed approximately 4 months after the PFS IA data cut-off date. The final OS analysis data cut-off date will be defined as 4 years after last subject randomized. [redacted]

2.9 Sample size calculation

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

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

[redacted]

The hypotheses to be tested and details of the testing strategy are described in Section 2.5.3 [redacted]

Complete remission rate

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

The randomization is stratified by use of HMA (azacitidine or decitabine) and the IPSS-R risk categories (intermediate, high and very high). It is anticipated that approximately 80% of subjects will use azacitidine. The CR rate will be tested using a stratified exact Cochran-Mantel-Haenszel chi-square test at the significance level described in Figure 2-2. The CR rate in the placebo + HMA treatment arm is expected to be 18% (azacitidine or decitabine), based on the literature for previous studies using azacitidine (Fenaux et al 2009) and decitabine (Kantarjian et al 2006) in MDS subjects. [redacted]

Progression Free Survival

PFS is the other primary endpoint. The hypotheses to be tested and details of the testing strategy are provided in Section 2.5.4 and Section 2.8. Based on available data from the literature for previous studies using azacitidine (Fenaux et al 2009) in MDS subjects, in which the median time to PFS was 14.1 months for azacitidine. The median PFS in the placebo + HMA arm is expected to be 12 months (for azacitidine or decitabine) as the study population is expected to have a poorer prognosis than in the reference publication. [redacted]

[redacted]

1- Probability to reject the CR null hypothesis at the CR rate analysis

[redacted]

[redacted]

[redacted]

[redacted]

Assessment	Target day of assessment	Time Window Definition
[redacted]		

5 References

[redacted]

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