NOVARTIS

Clinical Development

MBG453/ Sabatolimab

CMBG453B1US01 / NCT04878432

Single-arm, open label, phase II study of MBG453 (sabatolimab) added to FDA approved Hypomethylating agents of investigator's choice (IV/SC/Oral) for patients with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria (US multi-center)

(STIMULUS MDS-US)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07-09-2023	Before Interim analysis or DBL	As protocol was amended due to the halt in recruitment for the STIMULUS MDS-US study on 30-Sep-2022.	shortening the timeline of the study as well as various administrative changes. Amendment 01 (Based on protocol incl. amendment 02 from 08-Feb-2023)	Section 1.1 Study design Section 1.2 Study objectives and endpoints Section 2.2.1 Subgroup of interest Section 2.5.4 Supportive analyses Section 2.7.1.2 Progression Free Survival Section 2.7.1.3 Overall Survival, Section 2.7.1.8 Improvement in RBC/platelets transfusion independence Section 2.8.4.1 ECG and cardiac imaging data Section 3 Sample size calculation
05-11-2024	Before Final analysis or Final DBL	[redacted] Objectives and endpoints Survival follow-up missed	[redacted] Overall survival endpoints were updated from 12 months to 24 months survival follow-up added to summarize.	[redacted] Section 1.2 study objectives & endpoints Section 2.31

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Typo corrected	Typo corrected from randomization to enrollment. Typo corrected from randomization to enrollment. Dropped text 'Placebo'	2.7.1.1 Complete remission rate: 2.7.1.2 Progression Free Survival 2.8 Safety analyses
		[redacted]		
		As per CTT discussion, CRF collected Visits to be used instead windowing. CRF visits might be delayed, which is not unusual from a medical perspective. Additionally, the "End of Treatment" visits are patient-specific based on the study design.	For ePRO analysis, visit window will not be used and dropped from SAP.	5 Appendix Calculations for the date of last exposure to HMA drugs were updated Section 5 Appendix
28-11-2024	After DBL	Due to inconsistency in objectives/endpoints for final analysis	The objectives and endpoints analysis related to time to event is updated to 12 months post LPFT and also for	Section 1.2 & section 2.7

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			complete available data of the study. The primary objective i.e., safety profile will be analyzed considering all the data (not by 12 months, as agreed by the CTT).	
07-02-2025	After DBL	From the recent CTT discussion, it was decided to align the objectives and endpoints with the protocol v02 (which is available in CT.gov.in)	Objectives and endpoints will be aligned with the protocol v02. The primary objective i.e., safety profile will be analysed considering by the 12 months data (i.e., LPFT+12months). For Overall survival by 12 months (LPFT+12months) and 24 months (LPFT+24months) data will be analysed.	Section 1.2 & 2.7
		Per the clinical trial safety disclosure requirement to keep all analyses inline with the protocol.	For safety disclosure the text mentioned in section 2.8.1 should be added	Section 2.8.1
		[redacted]		

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List of abbreviations

[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
BLQ	Below the Limit of Quantitation
BMI	Body mass index
BOR	Best Overall Response
BP	Blood pressure
CI	Confidence interval
CR	Complete Remission
CSR	Clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DMS	Document Management System
DNA	Deoxyribonucleic acid
DOR	Duration of response
eCRF	Electronic Case Report/Record Form
eCRS	Electronic case retrieval strategy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set
Hgb	Hemoglobin
HLT	High level terms
HGLTs	High level group terms
HMA	Hypomethylating agent (Decitabine-IV, INQOVI (oral decitabine) and Azacitidine-IV or SC)
HSCT	Hematopoietic stem cell transplantation
IV	Intravenous
[redacted]	[redacted]
IPSS-R	International Prognostic Scoring System
IRT	Interactive Response Technology
INQOVI	Oral Decitabine
IWG	International Working Group
LPLV	Last Patient Last Visit

mCR	marrow Complete Remission
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NMQ	Novartis MedDRA queries
OS	Overall survival
ORR	Overall Response Rate
[redacted]	[redacted]
PD	Pharmacodynamics
PFS	Progression free survival
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PR	Partial remission
PRO	Patient Reported Outcome
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
[redacted]	[redacted]
RBC	Red blood cell(s)
SC	Subcutaneous
SAE	Serious adverse event
SAP	Statistical analysis plan
SMQ	Standardized MedDRA queries
SOC	Standard of Care
TFL	Tables Figures Listings
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TEAE	Treatment emergent adverse event
[redacted]	[redacted]
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 CMBG453B1US01, single-arm, open label, Phase II study evaluating the efficacy and safety of MBG453 in combination with hypomethylating agents (HMAs) in subjects with IPSS-R intermediate, high or very high-risk myelodysplastic syndrome (MDS).

A final analysis will be performed when all subjects complete the long-term extension phase and safety follow up. In this case a final CSR will be written.

In addition, as specified in the section 12.6 of the study protocol, interim analyses may be performed for publication or any regulatory purpose, e.g., an interim analysis can be performed after all subjects have completed 6 months follow-up from enrollment (cycle 1 day 1) or discontinued earlier.

This SAP is created for all the analysis including final analyses and a separate document for tables, figures and listings (TFL) will be created.

The main purpose of this document is to provide a summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. 'Analyses plan' in this document refers to the related statistical analysis sections in CSR.

The analysis described here will be conducted by), Novartis, using statistical software SAS® Version 9.4 according to the Statistical methods and data analysis Section 12 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information will be given in the following sections and further details are provided, as applicable, in the Appendix 16.1.9 of the CSR.

Unless otherwise specified, the statistical methodologies including the analysis sets, analysis models, algorithms, and conventions are following the Oncology study amended protocol CMBG4531US01 version 02.

1.1 Study design

This is a single-arm, non-randomized, open label, phase II multi-center study of intravenous MBG453 (Sabatolimab) added to FDA approved HMAs of investigator's choice (IV/SC/ Oral) in adult subjects with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria.

Study treatment will be administered for 12 months within the core phase of the study. After the 12 months core phase, subjects may enter the extension phase (based on investigator decision).

For subjects that will receive treatment in the extension phase, they are allowed to continue treatment with MBG453 only, HMA only or MBG453+HMA.

In addition, all subjects who discontinued (at core phase) study treatment (unless due to progression) may enter the extension phase. In the extension phase, subjects who discontinued study treatment due to reasons other than progression, death, lost to follow-up, or withdrawal of consent (i.e. transplantation, adverse events, etc.) will have hematology assessments, Patient Reported Outcomes (PRO) and response assessments at defined time points until documented disease progression, death, lost to follow-up, withdrawal of consent, or have reached the end of extension phase, whichever comes first. Subjects who progress on study [core phase (first 12 months) or extension phase (additional 12 months)] will enter the post treatment safety follow-up period.

Post treatment follow-up is for safety collection and is up to 150 days post core phase or extension phase discontinuation. Survival data will be collected until end of study inclusive of the extension and post treatment follow-up duration.

Subjects who become eligible for hematopoietic stem cell transplant (HSCT) or intensive chemotherapy at any time during the course of the study will be discontinued from study treatment. However, they may continue into the extension phase for safety.

The study treatment consists of cycles of MBG453 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.

Planned number of subjects

Novartis has decided to permanently halt recruitment based on a re-evaluation of the development strategy for sabatolimab. Subjects who are currently on study treatment or in follow-up will be continued per the protocol.

A total of 39 subjects were enrolled in this study. Subjects were recruited from sites within the United States. No pre-treatment stratification is planned. The investigator or designee must ensure that only subjects who meet all the inclusion and none of the exclusion criteria are enrolled in the study.

There are 4 types of periods/phases: Screening phase, core phase, extension phase and post treatment safety follow-up

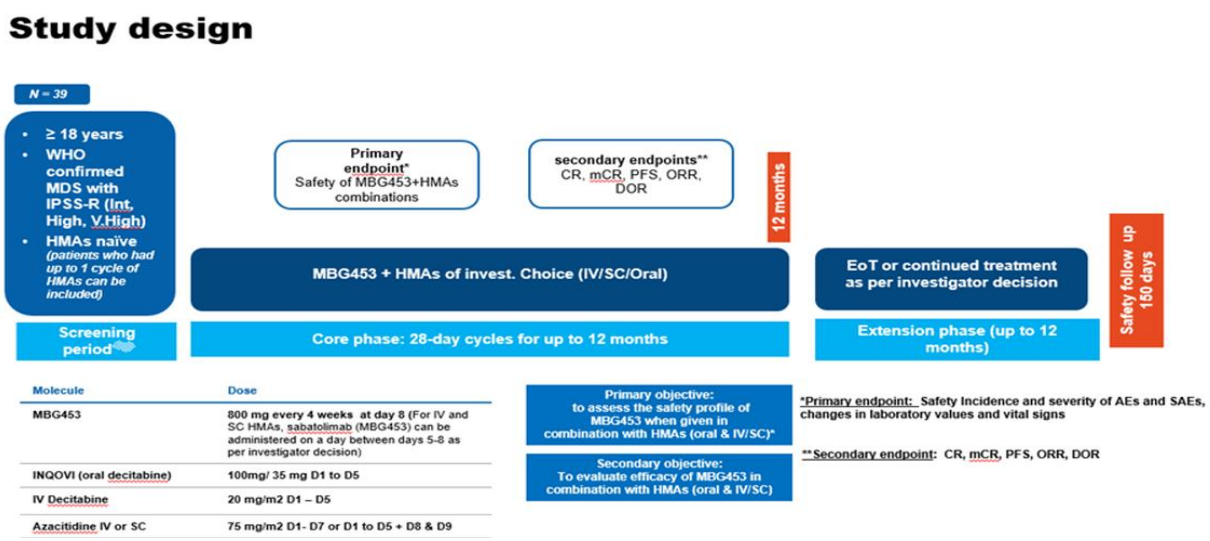
Screening phase: A signing of written informed consent obtained through day 1 of enrollment (from up to 28 days of period prior to core phase start date).

Core phase: A 12 months of treatment period is a **core phase**

Extension phase: Extension phase for efficacy and/or survival status (up to 24 months of last subject enrolling) or in addition to core phase (12 months), an additional 12 months of treatment period is **extension phase**.

Post treatment safety follow up: Post treatment safety follow-up monitoring for adverse events (AEs) for 30 days following the last dose of azacitidine or decitabine or INQOVI (oral decitabine), or 150 days following the last dose of MBG453 (sabatolimab), whichever is later.

Figure 1-1 Study design



1.2 Study objectives and endpoints

Main objective of this proposed study is to describe and evaluate safety and efficacy of MBG453 (sabatolimab) in combination with FDA approved HMAs of investigator's choice in a single-arm, non randomized, open label, phase II multi-center US study.

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Cut-off date: For analysis of the primary and secondary objectives and endpoints, 12 months post LPFT will be considered as cut-off date. Additionally, for OS of 24 months, the cut-off date will be considered as 24 months post LPFT.

Objective(s)	Endpoint(s)
Primary Objective 1. To assess the safety profile of MBG453 (sabatolimab) 800 mg (every 4 weeks) given in combination with HMAs (IV/SC/Oral) by 12 months	**Endpoint for primary objective** Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs

Secondary Objectives	**Endpoints for other secondary objectives**
1) To evaluate complete remission rate with MBG453 (sabatolimab) in combination with HMAs (IV/SC/Oral) in subjects with intermediate, high, or very high risk MDS by 12 months.	1) Complete remission (CR) rate according to International Working Group (IWG) for MDS (2006) * as per investigator assessment by 12 months.
2) To evaluate PFS rate by 12 months with MBG453 (sabatolimab) combined with HMAs (IV/SC/Oral) in subjects with intermediate, high or very high risk MDS.	2) PFS is defined as time from enrollment to disease progression (including transformation to 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 **by 12 months post LPFT.
3) To assess Overall Survival rate by 24 months.	3) Overall survival, time from enrollment to death due to any cause during 12 months post LPFT.
4) To assess Leukemia-free survival rate by 12 months.	4) Time from enrollment to ≥ 20% blasts in bone marrow/peripheral blood (per WHO 2016 classification) or death due to any cause.
5) To assess other response rates.	5) Percentage of CR/ mCR/ PR and according to IWG-MDS as per investigator assessment..
6) To assess duration of complete remission.	6) 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.
7) To assess time to complete remission.	7) Time from enrollment to the first documented CR..
8) To assess the improvement in RBC/platelets transfusion independence.	8) Number and percent of subjects who are RBC/platelets transfusion independent after enrollment as per IWG-MDS.

Notes:

*According to IWG-MDS

** Indicates as per investigator assessment by 12 months post LPFT.

2 Statistical methods

2.1 Data analysis general information

The analysis outlined in this document will be performed by, Novartis. SAS® version 9.4 or higher will be used for generating tables, figures and listings (TFLs). It is planned that the data from all subjects and centers will be used.

Note: After termination of MBG453 program, the clinical team agreed to go ahead with only one final CSR instead of separate CSR's for primary and the full study.

General analysis conventions

Data will be summarized for demographics and other baseline characteristics as well as efficacy data for the Full Analysis Set (FAS), safety and any other data (unless specified otherwise) for the Safety Set.

Categorical data (e.g. gender, race, etc.) will be presented in frequencies and percentages. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count will still be displayed.

For continuous data descriptive statistics (n, mean, standard deviation, median 25^{th} and 75^{th} percentiles, min and max) will be provided. As appropriate, 95% confidence intervals (CI) will also be reported. Kaplan Meier's estimates will be reported for the time to event variables. If not otherwise specified, p-values and confidence interval will be presented as two-sided. Unless otherwise stated, the default level of significance will be set to 5% (two-sided, family-wise type-I-error).

Summary statistics will also be presented graphically wherever applicable.

The following number of decimal places will be used: mean and median to 1 more decimal place than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data. p-value: 4 decimal places; if p-value is less than 0.0001, display < 0.0001.

- Standard error and standard deviation: data precision + 2 decimal places
- Mean, quartile, percentile and median: data precision + 1 decimal place
- Minimum and maximum: same as data precision
- Percentages: 1 decimal place, 0% will be displayed as 0 and 100% will be displayed as 100.
- Confidence interval (CI): data precision + 2 decimal place.
- p-value: 4 decimal places

All tables and listings will be presented by one treatment arm of the study. All data will be listed by center and subject number, unless stated otherwise.

2.1.1 General definitions

2.1.1.1 Study treatment and study drug

MBG453 (sabalotimab) is given with a combination of "HMAs" (INQOVI,azacitidine and decitabine) throughout this document and in the analyses. The treatment arm is MBG453 + HMAs.

Study treatment refers to the combination of MBG453 with HMAs.

Study drug refers to the individual components: MBG453 or HMAs.

2.1.1.2 Baseline assessment

For safety evaluations, the last available assessment prior to administration of MBG453 (on day 8) in combination with HMA (in any day between day 5-8) Study Day 1 (cycle 1 day 1) should be used as the baseline assessment. No assessments prior to Screening assessments will be used.

For all other parameters, baseline is defined as the last non-missing assessment on or before the enrollment (cycle 1 day 1) date.

If subjects have no assessment as defined above, the baseline results will be missing.

2.1.1.3 Date of first administration of study treatment

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 with HMAs) is administered.

2.1.1.4 Date of last administration of study treatment

The date of last administration of study treatment (or end date of study treatment) is defined as the last date when a non-zero dose of any component of the study treatment (MBG453 with HMAs) is administered.

2.1.1.5 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.

2.1.1.6 Study day

The study day describes the day of the event or assessment date, relative to the reference start date (enrollment date or 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 all the parameters will be the start of study treatment.

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.

2.2 Analysis sets

The analysis sets to be used as defined below. The FAS will be used for efficacy analysis. The Safety Set will be used for all the safety analysis.

Full Analysis Set

The FAS comprises all enrolled subjects to whom took any component of the study treatment.

Safety Set

The Safety Set includes all subjects who received at least one dose of any component of the study treatment (MBG453 + HMA).

[redacted]

1. [redacted]
2. [redacted]
3. [redacted]

[redacted]

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	Protocol deviations leading to exclusion	Non Protocol deviations leading to exclusion

FAS	No written informed consent	None
Safety Set	No written informed consent	No dose of any component of study treatment
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

Subgroup analyses will be performed on the primary and secondary endpoints (CR and PFS).

For sub-group analysis of primary (All AE/SAE) and secondary endpoints (CR and PFS) will be summarized with counts and percentage for the subgroups below.

The following subgroups based on the subject baseline assessment may be performed in this study: [redacted]

- IPSS-R (Intermediate, High & V. High)
- HMA (Oral, IV, SC)

Additionally, as the study will be ongoing during COVID 19 pandemic, in order to address the impact of COVID-19 (if any) the sensitivity analysis may be performed as appropriate:
- Discontinuation
- Protocol deviation
- Disease status
- Dose interruption/missing data
- AEs and labs

As appropriate, a sensitivity analysis may be performed on the primary safety evaluating the impact of COVID-19 on the study.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

Number and percentage of subjects screened, completed and discontinued along with reason for discontinuation will be summarized for each study periods (core phase, extension phase, post-treatment safety follow-up and survival follow-up period).

The number (%) of subjects in the FAS who started treatment core phase (i.e. core phase: 12 months of treatments), are still on treatment in core phase, who entered and discontinued the extension phase (i.e. next 12 months of core phase), who entered, discontinued post-treatment follow-up and survival follow-up will be summarized together with the respective reasons for core treatment phase/ extension phase/ post-treatment follow-up/ end of study discontinuation.

All disposition information will be listed.

Protocol deviations

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

2.3.2 Demographic and other baseline characteristics

Demographics (date of birth (Age), sex, height and weight, BMI, predominant race and ethnicity), ECOG Performance Status by grade will be summarized descriptively using FAS and listed, unless stated otherwise.

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 will be summarized by each risk classification.

Disease history (MDS), including date of diagnosis, confirmation of MDS diagnosis, IPSS-R risk classification for MDS subjects at time of screening, prior antineoplastic therapies.

Medical history

Medical history (e.g., important medical, surgical, and allergic conditions from the subject's medical history which could have an impact on the subject's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF must include the toxicity grade when applicable.

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

The duration of exposure will be summarized for study treatment and for each study drug (MBG453 (sabatolimab) and HMA (separately and combined together for all HMA)). The dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized for each study drug MBG453 and for HMA individual component by descriptive statistics.

For MBG453, the actual cumulative dose in mg is the sum of "dose administered" from the eCRF of all cycles during the exposure of MBG453. For HMA (azacitidine, decitabine and INQOVI (oral 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 drug 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. Details are provided in section 5. Appendix.

The relative dose intensity is then comparing the actual dose intensity during subject's exposure with the protocol planned dose of 800 mg Q4W for MBG453 and 20 mg/m^2 for decitabine, 75 mg/m^2 for azacitadine and Decitabine Oral (INQOVI) (100mg cedazuridine / 35mg decitabine), e.g. if a subjects received 300 mg Q2W on average throughout the study, the relative dose intensity for this subject is 0.75.

Dose réductions, interruptions or permanent discontinuations

The number and percentage of subjects with any dose changes of MBG453 (incl. interruptions, or permanent discontinuations) and the reasons will be presented.

The number and percentage of subjects with any dose changes (incl. reductions, interruptions, or permanent discontinuations) and the reasons (e.g. AE, dosing error, dispensing error, and physician decision) will be taken from the 'Study Treatment eCRF' and summarized 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 Prior, concomitant and post therapies

Prior and concomitant medications

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.

Each medication has the start and end dates recorded on the eCRF. Prior medications are defined as those medications which were taken and stopped prior to first dose of study treatment. Concomitant medications are defined as any medication given at least once between the day of first dose of study treatment and the last day of study visit, including those which were started pre-baseline and continued into the treatment period.

All concomitant medications will be listed and summarized in alphabetic order according to Anatomical Therapeutic Chemical (ATC) classification system and PT. All summaries will be performed on the Safety set.

Prior anti-neoplastic therapies

Prior anti-neoplastic medications, radiotherapy or surgery will be summarized using the FAS. Medications will be summarized by ATC class and preferred term. Radiotherapies and surgeries will be summarized by system organ class and preferred term.

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

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 of platelet and red blood cells will be summarized using the FAS. For that, the number of transfusion episodes will be normalized by time (e.g. fixed 8-weekly interval) prior to and on-treatment.

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 allogenic donor type if applicable. Both analyses will be using the FAS.

2.5 Analysis of the primary objective

The primary objective of this study is to assess the safety profile of MBG453(sabatolimab) 800mg (every 4 weeks) given in combination with HMAs (IV/SC/Oral).

2.5.1 Primary endpoint

The primary variables for this study are incidence of AEs and SAEs, and changes in laboratory values and vital signs.

Note: As primary objective of the study is safety objective and detailed analysis will be described in section 2.8, safety analysis

2.5.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing is planned for this study.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data for safety and efficacy endpoints will not be imputed.

2.5.4 Supportive analyses

Subgroup analysis may be performed as described in section 2.2.1.

2.6 Analysis of the key secondary objective

There is no key secondary objectives for this study and hence this section is not applicable.

2.7 Analysis of secondary efficacy objective(s)

For all secondary efficacy analyses, the Full Analysis Set (FAS) will be used for all subjects, unless stated otherwise.

2.7.1 Secondary endpoints

Following are the secondary endpoints to be considered for analysis by 12 months post LPFT and for complete available data for the study. Additionally for OS analysis by 24 months post LPFT will also be analyzed.

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 will be displayed via boxplots and corresponding tables displaying the summary statistics for these selected timepoints to be produced.

2.7.1.1 Complete remission rate:

Complete remission rate will be assessed according to International Working Group (IWG) for MDS (2006) with MBG453 (sabatolimab) in combination with HMAs (IV/SC/Oral) in subject with intermediate, high, or very high risk MDS.

Proportion of subjects achieving CR will be presented together with an exact 95% confidence interval.

A sensitivity analysis may be performed for CR by considering IWG-MDS & modified IWG-MDS of Peripheral blood.

If any subject who achieved CR and discontinued/lost to follow-up within 12 months will be considered as Responder.

If any subject who achieved CR and undergone to Bone Marrow Transplantation (BMT) within 12 months will be considered as Responder.

Subjects who discontinue early before achieving response will be considered as non-responders. Similarly subjects with transplant or subjects with progression before achieving response will be considered as non-responders. As appropriate, additional sensitivity analyses will be performed excluding discontinued subjects, transplant subjects and subjects with progression before documentation of CR.

Response assessment rules

Response assessment will be performed by the investigator according to the assessment schedule depicted in protocol Table 8-1 based on available bone marrow assessment and peripheral blood every 3 cycles for core phase during the first 07 cycles and every 6 cycles for extension phase and all transfusions records as detailed in Table 2-6 using the modified version of the published response criteria IWG for MDS. Moreover, response assessments can be performed at any time if clinically indicated, e.g. for confirmation of response but also for any suspicion of progression/relapse. These assessments are recorded as an unscheduled visit in the eCRFs and will be considered for the overall determination of response and progression/relapse with the respective assessment date.

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, the history of transfusions and myeloid growth factor received within the last 2 weeks.

The best overall response (BOR) will be derived based on the CR secondary endpoint rules by Novartis as below:

- CR = at least one determination of CR without progression or relapse from CR within the four after CR.
- mCR = at least one determination of mCR (and not qualifying for a CR).
- PR = at least one determination of PR (and not qualifying for a CR/mCR).
- SD = at least one SD assessment and not qualifying for CR, mCR or PR.
- PD = progression after enrollment and not qualifying for CR, mCR, PR or SD.
- UNK = all other cases (i.e., not qualifying for confirmed CR or mCR or PR and without SD or progression).

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 2-6 below.

Table 2-6 Modified response classification per IWG criteria in MDS

Response category	Definition[#]

Complete remission (CR)	**Bone marrow:** ≤ 5% blasts with normal maturation of all cell lineages. (Note: Persistence of dysplasia will be noted but does not preclude achievement of complete remission [CR]) **Peripheral blood** 1. Hgb ≥ 10 g/dL AND 2. Platelets ≥ $100*10^9$/L AND 3. Neutrophils ≥ $1.0*10^9$/L AND 4. Blasts 0% *Note: the subject must not receive RBC or platelet transfusions, myeloid growth factor within 2 weeks before this disease assessment*
marrow Complete remission (mCR)	**Bone marrow:** ≤ 5% blasts and blast count decrease by ≥ 50% compared to baseline **Peripheral blood/transfusion:** Marrow CR may be achieved with or without improved blood counts or with or without transfusions
Partial remission (PR)	**All CR criteria except** **Bone marrow:** ≥ 50% decrease from baseline in blasts in bone marrow AND blast count in bone marrow >5%
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Relapse from CR	**Only in subjects with a CR:** **At least 1 of the following criteria is met:** **[In absence of another explanation not due to MDS, such as acute infection, bleeding, hemolysis, etc. Note that observation of peripheral blasts is not a sufficient criterion for relapse. However in that case, a bone marrow examination should be made to determine whether relapse has occurred.]** • 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:** 1. Less than 5% blasts at baseline: ≥ 50% increase in blasts over baseline to >5% blasts 2. 5%- <10% blasts at baseline: ≥50% increase over baseline to >10% blasts 3. 10%- <20% blasts at baseline: ≥50% increase over baseline to >20% blasts. Subjects with more than 20% of blasts will be considered to have transformation to acute leukemia per 2016 WHO classification (**Arber et al 2016**) **Peripheral blood:** 1. Decrease of ≥50% from maximum remission/response*** levels in neutrophils AND neutrophils <1.0*10^9/L. Note: neutrophils counts during periods of active infection will not be considered in determining the maximum 2. Decrease of ≥50% from maximum remission/response*** levels in platelets AND platelets <100*10^9/L 3. Reduction from maximum remission/response*** levels in Hgb by ≥2g/dL AND Hgb <10g/dL Becoming transfusion dependent** Occurrence of acute leukemia or extramedullary leukemia per investigator's judgement

Modified Hematological Improvement per IWG-MDS criteria in MDS (Cheson et al 2006)	
HI category	**Definition# (HI must last at least 8 weeks)**
Erythroid response (HI-E) (pretreatment*, <11 g/dL)	1. Hgb increase from baseline by ≥1.5 g/dL, in at least 2 consecutive Hgb measurements and maintained over at least 8 weeks 2. Relevant reduction from baseline of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of <9 g/dL pre-treatment will count in the RBC transfusion response evaluation.
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 109/L platelets
Neutrophil response (HI-N) (pretreatment*, <1.0 x 10^9/L)	At least 100% increase and an absolute increase from baseline of >0.5 x 10^9/L

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

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

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

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

Transfusions Status Definitions for RBC/platelets

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

Transfusion dependence:

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

Transfusion independence:

1. At baseline: subjects having received 0 units of transfusion within any 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.

2.7.1.2 Progression Free Survival

Progression Free Survival (PFS) is defined as time from the date of enrollment (cycle 1 day 1) to disease progression (including transformation to leukemia per WHO 2016 classification), relapse from CR according to modified IWG-MDS or death due to any cause, whichever occurs first, as per investigator assessment.

For subjects without progression, the subject time is censored at the latest date where the subject was known to be alive, without progression and without relapse from CR (on or before the cut-off date).

PFS will be analyzed using the Kaplan-Meier Product-Limit method. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, Kaplan-Meier curves will be produced, if applicable.

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.

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

- **Start of further anti-neoplastic therapy**: For a subject without an event before the time he/she receives any further anti-cancer therapy, PFS would be censored at the date of the last adequate assessment prior to start of further anti-neoplastic therapy.

- **Hematopoietic Stem cell transplantation (HSCT)**: A subject with an event, regardless of whether it occurred before or after the time he/she receives a HSCT, would be considered as having an event at the date when the event is observed.
- **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, PFS will be censored at the last adequate assessment date.

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.

An exact rule to determine whether there are two missing assessments is therefore needed. This rule will be based on the distance between the last adequate response assessment date and the event date. If the distance is larger than threshold D2 then the analysis will assume that there are two missing assessments. This threshold D2 is defined as two times the protocol specified interval between the response assessments plus the allowed window around the assessments. The protocol defines that response assessment has to be done at least at the time of bone marrow assessments that are to be done every 3 cycles (12 weeks +/- 2 weeks) during the first 12 cycles and every 6 months (+/-1 month) thereafter. Therefore, for the first 12 cycles, any distance larger than D2 = 2*14 weeks = 28 weeks between last adequate assessment and the event means that there are two missing assessments. For the period beyond 12 cycles, any distance larger than D2 = 2*7 months = 14 months (56 weeks) means that there are two missing assessments.

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

2.7.1.3 Overall Survival

Overall Survival (OS) rate is defined as the proportion of subjects alive time from the date of enrollment (cycle 1 day 1) 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.

The OS censoring reason will be summarized as 'Alive' or 'Lost to follow-up'. 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'.

OS will be analyzed using the Kaplan-Meier Product-Limit method. Estimates of the 25th, median and 75th percentile of the OS and their 95% confidence intervals will be provided, Kaplan-Meier curves will be produced, if applicable.

2.7.1.4 Leukemia-free survival

Leukemia-free survival (LFS) is the time from the date of enrollment (cycle 1 day 1) to ≥ 20% blasts in bone marrow/peripheral blood (per WHO 2016 classification) or death due to any cause.

For a subject without event, the subject 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).

LFS will be analyzed using the Kaplan-Meier Product-Limit method. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, Kaplan-Meier curves will be produced, if applicable.

2.7.1.5 Response Rates

Response rate is defined as the proportion of subjects with best overall response of either complete remission (CR)/marrow remission (mCR)/partial remission as per investigator assessment according IWG- MDS at any time during the study (on or before cut-off date) (Table 2-6). The number and percentage of subjects with all other responses rates will be summarized.

2.7.1.6 Duration of Complete Remission

Duration of Complete Remission (DOR) is the 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.

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 their last adequate response assessment.

DOR will be analyzed using the Kaplan-Meier method. Estimates of the 25th, median and 75th percentile of the DOR and their 95% confidence intervals will be provided, Kaplan-Meier curves will be produced, if applicable.

- DOR applies only to subjects who have CR (responded).

2.7.1.7 Time to Complete Remission

Time to Complete Remission is defined as the time from the date of enrollment (cycle 1 day 1) to the first documented CR.

Time to complete remission will be analyzed using the Kaplan-Meier Product-Limit method. Subjects who are known to be without CR will be censored at study-maximum follow-up time (i.e. Last Subject Last Visit (LPLV) for final analysis, for analysis of cut-off date min (LPLV, Cut-off date)) 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. Estimates of the 25th, median and 75th percentile of the time to CR and their 95% confidence intervals Kaplan-Meier plots will be provided, if applicable. Improvement in RBC/platelets transfusion independence

The number and percent of subjects who are RBC/platelets transfusion independent after the date of enrollment as per IWG-MDS will be provided.

RBC/Platelets transfusion independence rate is defined as the proportion of subjects having received <0 units (no RBC/Platelets transfusions) during at least 8 consecutive weeks after enrollment (Table 2-6). The number and percentage of subjects will be shown for the overall FAS and then also in only those with transfusion dependence at baseline. Percentages will be provided with exact 95% Clopper-Pearson confidence intervals. Bar graphs will be provided.

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.

2.7.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing is planned for this study.

2.7.3 Handling of missing values/censoring/discontinuations

Missing data for safety and efficacy endpoints will not be imputed.

For the determination of CR, only assessments post enrollment and prior start of any other anti-neoplastic therapy or HSCT are considered.

For the determination of PFS events, only assessments post enrollment and prior start of any other anti-neoplastic therapy are considered. If disease progression/relapse from CR or death is documented after two or more missing response assessments, PFS will be censored at the last adequate response assessment prior to the event.

For PFS and duration of CR, an adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”.

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 2.7.1.

2.8 Safety analyses

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).

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

- **Pre-treatment period:** from day of subject's informed consent to the day before first administration of study treatment
- **On-treatment period:** from day of first dose of study treatment to last dose of study treatment and up to 30 days after last administration of study treatment.
- **Post-treatment period:** starting at day 31 after last administration of study treatment (MBG453 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 whichever is later.

2.8.1 Adverse events (AEs)

All information obtained on adverse events will be listed.

Treatment emergent adverse event (TEAE) defined as any adverse event which started on or after the day of first dose of study treatment and before 30 days after last dose of study treatment.

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).

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.

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, on-treatment, post-treatment and after the overall safety period will be flagged.

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, non-serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose adjustment by primary system organ class and preferred term.

Selected summaries of adverse events will be produced for the overall safety period. All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment, post-treatment and overall safety period will be flagged. Subjects who are having AE after transplantation or antineoplastic therapies will be listed & flagged.

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/HMA discontinuation and by HMA
- Related to study treatment AEs leading to study treatment discontinuation
- AEs leading to dose adjustment/interruption for (MBG453/HMA) and study treatment
- AEs requiring additional therapy
- COVID-19 related adverse events by MedDRA COVID-19 (SMQ) terms.

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 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 study drug) will be described by system organ class and preferred term.
For the legal requirements of ClinicalTrials.gov, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.
If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT."

2.8.1.1 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, number and percentage 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 and percentage 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.

Of note, AESI will be included only in the final CSR.

2.8.2 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 SOC and preferred term.

All deaths (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.

2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per NCI 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. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5, results will be categorized as low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology and biochemistry tests:

For laboratory tests where grades are defined by CTCAE v5.

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables to compare baseline CTCAE grades to the worst on-treatment grade.

  We will be plan two shift tables (i) One for up to end of core treatment period and (ii) another from Day 1 to end of extension period.

For laboratory tests where grades are not defined by CTCAE v5

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

Listing of all laboratory data with values flagged to show the corresponding CTCAE v5 grades.

If applicable and the classifications relative to the laboratory normal ranges will be presented.

Data summaries will be provided in SI units. The summary of laboratory evaluations will be presented for three groups of laboratory tests: Hematology, Chemistry and Urinalysis. On presenting summary statistics, laboratory data will be grouped and displayed in an alphabetical order within the Hematology and Chemistry groups.

All laboratory data will be listed by subject and visit. If normal ranges are available, abnormalities will be flagged.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

No ECG data collected in eCRF only collected in source, if clinically significant ECG findings is recorded on the CRF as either medical history, current medical conditions or adverse events as appropriate.

2.8.4.1.1 Cardiac Imaging Data

No cardiac imaging data collected. Hence Not applicable

2.8.4.2 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 2-4 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	-

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2.10 Interim analysis

An interim analysis was performed after all subjects who have completed 6 months follow-up from enrollment (cycle 1 day 1) or discontinued earlier for publication purpose.

Final Analysis will be performed when all subjects complete the core and extension phase and safety follow-up or discontinued early. A final CSR will be written.

3 Sample size calculation

This is an open label, non-randomized, single-arm combination study to assess safety and efficacy of MBG453 (sabatolimab) given with HMAs of investigator's choice (IV/ SC/ Oral). The primary objective of the study is to assess safety profile of this combination drug by 12 months.

Given the above expected incidence rates of AEs with the combination (Table 1-3 of protocol), a sample size of 81 evaluable subjects is estimated based on a two sided 95% confidence interval for an incidence rate of an AE using the large sample normal approximation that will extend 0.10 from the observed incidence rate of an AE (precision or margin of error of 10%) for an expected incidence rate of 30%.

Thus, with the estimated sample size of 90 subjects there is at least 90% probability to detect an AE with a true incidence rate of 2.5%. Considering drop-out rate of 10%, approximately 90 subjects will be enrolled for safety and efficacy assessment of this study.

Novartis has decided to permanently halt recruitment based on a re-evaluation of the development strategy for sabatolimab. Subjects who are currently on study treatment or in follow-up will be continue per the protocol. At the time of this amendment, 39 subjects have been enrolled into the study.

4 Change to protocol specified analyses

- [redacted]
- No supportive/subgroup/sensitivity analysis performed due to MBG program closing/due to fewer sample size. Additionally it is mentioned in protocol that subgroup analysis may be performed. Hence it is agreed to not have these analysis.

5 Appendix

5.1 Date of first administration of investigational drug /HMA

The date of first administration of investigational drug /HMA is defined as the first date when a non-zero dose of investigational drug /HMA is administered and recorded on the study treatment eCRF page.

5.2 Date of last administration of of investigational drug /HMA

The date of last administration of the investigational drug /HMA is defined as the last date when a non-zero dose of the respective investigational drug /HMA is administered and recorded on the study treatment eCRF page. So both, first and last date of investigational drug /HMA, are derived separately for each drug which is part of the study treatment.

5.3 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 (sabatolimab) in combination with HMAs (IV/SC/Oral)) is administered.

5.4 Date of last administration of study treatment (combination)

The date of last administration of study treatment (or end 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 (sabatolimab) in combination with HMAs (IV/SC/Oral)) is administered.

5.5 Date of last exposure to HMA and investigational drug and date of last exposure to study treatment (combination)

One planned cycle length is 28 days. HMA drugs are planned to be administered every cycle between Day 1 and Day 9 with different schedules. MGB453 is administered every 4 weeks, on Day 8 out of a 28 days cycle, unless there was a toxicity leading to a dosing interval increase.

As treatment is given in cycles, the date of last administration of study treatment is not considered the date of last exposure but instead the planned end date of the last cycle in which the last non-zero dose was given.

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

- Minimum (last date of administration of investigational drug + 27 days, date of death, last contact date in case subject is lost to follow-up), as MBG453 injections is given Q4W (in case of change to Q8W, the cycle would end after 55 days)

The **date of last exposure to HMA** drugs is calculated as:

The date of last exposure to azacitidine

- Minimum (last date of administration of azacitidine + 20 days, date of death, last contact date in case subject is lost to follow-up) as azacitidine is given daily every cycle during

7 days at the beginning of each cycle (between Day 1 to Day 9) (total cycle length 28 days).

The date of last exposure to decitabine

- Minimum (last date of administration of decitabine + 22 days, date of death, last contact date in case subject is lost to follow-up) as decitabine is given daily every cycle during 5 days at the beginning of each cycle (between Day 1 to Day 5) (total cycle length 28 days).

The **date of last exposure to study treatment (combination)** is calculated as the minimum date between the end date of the last cycle initiated with any component of the study treatment, the date of death and the last contact date in case subject is lost to follow-up. The end date of the last cycle initiated is the planned end date (Day 28) of the last cycle initiated where MBG453 and/or HMA were last administered or the date of the last administration of a non-zero dose of any last component of the study treatment (MBG453, HMA), whichever is the latest. 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.

The planned end date of a cycle (Day 28) will be applicable even if this date goes beyond the data cutoff date (it should not be truncated to the date of data cutoff).

5.6 Duration of study treatment (combination) used to calculate the dose intensity and the relative dose intensity

For the calculation of the dose intensity and relative dose intensity, the cycle-based exposure to study treatment (combination) will be derived from the date of first administration of study treatment (combination) to the actual or planned end date of the last cycle initiated (whichever is the latest) irrespective of date of death, last contact date for withdraw consent and cut-off date.

The start date of the first cycle initiated is the first date when a non-zero dose of HMA.

The end date of the last cycle initiated is the planned end date (Day 28) of the last cycle initiated where MBG453 and/or HMA were last administered or the date of the last administration of a non-zero dose of any component of the combination, whichever is the latest.

The duration of study treatment in days used to derive the dose intensity and the relative dose intensity will be calculated as follow: end date of the last cycle initiated – date of first administration of study treatment (combination) + 1.

The planned end date of a cycle (Day 28) will be applicable even if this date goes beyond the data cutoff date, the date of death or the date of last contact date for withdraw consent (it should not be truncated to the date of data cutoff, the date of death or the date of last contact date).

5.7 Windows for multiple assessments

Note: As per CTT discussion, It was suggested to use CRF visits for ECOG and ePROs and remove the visit window from the SAP. It is acknowledged that CRF visits might be delayed,

which is not unusual from a medical perspective. Additionally, the "End of Treatment" visits are subject-specific based on the study design. These point should be mentioned in the footnotes of the respective tables.

5.8 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 enrollment	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 [redacted] 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

5.9 Imputation rules

A project level study macro to be considered for imputation rules from GPS as mentioned below path.

CMBG453b1/util

5.10 AEs coding/grading

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The latest MedDRA version will be used and will be described in the footnote of relevant outputs.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is not used; rather, 'fatal' is collected as AE outcome and death information is also collected on a separate eCRF page.

5.11 Laboratory parameters derivations

Not applicable

5.12 Statistical models

5.12.1 Primary analysis

There is no hypothesis testing planned for this study.

5.12.2 Key secondary analysis

There is no key secondary analysis planned for this study.

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