STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Multi-Arm Study of Magrolimab Combinations in Patients with Relapsed/Refractory Multiple Myeloma
Name of Test Drug:	Magrolimab
Study Number:	GS-US-558-5915
Protocol Version (Date):	Protocol Amendment 6 (02 November, 2023)
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	13 May 2024
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ADA	antidrug antibody
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
BSA	body surface area
BLQ	below the limit of quantitation
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
HLT	high-level term
LLT	lower-level term
IV	intravenous
KM	Kaplan-Meier
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
NCI	National Cancer Institute
ORR	objective response rate
PD	progressive disease
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	recommended Phase 2 dose

RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
StD	standard deviation
SOC	system organ class
SRT	Safety Review Team
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
VGPR	very good partial response
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and defines key elements including variable definitions for analysis of data of Study GS-US-558-5915 in support of the synoptic clinical study report (CSR). This SAP is based on the study protocol amendment 6 dated 02 November 2023. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives and Endpoints

Table 1-1. Safety Run-in Cohorts

Primary Objective	Primary Endpoint
• To evaluate the safety and tolerability of magrolimab in combination with other anticancer therapies and to determine the recommended Phase 2 dose (RP2D) of magrolimab for the following combinations in patients with relapsed/refractory multiple myeloma (MM): – Magrolimab in combination with daratumumab – Magrolimab in combination with pomalidomide and dexamethasone – Magrolimab in combination with carfilzomib and dexamethasone – Magrolimab in combination with bortezomib and dexamethasone	• The incidence of dose-limiting toxicities (DLTs), adverse events (AEs), and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Table 1-2. Dose-expansion Cohorts

Primary Objective	Primary Endpoint
• To evaluate the efficacy of magrolimab in combination with other anticancer therapies in patients with relapsed/refractory MM as determined by objective response rate (ORR)	• ORR, defined as the percentage of patients who achieve stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)[a]
Secondary Objectives	**Secondary Endpoints**
• To evaluate the safety and tolerability of magrolimab in combination with other anticancer therapies	• The incidence of AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0
• To investigate other parameters of efficacy including the duration of response	• Duration of response (DOR)[a]
• To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab in combination with other anticancer therapies in patients with relapsed/refractory MM	• Magrolimab concentration versus time • Measurements of antidrug antibody (ADA) against magrolimab

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1.2. Study Design

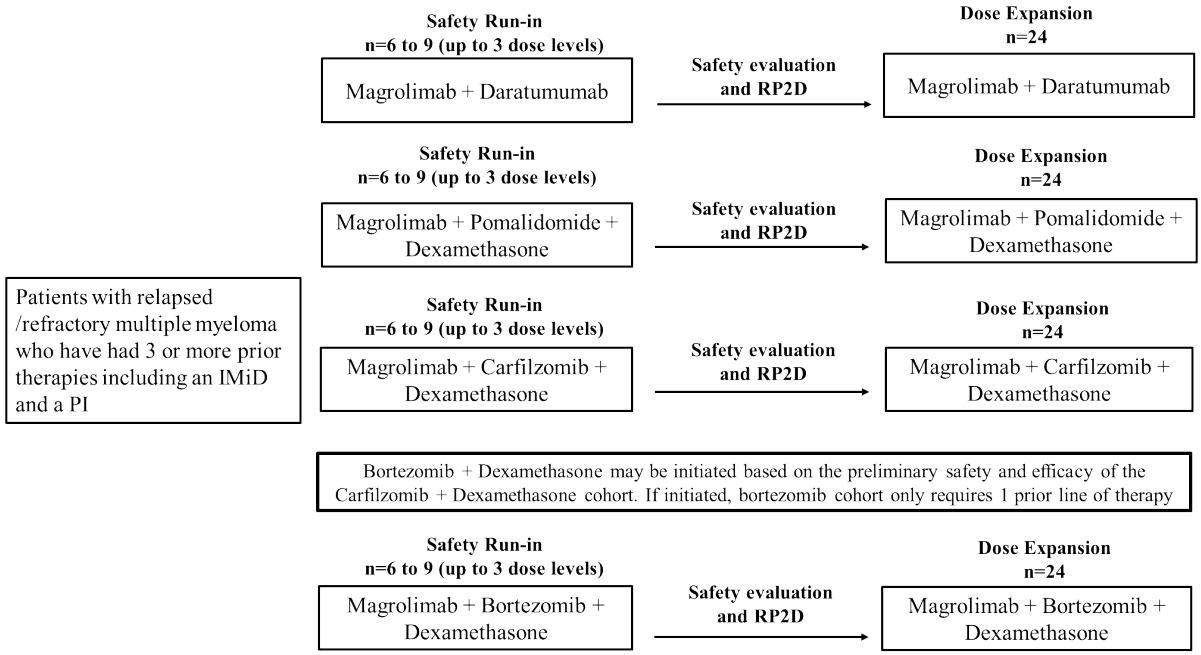
This is a Phase 2, open-label, multicenter, multi-arm study evaluating magrolimab in combination with anticancer therapies for patients with relapsed/refractory MM. This study will include safety run-in cohorts for the following combination therapies:

- Magrolimab in combination with daratumumab
- Magrolimab in combination with pomalidomide and dexamethasone
- Magrolimab in combination with carfilzomib and dexamethasone
- Magrolimab in combination with bortezomib and dexamethasone – this cohort will only be initiated at the sponsor's discretion based upon the preliminary safety and efficacy results from the carfilzomib/dexamethasone combination cohort.

After completion of the safety run-in cohorts, dose-expansion cohorts using the same combination therapies will occur.

The study schema is presented in Figure 1-1.

Figure 1-1. Study Schema



IMiD = immunomodulatory drug; PI = proteasome inhibitor; RP2D = recommended Phase 2 dose

Approximately 153 patients will be enrolled in the study, with up to 27 in each safety run-in cohort (up to 9 patients at each of the 3 possible dose levels; total up to 81 patients) and approximately 72 patients in the dose-expansion cohorts.

1.2.1. Safety Run-in Cohorts

All safety run-in cohorts may progress concurrently. The DLT assessment period will be the first cycle (35 days). Patients who are not evaluable (Section 3.1.5) for DLT assessment will be replaced.

For each of the safety run-in cohorts, a 6 + 3 de-escalation algorithm will be implemented. Six patients will be enrolled in each of the safety run-in cohorts. Dose de-escalation decisions will be made after the first 6 patients in each cohort have completed the Cycle 1 DLT evaluation period and the Safety Review Team (SRT) has reviewed safety and clinical data for the first cycle as follows:

- If no more than 1 patient experienced a DLT in Cycle 1, enrollment into the dose-expansion cohort will begin at this dose level.

- If 2 patients experienced DLTs, 3 additional patients will be enrolled into the cohort at the same dose level. If no additional DLTs occur in these 3 patients, the dose level will be deemed safe by the SRT. If 1 or more DLTs occur in these 3 patients, a lower-dose cohort will be evaluated using the same 6 + 3 de-escalation algorithm to define the recommended dose for the combination regimens.

- If more than 2 patients experienced DLTs, another 6 patients will be enrolled at a lower dose and evaluated in the same manner to define the recommended dose for the combination regimens.

The RP2D will be determined by Gilead in discussion with SRT based on all relevant clinical and PK data from all patients treated in the safety run-in cohorts.

1.2.2. Dose-expansion Cohorts

Once any of the safety run-in cohorts has been completed and an RP2D established for that combination, a dose-expansion cohort using the dose level and schedule specified in Table 1-3 may be initiated. Each dose-expansion cohort may enroll up to 24 patients. Patients may be enrolled simultaneously into the dose-expansion cohorts without an observation period between patients.

Table 1-3. Magrolimab Dose Level and Schedule (All Dose-expansion Cohorts)

	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
RP2D[a]	**Cycle 1**	**Cycle 2**	**Cycle 3+**
30 mg/kg	1 mg/kg IV Day 1 (priming dose) and 30 mg/kg IV Days 8, 15, 22, 29	30 mg/kg IV Days 1, 8, 15, 22	30 mg/kg IV Days 1, 15
20 mg/kg	1 mg/kg IV Day 1 (priming dose) and 20 mg/kg IV Days 8, 15, 22, 29	20 mg/kg IV Days 1, 8, 15, 22	20 mg/kg IV Days 1, 15
15 mg/kg	1 mg/kg IV Day 1 (priming dose) and 15 mg/kg IV Days 8, 15, 22, 29	15 mg/kg IV Days 1, 8, 15, 22	15 mg/kg IV Days 1, 15

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in the safety run-in cohorts.

1.3. Sample Size and Power

For each of the dose-expansion cohorts, a sample size of 30 (24 expansion patients together with the 6 patients from the safety run-in cohort), provides 86.1% power for a 1-group Chi-square test at a 1sided alpha of 0.1 to detect an ORR of ≥ 45% for the combination treatment compared with a historical control ORR of 25%.

The historical control ORR of 25% is based on outcomes from the MAMMOTH study; the subset of patients treated with any daratumumab containing regimen, including daratumumab in combination with an IMiD or PI, following at least 1 prior treatment {Gandhi 2019}.

2. TYPE OF PLANNED ANALYSIS

There is no planned interim analyses. The final analysis will be performed after all patients have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of patients in each category will be presented; for continuous variables, the number of patients (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-patient listings will be presented for all patients in the All Enrolled Analysis Set, unless otherwise specified, and sorted by cohort, patient ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the patient. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the patients to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of patients eligible for inclusion will be summarized by cohort.

3.1.1. All Screened Analysis Set

The All Screened Analysis Set includes all patients who receive a study screening identification (ID) number in the study at screening stage.

3.1.2. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all patients who receive a study patient identification (ID) number in the study after screening. This will be the primary analysis set for analyses of patient demographic and baseline characteristics, enrollment, and disposition.

3.1.3. Full Analysis Set

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS). The FAS includes all enrolled patients who took at least 1 dose of study treatment with treatment group designated according to the planned treatment assigned at enrollment.

3.1.4. Safety Analysis Set

The primary analysis set for safety analyses is the Safety Analysis Set. It includes all patients who received at least 1 dose of study treatment with treatment group designated according to the actual treatment received. This analysis set will be used in the analyses of safety endpoints and study treatment administration. All data collected during treatment up to 70 days after treatment discontinuation will be included in the safety summaries.

3.1.5. Dose-Limiting Toxicity (DLT) Evaluable Analysis Set

The DLT Evaluable Analysis Set includes all patients in the Safety Analysis Set who are enrolled in the safety run-in cohorts and fulfill either of the following criteria:

- Experienced a DLT after initiation of the first infusion of magrolimab during the DLT assessment period (i.e. the first Cycle (35 days))
- Completed DLT assessment period and received at least 3 infusions of magrolimab and the following cohort-specific criteria:
  - Magrolimab in combination with daratumumab cohort: Completed at least 2 doses of daratumumab
  - Magrolimab in combination with pomalidomide and dexamethasone cohort: Completed at least 10 doses of pomalidomide and 2 doses of dexamethasone
  - Magrolimab in combination with carfilzomib and dexamethasone cohort: Completed at least 2 doses of carfilzomib and 2 doses of dexamethasone
  - Magrolimab in combination with bortezomib and dexamethasone cohort: Completed at least 2 doses of bortezomib and 2 doses of dexamethasone

The recommended dose for the expansion cohorts will be based on the DLT Evaluable Analysis Set.

3.1.6. Pharmacokinetic Analysis Set

The PK Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

3.1.7. Immunogenicity Analysis Set

The Immunogenicity Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have at least 1 evaluable anti-magrolimab antibody test result.

3.2. Subject Grouping

For analyses based on the Full Analysis Set, patients will be grouped according to the treatment to which they were assigned. For analyses based on the Safety Analysis Set, patients will be grouped according to the actual treatment received.

Safety Run-in cohorts and corresponding Dose-expansion cohorts will be grouped together to be summarized in tables except for DLT related summaries, which include Safety Run-in cohorts only.

For the PK Analysis Set and the Immunogenicity Analysis Set, patients will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling patients.

3.4. Examination of Subject Subgroups

No subgroup analysis is planned.

3.5. Adjustment for Multiplicity

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3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document Appendix 2.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

Baseline value is defined as the last measurement that was observed on or prior to the date of first dose of study treatment, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug (ie, the first dosing date of any study drug) and derived as follows:

- For post dose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of the first dose of any study drug administration.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. The analysis windows for lab are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for Lab By-visit Summaries

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1[a]
Week 1	8	1[b]	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	32
Week 5	36	33	39
Week 6	43	40	46
Week 7	50	47	53
Week 8	57	54	63
Week 10	71	64	77
Week xx	xx*7+1	(xx-1)*7+1	(xx+1)*7

a Prior to first dose date time.
b Post first dose date time.

For any data relating to unscheduled visits, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of the study drug will be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade and anti-magrolimab antibody status.
- Response assessments performed at unscheduled visits after the date of first dose of study drug will be included in the analyses of the efficacy endpoints.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the arithmetic average of the measurements for continuous data, or the measurement with the lowest severity for categorical data.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the arithmetic average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

3.9. Assessment of COVID-19 Impact

This study was ongoing during the coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some patients were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. The following special situations due to COVID-19 may be handled in the analysis:

- Study treatment or study discontinuation due to COVID-19
- Protocol deviations due to COVID-19
- Missed and Virtual Visits due to COVID-19

4. PROTOCOL DEVIATIONS

A by-patient listing will be provided for those patients who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that patients did not meet and related comments, if collected.

Protocol deviations occurring after patients entered the study are documented during routine monitoring. The number and percentage of patients with important protocol deviations, with 1, 2, or 3 or more important protocol deviations, and the total number of important protocol deviations by deviation reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by cohort for the All Enrolled Analysis Set. A by-patient listing will be provided for those patients with important protocol deviation.

5. SUBJECT INFORMATION

5.1. Patient Enrollment and Disposition

A summary of patient enrollment will be provided by cohort for each country, investigator and overall. The summary will present the number and percentage of patients enrolled. For each column, the denominator for the percentage calculation will be the total number of patients analyzed for that column.

A summary of patient disposition will be provided by cohort. This summary will present the number of patients screened, the number of patients enrolled, and the number of patients in each of the categories listed below:

- Full Analysis Set
- Safety Analysis Set
- DLT-evaluable Analysis Set
- Study drug discontinuation with the reasons
- Study discontinuation with the reasons

For the status of study drug and study completion and reasons for discontinuation, the number and percentage of patients in each category will be provided. The denominator for the percentage calculation will be the total number of patients in the All Enrolled Analysis Set corresponding to that column.

The following by-patient listings will be provided by patient ID number in ascending order to support the above summary tables:

- Reasons for study drug discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Reasons for study discontinuation

5.2. Extent of Study Drug Exposure

Extent of exposure to study drugs (ie. magrolimab,daratumumab, pomalidomide, dexamethasone, carfilzomib, and bortezomib (when applicable) will be examined by assessing the total duration of exposure to each study drug respectively.

Total duration of exposure to each study drug will be defined for a patient as last dosing date minus first dosing date plus 1 day, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place.

The total duration of exposure to each study drug will be summarized using descriptive statistics for continuous variables, as well as using the number and percentage of patients exposed for at least the following time periods: 1 day, 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, etc. Summaries will be provided for the Safety Analysis Set.

The number of cycles patients were exposed to each study drug will be summarized using descriptive statistics, as well as the number and percentage of subjects exposed to a given cycle category (eg, 1 cycle, ≥1, ≥2, ≥3, etc).

The number and percentage of patients who have infusion interruption, dose reduction, dose delay, or dose missed for study drug and the reasons will be summarized.

A by-patient listing of magrolimab administration will be provided by cohort, patient ID number (in ascending order), and visit (in chronological order).

5.3. Demographics and Baseline characteristics

Patient demographic variables (eg, age, sex, race, ethnicity) and baseline characteristics (eg, body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], Body Surface Area [BSA; in m^2]) and Eastern Cooperative Oncology Group (ECOG) status at baseline as well as type and stage of myeloma will be summarized by cohort and overall using descriptive statistics for continuous variables and using number and percentage of patients for categorical variables. The ECOG status at baseline is the ECOG status at screening. The summary of demographic data will be provided for the All Enrolled Analysis Set.

A by-patient demographic listing, including the informed consent date, will be provided by cohort and patient ID number in ascending order.

Other baseline characteristics, including but not limited to time since disease diagnosis, type of myeloma, stage at diagnosis and screening, cytogenetic results at baseline, clonal plasma cell Results, and Extramedullary plasmacytoma, will also be listed

In deriving the time since disease diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If a day is missing but the month and year are available, then the imputed day will be the first day of the month.
- A partial date will not be imputed if the year is missing.

5.4. Medical History

Prior anti-cancer therapies that patients received will be summarized. The details of prior anti-cancer therapy will be listed by cohort and patient ID number in ascending order including line of therapy, regimen name, regimen start/stop date and best response of the regimen.

For prior anti-cancer therapies, number of prior regimens, time since the completion of last regimen, and time since disease progression in the last regimen will be summarized using descriptive statistics based on the All Enrolled Analysis Set.

A partial completion date will be imputed using the same algorithm defined above for imputing partial date of diagnosis.

5.5. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Prior medications include medication with a start and end date prior to the first dose of study drug.

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by anatomical therapeutic chemical (ATC) drug class Level 2 preferred name using the number and percentage of patients for cohort. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of patients who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on 70 days after the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or 70 days after the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug plus 70 days will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date plus 70 days will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Analysis will be based on the Safety Analysis Set. No formal statistical testing is planned.

5.6. Post Treatment Anti-cancer Therapies

Post-treatement anti-cancer therapies will be provided in a by patient listing sorted by cohort, patient ID.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Primary Efficacy Endpoints

The primary endpoint for the dose-expansion cohorts is Objective response rate (ORR), defined as the percentage of patients who achieve sCR, CR, VGPR, or PR, as determined by the investigator based on International Myeloma Working Group (IMWG) 2016 criteria (Appendix 1) while on study prior to initiation of any new anti-cancer therapy (including SCT).

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

The primary efficacy null hypothesis for each of the dose-expansion cohorts to be tested is:

H_0: ORR $\leq$ 25%

H_1: ORR $>$ 25%

6.1.3. Analysis of the Primary Efficacy Endpoint

The analysis of primary efficacy endpoint will be based on confirmed response assessments using the FAS.

For the primary efficacy endpoint ORR, the point estimate and the corresponding 2-sided exact 95% CI using ClopperPearson method will be provided for each cohort. Objective response rate will also be tested against the historical control rate of 25% at 1-sided alpha of 0.1 significance level using Chi-square test for each cohort separately.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoint for the dose-expansion cohorts is Duration of Response (DOR), which is measured from the earliest date of confirmed sCR, CR, VGPR, or PR, whichever is first recorded, until the earliest date of confirmed documented PD (or the first unconfirmed PD after confirmed objective response when the PD is the last evaluable response assessment), documented relapse, or death from any cause, whichever occurs first. Those who are not observed to have documented relapse, documented PD, or death will be censored at the date of their last response assessment. If patients start taking new anti-cancer therapies (excluding SCT) before relapse, or PD, or death, duration of response will be censored at the last response assessment prior to the initiation of the new anti-cancer therapies.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

The median, first quartile (Q1), and third quartile (Q3) for DoR will be estimated using the Kaplan-Meier (KM) method along with the corresponding 95% CIs. KM curves will be provided. The proportion of patients who are event-.free at benchmark time points, such as 6 months and 12 months from the first dosing date, will be estimated by cohort using the KM method and the corresponding 95% CIs will be reported. For DOR, the analysis will include only patients who achieve a confirmed objective response (sCR, CR, VGPR, or PR).

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

All Adverse Events (AEs) will be listed. The focus of AE summarization will be on treatment emergent adverse events (TEAEs).

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 5.0. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Treatment

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment" Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-patient data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs occurring on or after the date of initiation of study drug and no later than 70 days after the date of the last dose of study drug or the initiation of any new anti-cancer therapy or SCT, whichever comes first.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment-emergent. The event is considered treatment-emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to the cutoff date of TEAE period, which is defined as the 70 days after the study drug last dose date or the day before initiation of any new anti-cancer therapy including SCT, whichever occurs first.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first dosing date if they have the same month and year, or the first day of the month otherwise.
- If the day and month are missing but year is available, then the imputed day and month will be the first dosing date if they have the same year, or 01Jan otherwise.

7.1.6. Summaries of Adverse Events and Deaths

TEAEs and deaths will be summarized by cohort based on the Safety Analysis Set unless otherwise specified.

7.1.6.1. Summaries of TEAEs

A brief, high-level summary of the number and percentage of patients who experienced at least one TEAE in the categories described below will be provided. All deaths observed in the study will also be included in this summary.

For the TEAE categories described below, summaries will be provided by SOC and PT (and maximum severity where applicable):

- TEAEs
- TEAEs with Grade 3 or higher
- TE SAEs
- TEAEs leading to death

The number and percentage of patients who experienced at least one TEAE will be provided and summarized by PT and severity in descending order of total frequency:

- TEAEs
- TEAEs with Grade 3 or higher
- TE SAEs
- TEAEs related to any study drug
- TEAEs related to magrolimab

For the AE categories described below, summaries will be provided by PT in descending order of total frequency:

- TEAEs
- TEAEs with Grade 3 or higher
- TE SAEs
- TE SAEs related to any study drug
- TE SAEs related to magrolimab
- TEAEs leading to discontinuation of any study drug
- TEAEs leading to discontinuation of magrolimab
- TEAEs leading to interruption of any study drug
- TEAEs leading to interruption of magrolimab
- TEAEs leading to death

Multiple events will be counted only once per patient in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by PT, multiple events will be counted only once per patient for each preferred term. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given patient during the study.

In addition, by-patient data listings will be provided for the following:

- All AEs
- All AEs leading to death

A flag will be included in the listings to indicate whether the event is treatment emergent.

7.1.6.2. Summaries of Death

A summary (number and percentage of patients) of deaths will be provided. The summary will include the following categories:

- All deaths
- Deaths within 30 days of the first dosing of any study drug
- Deaths beyond 30 days of the first dosing of any study drug
- Deaths within 70 days of the last dosing of any study drug
- Deaths beyond 70 days of the last dosing of any study drug.

A by-patient listing of all deaths occurred during this study will be listed by cohort and patient ID number in ascending order.

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Dose Limiting Toxicity

DLT will be summarized by PT and severity for each cohort based on DLT-Evaluable Analysis Set (Section 3.1.5). The details will be provided in patient data listings.

7.1.7.2. Infusion-Related Reaction (IRR)

Infusion-related reaction are defined by the NCI CTCAE Version 5.0 (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances". For the purpose of this study, they are defined as AEs that occur within the 24-hour period beginning from the start of the infusion.

The number and percentage of patients who experienced any of the infusion reaction AEs will be summarized by PT.

7.1.7.3. Treatment-Emergent Adverse Events (TEAE) of Special Interest

Number and percentage of subjects with the following TEAEs of special interest will be summarized by search category and PT:

- Anaemia (MST Anemia Extravascular Transient Hemolysis)
- Infusion Related Reaction (IRR) (SMQ-Hypersensitivity Narrow Terms) + within one day of latest infusion
- Transfusion reactions due to magrolimab interference with RBC typing (Gilead's MST)
- Thromboembolic Events (SMQ- Embolic and Thrombotic Events Broad Terms)
- Pneumonitis (SMQ- Interstitial Lung Disease Broad Terms)
- Serious infection (SOC: Infections and infestations [just SAE in this SOC])
- Severe neutropenia (PTs : ≥ Grade 3 Neutrophil count decreased, ≥ Grade 3 Neutropenia and, ≥ Grade 3 Febrile neutropenia)

7.1.7.4. Other Important Safety Topics

The number and percentage of patients with the following AEs of important safety topics will be summarized by search category and PT:

- Immune-Mediated Events (SMQ-Immune-mediate and autoimmune disorder Narrow Terms)
- Hemorrhages (SMQ- Hemorrhages Broad Terms)

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to and including the date of last dose of study drug plus 70 days for patients who permanently discontinued study drug, or the day before initiation of new anticancer therapy including SCT (whichever is earlier). The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by cohort for laboratory tests (eg, chemistry, hematology, coagulation) as follows:

- Baseline values
- Postbaseline maximum value
- Postbaseline minimum value
- Change and percentage change from baseline to postbaseline maximum value
- Change and percentage change from baseline to postbaseline minimum value

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values will be plotted using a line plot by cohort and visit for the laboratory tests including but not limited to hemoglobin.

In the case of multiple values associated with a visit, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

Local labs will be graded based on central lab normal ranges with in-house macro.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 70 days for patients who permanently discontinued study drug, or the day before initiation of new anticancer therapy including SCT (whichever is earlier). If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of patients in the study with the given response at baseline and each scheduled postbaseline time point.

The TE laboratory abnormalities summaries (number and percentage of patients) will be provided by lab test and cohort; patients will be categorized according to the most severe postbaseline abnormality grade for a given lab test.

For all summaries of laboratory abnormalities, the denominator is the number of patients with nonmissing postbaseline values up to 70 days after the last dosing date or the day before initiation of new anticancer therapy including SCT (whichever is earlier).

A by-patient listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by patient ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of patients who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): > 3 times of the upper limit of reference range (ULN)
- Alanine aminotransferase (ALT): > 3 x ULN
- AST or ALT: > 3 x ULN
- Total bilirubin: > 2 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase (ALP) < 2 x ULN

The summary will include data from all postbaseline visits up to 70 days after the last dose of study drug. For individual laboratory tests, patients will be counted once based on the most severe postbaseline values. For the composite endpoints of AST or ALT, total bilirubin, and ALP, patients will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of patients in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date.

7.2.4. Shifts Relative to the Baseline Grade

Shift tables will be presented by showing change in severity grade from baseline to the worst postbaseline grade for hematology and chemistry laboratory tests.

7.3. Body Weight and Vital Signs

No summary or listing of body weight, BMI, or vital signs will be provided to aligh with the planned scope of the study synotic CSR.

7.4. Other Safety Measures

A by-patient listing of ECOG performance status will be provided by cohort and patient ID number in ascending order.

8. PHARMACOKINETIC (PK) AND IMMUNOGENICITY ANALYSES

8.1. PK Sample Collection

Blood samples for evaluating magrolimab serum concentrations will be collected as described in Protocol Appendix 2.

8.2. PK Analyses

The magrolimab PK concentration will be summarized for the PK Analysis Set. Individual subject's concentration data for magrolimab will be listed based on the sampling time point. Magrolimab PK data will be summarized per nominal time point using descriptive statistics. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for magrolimab serum concentration data at time point.

The sample size (number of patients) at each time point will be based on the number of patients with nonmissing concentration data at that time point. Missing concentration values will be reported as is in data listings. The number of patients with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0.

Sparse PK concentration values that are BLQ will be presented as "BLQ" in the concentration data listing.

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the patients have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of order statistics for postdose time points:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the patients have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the patients have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the patients have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all patients have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

Due to the sparse nature of PK collection, PK parameters will not be calculated.

8.3. Immunogenicity analysis

The rate and magnitude of magrolimab anti-drug antibody (ADA) prevalence, incidence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. Neutralizing antibody occurrence rate will also be summarized.

ADA Prevalence: the proportion of subjects who had at least one positive ADA sample (baseline or post-baseline) based on the Immunogenicity Analysis Set.

Treatment-Induced ADA Rate: the proportion of subjects who had negative baseline ADA sample and at least one positive post-treatment ADA sample based on subjects who had both non-missing baseline and at least one post-treatment ADA result reported (i.e. ADA Incidence Analysis Set).

Treatment-Boosted ADA Rate: the proportion of subjects who had positive baseline ADA sample and at least one positive post-treatment ADA sample and the (max titer of the post-treatment ADA) / (titer of baseline ADA) >= 4 based on the ADA Incidence Analysis Set.

ADA Incidence (treatment-emergent ADA): the proportion of subjects who had treatment-induced or treatment-boosted ADA based on subjects who had non-missing baseline ADA sample and at least one post-treatment ADA result reported in Immunogenicity Analysis Set.

Persistent ADA is defined as:

a) Treatment-Induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive sample (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer.

or

b) Treatment-Induced ADA detected in the last sampling time point of the treatment study period.

ADA Persistence Rate: the proportion of subjects who had persistent ADA based on the ADA Incidence Analysis Set.

Transient ADA is defined as:

Treatment-Induced ADA that does not meet the definition of persistent ADA. The proportion of subjects who had transient ADA is based on the subjects evaluable for ADA incidence.

Neutralizing antibody (NAb) Incidence: the proportion of subjects who had at least one positive neutralizing antibody result reported based on the treatment-emergent ADA (treatment-induced or treatment-boosted ADA) among the subjects evaluable for ADA incidence.

Titer summaries may also be generated, if relevant. CCI [redacted]

9. BIOMARKER ANALYSIS

Biomarker analyses will be provided by the biomarker sciences group, and methods will be described in a separate Biomarker Analysis Plan.

10. REFERENCES

Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy [Author Manuscript]. Leukemia 2019;33 (9):2266-75.

Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17 (8):e328-e46.

11. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

12. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

Appendix 1. Disease Response Criteria Based on International Myeloma Working Group (IMWG) 2016 Criteria

Appendix Table 1. IMWG 2016 MRD Criteria

Response	MRD Criteria
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)[a]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[b] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[c] or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

CT = computed tomography; IMWG = International Myeloma Working Group; MFC = multicolor flow cytometry; MM = multiple myeloma; MRD = minimal residual disease; NGF = next-generation flow; NGS = next-generation sequencing; PET = positron emission tomography; SUV = standard uptake value

a Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

b Bone marrow multicolor flow cytometry should follow NGF guidelines. The reference NGF method is an 8-color 2-tube approach, which has been extensively validated. The 2-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The 8-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete 8-color method is most efficient using a lyophilized mixture of antibodies which reduces errors, time, and costs. Five million cells should be assessed. The MFC method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

c DNA sequencing assay on bone marrow sample should use a validated assay such as LymphoSIGHT (Sequenta).

Appendix Table 2. Standard IMWG 2016 Response Criteria

Response	IMWG Criteria
Stringent Complete Response (sCR)	Complete response as defined below, plus normal FLC ratio[a] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)
Complete Response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
Partial Response (PR)	≥ 50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (sum of products of 2 longest perpendicular diameters [SPD])[b] of soft tissue plasmacytomas is also required
Minimal Response (MR)	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50 to 89%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)[b] of soft tissue plasmacytomas is also required
Stable Disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease

Progressive Disease (PD) [c,d]	Any 1 or more of the following criteria:
	• Increase of 25% from lowest confirmed response value in 1 or more of the following criteria:
	  • Serum M-protein (absolute increase must be ≥ 0.5 g/dL);
	  • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥ 5 g/dL;
	  • Urine M-protein (absolute increase must be ≥ 200 mg/24 h);
	• In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);
	• In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%);
	• Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD[b] of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis; ≥ 50% increase in circulating plasma cells (minimum of 200 cells/μL) if this is the only measure of disease

Response	IMWG Criteria
Clinical Relapse	Clinical relapse requires 1 or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasmacell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD[b] • of the measurable lesion; • Hypercalcemia (> 11 mg/dL); • Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other nonmyeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein
Relapse from Complete Response (to be Used Only if the End Point is Disease-free Survival)	Any 1 or more of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of ≥ 5% plasma cells in the bone marrow; • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD Negative (to be Used Only if the End Point is Disease-free Survival)	Any 1 or more of the following criteria: • Loss of MRD-negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of ≥ 5% clonal plasma cells in the bone marrow; • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

CR = complete response; CRAB = Calcium, Renal Failure, Anemia, Bone Lesions; CT = computed tomography; FLC = free light chain; IMWG = International Myeloma Working Group; MR = minimal response; MRD = minimal disease residue; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PR = partial response; sCR = stringent complete response; SD = stable disease; SFLC = serum free light chain; SPD = sum of products of 2 longest perpendicular diameters; UK = United Kingdom; VGPR = very good partial response

a All recommendations regarding clinical uses relating to SFLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

b Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

c Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRDnegative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating diseasefree survival.

d In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Appendix Table 3. Required Baseline and Follow-up Tests for Response Assessment Using IMWG 2016 Criteria

	Every Response Assessment Time Point (Every Cycle)	If Electrophoresis Shows No Measurable Protein	At Suspected CR	At Suspected Progression (Clinical or Biochemical)
Serum Electrophoresis (Serum M-spike ≥ 1 g/dL)[a]	X		X	X
Serum Immunofixation (Any)		X	X	X
Urine Electrophoresis (Urine M-spike ≥ 200 mg/24 h)	X		X	X
Urine Immunofixation		X	X	
SFLC				
Serum M-spike < 1 g/dL, Urine M-spike < 200 mg/24 h, but Involved Ig FLC is ≥ 10 mg/dL	X		X	X
Any	–		X	X
Bone Marrow Aspirate/Biopsy				
Serum M-spike, Urine M-spike, or Involved Ig FLC not Meeting Above Criteria but Bone Marrow Plasma Cell Percentage ≥ 30%	X[b]		X	
Any	–		X	
58568 Serum M-spike, Urine M-spike, Involved Ig FLC or Bone Marrow not Meeting Above Criteria, but at Least One Lesion that has a Single Diameter of ≥ 2 cm	X[b]		X	
Any	-		X	
Hemoglobin, Serum Calcium, Creatinine (Any)	X			X

CR= complete response; FLC = free light chain; Ig = immunoglobulin; IMWG = International Myeloma Working Group; SFLC = serum free-light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; X = test performed; – = test not performed

a A baseline M-spike of ≥ 0.5 g/dL is acceptable if very good partial response or higher is the response end point to be measured and in situations where progression-free survival or time to progression are the end points of interest.

b To be done every 3 or 4 cycles till a plateau or CR, or as clinically indicated and then at suspected progression.

Source: {Kumar 2016}

GS-US-558-5915-SAP_v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	13-May-2024 20:16:19
PPD	Clinical Development eSigned	15-May-2024 22:11:10