Protocol C1071002

A Phase I, Open Label Study to Evaluate the Safety and Pharmacokinetic of Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA)—CD3 Bispecific Antibody, As a Single Agent in Japanese Participants with Relapsed/Refractory Advanced Multiple Myeloma

Statistical Analysis Plan (SAP)

Version: 5

Date: 28 Apr 2022

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study C1071002 is based on the protocol dated 10JUN2021.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 22 Dec 2020	Amendment 1 03 Dec 2020	N/A	N/A
2 14 Apr 2021	Amendment 1 03 Dec 2020	• Reviewed the content to be analyzed.	• Physical examination was deleted from Section 3.4 because physical examination was not reported on the CRF. • Additional summaries of TEAEs were described in Section 6.2.1. • Section 6.5.3 in version 1 was deleted because physical examination was not reported on the CRF. • Ad-hoc analyses for a regulatory submission was added in Section 7.
3 09 Jul 2021	Amendment 2 10 Jun 2021	• Reviewed the analysis for regulatory submission	• The definition of treatment-emergent adverse event was changed to align with the protocol amendment 2. • Section 4.1 "Full Analysis Set" in version 2 was deleted and the full analysis set will be no longer used in the C1071002 study. The DLT confirmation meeting was held on 11 Jun 2021. The followings were confirmed in the meeting: 1) all 4 enrolled patients were DLT-evaluable, ie, received at least 1 study intervention and completed the DLT observation period without any DLTs and major protocol deviations, and 2) an additional enrollment was not necessary. This means that all patients were included in both the full analysis set and the safety analysis set. Therefore, the full analysis set was identical to the safety analysis set. The full analysis set was removed to avoid redundant analyses and to reduce the number of TLFs. • Additional summaries related to CRS and ICANS were described in Section 6.2.1. • The analysis set for the all efficacy analyses was changed from the full analysis set to the safety analysis set.

4 14 Dec 2021	Amendment 2 10 Jun 2021	• Aligned with protocol amendment 2 • Added some safety analyses • Reviewed the summary of treatment exposure	• Section 3.2.10 for a new secondary endpoint was inserted. • The minimal residual disease (MRD) was moved from Section 3.3.1 to Section 3.2.10 because the MRD was changed to a secondary endpoint. • Clustered cytopenia was defined in Section 6.2.1. • Section 6.2.1.1 where the summary of AESI was described was inserted. • Peripheral neuropathy was added into AESI in Section 6.2.1.1. • Some analyses for AESI were added in Section 6.2.1.1. • Section 6.2.1.2 where the summary of oAECI was described was inserted. • The definition of oAECI was presented in Section 6.2.1.2. • Analyses for oAECI were described in Section 6.2.1.2. • Section 6.2.1.3 where the summary of deaths was described was inserted. • Analyses for deaths was presented in Section 6.2.1.3. • eDISH plot was added in Section 6.2.2. [redacted] • A box and whisker plot were removed from summaries of PK concentration in Section 6.2.8.1. • PK plot for assessing he relationship were added in Section 6.2.8.2. • Section 6.2.10 where the summary of MRD was described was inserted. • Analyses for MRD was presented in Section 6.2.10.

			• Some items of disease characteristics were added in Section 6.4.1. • Summaries of study treatment exposure were changed to align with the C1071003 study in Section 6.4.3. • Some of additional safety analyses were removed from Section 6.5.3 due to no longer concern about them. • IMWG MRD Criteria was added in Appendix. • Administrative and typographical modifications were made.
5 28 Apr 2022	Amendment 2 10 Jan 2021	• Reviewed the analysis for regulatory submission	• The end of observation period for TEAEs was changed in Section 3.2.1. • The term was changed from cumulative complete response to complete response in Section 3.2.3. • The time point of confirmed objective response for participants with extramedullary disease at baseline was specified in Section 3.2.6. • Time to very good partial response and time to complete response were defined in Section 3.2.6. • PK parameter at C2D1 was removed from Section 3.2.8 due to insufficient PK sampling point. • AUC_{last} was removed because AUC_{τ} was calculated instead of AUC_{last} in Section 3.2.8. • The threshold of 10^{-6} was used only if available in Section 3.2.10. • The sentences about coding system for CRS and ICANS was moved from Section 6.2.1.1 to Section 6.2.1. • Some terms for Lymphopenia cluster term were added in Section 6.2.1. • The definition of peripheral neuropathy was made clear in Section 6.2.1.1. • An overview of treatment-related AESI was removed in Section 6.2.1.1 because AESI,

			especially CRS/ICANS, are reported as treatment-related and an overview of all causality AESI is sufficient to investigate AESI. • Injection site reactions and Secondary malignancies were added as oAECI in Section 6.2.1.2. • Death within 28 days of the first dose of study intervention was added in Section 6.2.1.3. • As there were no participants who have no adequate baseline disease assessment, the related sentence was removed in Section 6.2.4. • Summary of duration of follow-up time was added in Section 6.2.4, Section 6.2.5 and Section 6.2.7. • Summary of time to very good partial response and time to complete response were added in Section 6.2.6. • Time points deriving PK parameter was clarified in Section 6.2.8.1. • Some PK parameters were removed due to insufficient PK sampling point in Section 6.2.8.2. • The subset for summary of MRD negativity rate was added in Section 6.2.10. • Summary of prior anticancer therapy was newly added in Section 6.4.5. • Summary of subsequent anticancer therapy was newly added in Section 6.4.6. • Administrative and typographical modifications were made.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1071002. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Study Objectives

A primary objective of this study is to assess the safety and tolerability at the recommended phase 2 dose (RP2D) with a priming dose approach of single-agent elranatamab administered to Japanese participants.

Secondary objectives are:

- To evaluate the overall safety profile,
- To evaluate the single-dose and multiple-dose pharmacokinetics (PK) of elranatamab,
- To evaluate the immunogenicity of elranatamab,
- To evaluate preliminary anti-tumor activity, and
- To characterize the impact of elranatamab on systemic soluble immune factors.

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2.1.2. Primary Estimand

Dose-limiting toxicity (DLT) rate estimated based on data from DLT-evaluable participants during the DLT observation period is the primary estimand of this study.

- Variable: Occurrence of DLTs. DLTs are defined in Section 3.1.1.1.
- Analysis population: DLT-evaluable participants defined as participants who have at least 1 dose of study intervention in the first cycle including a priming dose (4 weeks), and either experiences a DLT (irrespective of whether they received all of the planned doses of study intervention and scheduled safety assessments during the DLT observation period) or receives all of the planned doses of study intervention without experiencing any DLTs and has received scheduled safety assessments during the DLT observation period. Participants without DLTs who withdraw from study treatment and fails to meet these criteria above are not evaluable for DLT. All participants deemed non-evaluable for DLT will be replaced.
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants in the DLT observation period.

2.1.3. Secondary Estimand

Incidence of treatment-emergent adverse events (TEAEs) estimated in the analysis population during the TEAE-evaluation period, defined as the time from the first dosing date

to 90 days post last dosing date or a day before start date of a new anticancer therapy, whichever occurs first, is the secondary estimand for this study.

- Variable: Occurrence of TEAEs. TEAEs are defined in Section 3.2.1.

- Analysis population: Safety analysis set defined as participants who receive at least one dose of study intervention without regard to tolerability or duration of treatment.

- Population-level summary measure: Incidence of TEAEs defined as the number of participants with TEAEs in the TEAE-evaluation period divided by the number of participants in the safety analysis set. TEAEs will be summarized by type, frequency, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 5.0), timing, seriousness and causality.

2.2. Study Design

This is a phase 1, open-label, multi-center study to evaluate the safety and PK of elranatamab in Japanese adult participants with relapsed or refractory multiple myeloma (MM) who have received at least 3 prior therapies, including immunomodulatory drug (IMID), proteasome inhibitor (PI) and anti-cluster of differentiation 38 (CD38) antibody. Approximately 4–6 participants are expected to be enrolled overall in this study, and the RP2D (1000 µg/kg) which was declared in Study C1071001 with a priming dose (600 µg/kg) will be administered to each participant.

Treatment with study intervention will continue until either disease progression, withdrawal from treatment, or unacceptable toxicity occurs, whichever occurs first.

The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data.

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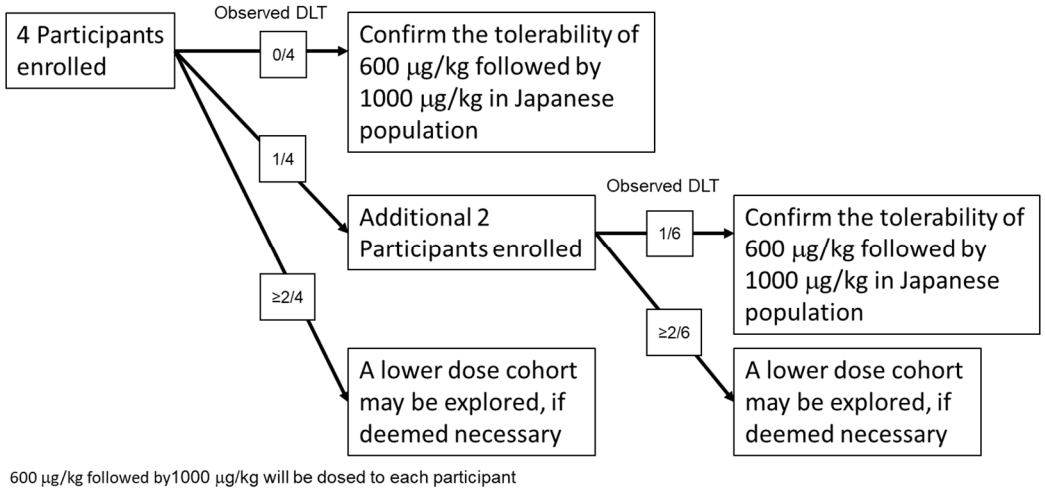
Figure 1. Schema



2.2.1. Sample Size Determination

The total number of participants will depend on the absence/presence of DLT in the initial 4 participants and the number of participants evaluable for DLT. Additional 2 participants will be enrolled to verify the toxicity in Japanese population if at least one DLT is observed in the initial 4 participants. Thus, maximum of 6 evaluable participants may be enrolled in this study.

The target DLT rate is 25%. Although the sample size is not based on any statistical considerations, the study would have 55.82% chance to declare the RP2D determined in Study C1071001 with a priming dose exceeded the maximum tolerated dose (MTD) for Japanese participants if the true DLT rate for Japanese participants is 30%. Additionally, this probability increases to 74.6% and 87.5% if the true DLT rate is 40% and 50%, respectively. It is determined that the RP2D with a priming dose exceeds the MTD in the Japanese participants if ≥2 DLTs are observed in this study. These probabilities are calculated based on a binomial probability.

Table 2. Operating Characteristics of C1071002 Study Design

Scenario	Total Sample Size	Number of DLTs Observed			True DLT Rate in Japanese Participants				
		Initial 4 Participants	Additional 2 Participants	Total	0.20	0.25	0.30	0.40	0.50
1	4	0	NA	0	40.96%	31.64%	24.01%	12.96%	6.25%
2	6	1	0	1	26.21%	23.73%	20.17%	12.44%	6.25%
3	6		≥1	≥2	14.75%	18.46%	20.99%	22.12%	18.75%
4	4	≥2	NA	≥2	18.08%	26.17%	34.83%	52.48%	68.75%
Probability C1071001 RP2D is Confirmed in Japanese Participants (Scenarios 1 + 2)					67.17%	55.37%	44.18%	25.40%	12.50%
Probability C1071001 RP2D Exceeds MTD in Japanese Participants (Scenarios 3 + 4)					32.83%	44.63%	55.82%	74.60%	87.50%

NA: Not Applicable

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

3.1.1. DLT

The DLTs observed during the DLT observation period are the primary endpoint of this study. This endpoint will be used to confirm the tolerability of the RP2D, which includes a priming dose, that was determined in Study C1071001. If the proportion of evaluable participants in this study experiencing a DLT is less than or equal to 30%, the tolerability of the RP2D with the priming dose in Japanese population will be confirmed.

3.1.1.1. Definition of DLT

Cycle 0 consists of 7 days. Cycle 0 Day 1 (C0D1) is 7 days prior to Cycle 1 Day 1 (C1D1). Each cycle except for Cycle 0 consists of 3 weeks. Any of the following TEAEs occurring in Cycle 0 and Cycle 1 (total 4 weeks) will be classified as DLTs:

Hematological:

- Grade 4 neutropenia lasting >7 days.
- Febrile neutropenia (defined as an absolute neutrophil count [ANC] <1,000/mm^3 with a single temperature of >38.3°C, or a sustained temperature of ≥38°C for more than one hour). If fever is determined to be a symptom of cytokine release syndrome (CRS) confirmed by clinical course and cytokine levels and resolves in a manner consistent with CRS, this would no longer be considered a DLT, and the participant may resume treatment.
- Grade ≥3 neutropenia with infection.
- Grade 4 thrombocytopenia (unless the study entry baseline count was ≥25,000/mm^3 and <50,000/mm^3 to take into account bone marrow suppression due to MM, in this case Grade 4 thrombocytopenia needs to be accompanied by ≥Grade 2 bleeding to be a DLT). For participants who experience a platelet count <10,000/mm^3, this is considered a DLT irrespective of other factors.
- Grade 3 thrombocytopenia with ≥Grade 2 bleeding.

Non hematological:

- Grade 4 adverse events (AEs).
- Grade 3 AE lasting ≥5 days despite optimal supportive care, with the exception of AE attributed to a CRS event (ie, Grade 3 transaminitis).
- Grade 3 CRS, except those CRS that have i) not been maximally treated (ie, lack of administration of standard of care treatment per the institution's, investigator's, or

treating physician's guidelines for the management of CRS) or ii) improved to ≤Grade 1 within 48 hours.

- Grade 4 CRS.
- Confirmed drug induced liver injury (DILI) meeting Hy's law criteria outlined in Section 10.6 of Study C1071002 protocol.
- Grade 4 laboratory abnormalities deemed clinically significant by the investigator shall be reported as Grade 4 AE.

Clinically important or persistent toxicities (eg, toxicities leading to dose interruption for ≥7 days including skipping planned dose during the DLT observation period) that are not included in the above criteria may also be considered a DLT following review by the investigators and the sponsor. All DLTs need to represent a clinically significant shift from baseline.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset or deemed not clinically insignificant by the investigator.
- Grade 3 injection site reactions (ISR), allergic reaction or anaphylaxis will not be considered as DLTs but may be a reason for study discontinuation and will be reviewed with the sponsor's medical monitor.

3.2. Secondary Endpoints

3.2.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

A TEAE is defined as an AE that first occurred from the first dose of the study intervention until 90 days after the last dose or the day before starting a new anticancer therapy, whichever occurs first. TEAEs will be assessed mainly in this study.

3.2.2. Laboratory Test Abnormalities

The following laboratory parameters will be assessed:

- Hematology: hemoglobin, platelets, white blood cell (WBC), neutrophils, lymphocytes, monocytes, eosinophils, and basophils,

- Chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, c-reactive protein (CRP), alkaline phosphatase (ALP), sodium, potassium, magnesium, chloride, total calcium, total bilirubin, total protein, blood urea nitrogen (BUN), creatinine, uric acid, glucose (nonfasted), lactate dehydrogenase (LDH), albumin, and phosphorus or phosphate,

- Serology: hepatitis B virus (HBV), and hepatitis C virus (HCV),

- Coagulation: prothrombin time (PT), and partial thromboplastin time (PTT)/activated PTT (aPTT),

- Urinalysis: urine protein, and urine blood,

- Pregnancy test: serum for female participants of childbearing potential,

- Ad hoc central lab cytokine analysis: interleukin (IL)-6, IL-10, IL-2, soluble IL-2 receptor (sIL-2R), IL-12, IL-4, IL-5, IL-13, IL-17, IL-1b, IL-8, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α,

- Optional ad hoc local lab cytokine analysis: IL-6, IL-1β, IL-10, TNF-α, and other cytokines.

For potential Hy's Law cases, the following laboratory tests will be reported: albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, PT-international normalized ratio (PT/INR), ALP, total bile acids, and acetaminophen drug and/or protein adduct levels.

Cytokines for central lab evaluation will be collected if CRS is suspected. Local lab evaluation of cytokine is only required if the site require this information for participant management.

3.2.3. Best Overall Response

Best overall response (BOR) will be assessed based on reported overall responses at different evaluation time points using International Myeloma Working Group（IMWG) response criteria.

- Complete Response (CR) will encompass stringent Complete Response (sCR) and CR.

- Objective Response (OR) will encompass sCR, CR, very good partial response (VGPR) and partial response (PR).

- Clinical Benefit (CB) will encompass sCR, CR, VGPR, PR and minimal response (MR).

3.2.4. Progression Free Survival

Progression free survival (PFS) is the time from the first date of the study intervention to the date of the first documentation of confirmed progression, or death due to any cause,

whichever occurs first. Progression is defined per the IMWG response criteria for progressive disease (PD). It does not include second primary malignancies of unrelated types.

3.2.5. Overall Survival

Overall survival (OS) is the time from the first date of the study intervention to the date of death due to any cause.

3.2.6. Time to Response

Time to response (TTR) is defined for participants with confirmed objective response (sCR, CR, VGPR and PR) as the time from the first date of the study intervention to the date of the first documentation of objective tumor response. For participants with extramedullary disease at baseline, MR or better cannot be confirmed until a post-baseline extramedullary disease assessment is performed, and the date of confirmed response cannot be prior to the initial extramedullary disease assessment date.

Time to VGPR (TTVGPR) and time to CR (TTCR) are also defined similar to TTR but for participants with BOR of VGPR or better and sCR/CR, respectively.

3.2.7. Duration of Response

Duration of Response (DOR) is defined for participants with confirmed objective response (sCR, CR, VGPR and PR) as the time from the first documentation of objective tumor response to the first documentation of confirmed PD per the IMWG response criteria or to death due to any cause, whichever occurs first.

3.2.8. PK

Drug concentrations of elranatamab will be measured using validated methods.

The PK parameters estimated for C0D1 and C1D1 will be derived from the concentration-time data as described in Table 3 using standard noncompartmental methods. Actual sample collection times will be used for the parameter calculations. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 3. Definition of PK Parameters

Parameter	Definition	Method of Determination
AUC_{τ}	Area under the concentration-time profile from time zero to the time τ, the dosing interval (τ = 1 week)	Linear/Log trapezoidal method
AUC_{inf} [a)]	Area under the concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis and k_{el} is a terminal phase rate constant.
C_{min} [b)]	Lowest concentration observed during the dosing interval	Observed directly from data

Parameter	Definition	Method of Determination
C_{max}	Maximum observed concentration over the dosing interval	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$ a)	Terminal elimination half-life	$Log_e(2)/k_{el}$, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F a)	Apparent clearance	$Dose/AUC_{inf}$ following a single dose and $Dose/AUC_{\tau}$ following multiple dosing
V_z/F a)	Apparent volume of distribution during terminal phase	$Dose/(AUC_{inf}*k_{el})$ following a single dose and $Dose/(AUC_{\tau}*k_{el})$ following multiple dosing

a) if data permit
b) PK parameters are calculated for C1D1 only

3.2.9. Immunogenicity Data

For the immunogenicity data, the percentage of subjects with positive antidrug antibodies (ADA) of elranatamab will be further characterized in terms of antibody specificity. Samples may also be analyzed for the presence of neutralizing antibodies (NAb).

3.2.10. Minimal Residual Disease

Minimal residual disease (MRD) negativity rate is defined as the proportion of participants with negative MRD per IMWG sequencing criteria by bone marrow aspirate (BMA) from the first date of the study intervention until the first documentation of confirmed PD, death or start of a new anticancer therapy, whichever occurs first.

MRD negativity will be defined by two thresholds, 10^{-5} and 10^{-6} if applicable.

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3.4. Baseline Variables

Baseline will be defined as the last non-missing assessment prior to the first date of study intervention. An assessment on C0D1 is assumed to be pre-dose of study intervention unless otherwise specified.

The following variables will be collected during screening period.

- Demographics (gender, age and race)
- Myeloma history
- Medical history

3.5. Safety Endpoints

In addition to safety endpoints described in Section 3.2.1 and Section 3.2.2, electrocardiograms (ECGs), temperature, blood pressure (BP), pulse rate and continuous cardiac monitoring will also be reviewed on an ongoing basis during the study to evaluate the safety of participants.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

4.1. Safety Analysis Set

A safety analysis set (SAS) will include all enrolled participants who receive at least 1 dose of study intervention. The SAS will be the default analysis set used for all safety analyses unless otherwise specified.

4.2. Per Protocol Analysis Set (evaluable for RP2D)

The per protocol analysis set (PPS) will include all enrolled participants who had at least 1 dose of study intervention and either experienced DLT or do not have major treatment deviations during the DLT observation period. Replaced participants will be excluded from the PPS. The PPS will be the default analysis set used for DLT evaluation.

4.3. PK Analysis Sets

4.3.1. PK Parameter Analysis Population

The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest.

4.3.2. PK Concentration Population

The PK concentration population is defined as all enrolled participants who are treated and have at least 1 analyte concentration.

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4.5. Immunogenicity Analysis Set

The immunogenicity analysis set includes all enrolled participants who receive at least 1 dose of study intervention and have at least 1 sample tested for ADA.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses in this study so that no formal statistical testing will be performed.

5.1.1. Confirmation of the RP2D with the Priming Dose

If there is either no DLT in the initial 4 participants or one DLT in 6 participants, the RP2D with the priming dose will be confirmed. If DLT observed in ≥2 of the initial 4 participants or ≥2 of 6 participants, a lower dose level may be explored, if deemed necessary.

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Binary data will be summarized using the frequency table (the number of patients, frequency and percentage). A Clopper-Pearson confidence interval (CI) of estimated proportion will also be presented as needed.

5.2.2. Analyses for Continuous Endpoints

Continuous data will be summarized descriptively (the number of patients, mean, standard deviation, minimum, median and maximum) unless otherwise specified.

5.2.3. Analyses for Categorical Endpoints

Categorical data will be summarized using the frequency table (the number of patients, frequency and percentage). A Clopper-Pearson CI of estimated proportion will also be presented as needed.

5.2.4. Analyses for Time-to-Event Endpoints

Time-to-event data will be summarized using a data listing and/or be presented graphically such as a swimmer plot due to a small sample size. Time-to-event data may be summarized using the Kaplan-Meier method and estimated survival curves may be displayed graphically when appropriate. A censoring rule for each endpoint is described in Section 6.

5.3. Methods to Manage Missing Data

Missing safety data will be handled according to Pfizer standards. Other missing data except for PK will be excluded from the tabular summaries.

5.3.1. PK

5.3.1.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

5.3.1.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of the median values at each time point, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (i.e. not done) or NS (i.e. no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

5.3.1.3. PK Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie, not calculated). Note that NC values will not be generated beyond the day that a participant discontinues.

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. DLT

The PPS will be used to assess DLTs.

The number and percentage of participants with DLTs will be presented. AEs constituting DLTs will be listed including DLT start/end date (both actual and study day), cycle, severity, outcome, action taken and causality. Also refer to Section 3.1.1.

6.2. Secondary Endpoints

6.2.1. AE

The SAS will be used for all summaries of AEs.

AEs (except CRS and immune effector cell-associated neurotoxicity [ICANS]) will be graded by the investigator according to the CTCAE version 5.0. CRS and ICANS will be graded by the investigator according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The focus of AE summaries will be on TEAEs. The number and percentage of participants who experienced any TEAEs (all causality and treatment-related), TEAEs leading to death (all causality and treatment-related), TEAEs leading to permanent discontinuation (all causality), TEAEs leading to dose interruption (all causality), TEAEs leading to dose reduction (all causality), TEAEs leading to dose interruption or reduction (all causality) and serious AEs (SAEs) (all causality and treatment-related) will be summarized according to worst toxicity grades. The summaries will present TEAEs both on the entire study period and by cycle (Cycle 0, Cycle 1 and cycles beyond 1). For all the AE summaries by system organ class (SOC) and preferred term (PT), or PT only, the following cytopenias will be clustered. Each participant will be counted only once within each SOC and clustered terms. However, the number of total events will be based on the individual PTs.

- Thrombocytopenia (PT = Thrombocytopenia, Platelet count decreased)
- Anaemia (PT = Anaemia, Haemoglobin decreased, Red blood cell count decreased, Haematocrit decreased, Normochromic anaemia, Normocytic anaemia, Normochromic normocytic anaemia)
- Neutropenia (PT = Neutropenia, Neutrophil count decreased, Neutrophil percentage decreased, Cyclic neutropenia, Agranulocytosis, Granulocytopenia, Granulocyte count decreased)
- Leukopenia (PT = Leukopenia, White blood cell count decreased)
- Lymphopenia (PT = Lymphopenia, Lymphocyte count decreased, Lymphocyte percentage decreased, CD4 lymphocytes decreased, CD4 lymphocyte percentage decreased, CD8 lymphocytes decreased, CD8 lymphocyte percentage decreased)

6.2.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) include CRS, ICANS and peripheral neuropathy.

Table 4. AESI

AESI	Definition
CRS	PT coded as “Cytokine release syndrome” and collected on the AE CRF page

Table 4. AESI

AESI	Definition
ICANS	PT coded as "Immune effector cell-associated neurotoxicity syndrome" and collected on the AE CRF page
Peripheral Neuropathy	Peripheral neuropathy standardized MedDRA queries (SMQ) (narrow and broad excluding PTs included in the Guillain-Barre syndrome SMQ (narrow)) and Guillain-Barre syndrome SMQ (narrow)

All the analyses will be performed for each individual AESI separately. The number and percentage of participants who experienced any AESI (all causality), AESI leading to permanent discontinuation (all causality), AESI leading to dose interruption (all causality), AESI leading to dose reduction (all causality), AESI leading to dose interruption or reduction (all causality) and serious AESI (all causality) will be summarized according to worst toxicity grades. Further, had >1 AESI (for CRS and ICANS only; all causality) and peripheral neuropathy with outcome as resolved (all causality) will also summarized. If there are >1 AESI with different grades, it will be considered as one event. In addition, time to onset of the AESI and time to resolution of the AESI will be separately summarized with descriptive statistics by each AESI. For CRS and ICANS, time relative to dose (ie, after the first dose, after the second dose, after >2 doses) will be summarized descriptively.

A summary of CRS and ICANS as collected from "CRS AE", "ICANS" and "ICE" CRFs will be provided. The most severe symptom will be summarized if participants have multiple occurrences of AESI symptoms. In addition, the number and percent of participants with CRS or ICANS who received tocilizumab/steroids (from Concomitant Medications CRF) will be summarized. A listing of CRS and ICANS with supportive information will also be provided.

For peripheral neuropathy, peripheral neuropathy TEAEs by PT and maximum severity grade (all-causality and treatment-related), and medical history for participants with peripheral neuropathy will be provided.

6.2.1.2. Other Adverse Events of Clinical Interest

Other adverse events of clinical interest (oAECI) include infections and cytopenias.

Table 5. oAECI

oAECI	Definition
Infection	SOC coded as "Infections and infestations"

Table 5. oAECI

oAECI	Definition
Cytopenias	PTs coded as either of the following terms: “Cytopenia", "Bicytopenia”, “Pancytopenia”, “Full blood count decreased”, “Bone marrow failure”, “Myelosuppression”, “Red blood cell count decreased”, “Haematocrit decreased”, “Haemoglobin decreased”, “Anaemia”, “Normochromic anaemia”, “Normocytic anaemia”, “Normochromic normocytic anaemia”, “Leukopenia”, “Agranulocytosis”, “Granulocytopenia”, “Granulocyte count decreased”, “White blood cell count decreased”, “Neutropenia”, “Neutrophil count decreased”, “Neutrophil percentage decreased”, “Band neutrophil count decreased”, “Band neutrophil percentage decreased”, “Cyclic neutropenia”, “Metamyelocyte count decreased”, “Lymphopenia”, “Lymphocyte count decreased”, “Lymphocyte percentage decreased”, “Thrombocytopenia”, “Platelet count decreased”, “Platelet production decreased”
Injection site reactions	HLT coded as “Injection site reactions”
Secondary malignancies	SOC coded as “Neoplasms benign, malignant and unspecified (incl cysts and polyps)”

All the analyses will be performed by each individual oAECI separately. For cytopenias, the individual PTs (ie, not clustered terms) will be reported in the summary.

The number and percentage of participants who experienced any oAECI (all causality and treatment-related), oAECI leading to permanent discontinuation (all causality), oAECI leading to dose interruption (all causality), oAECI leading to dose reduction (all causality), oAECI leading to dose interruption or reduction (all causality) and serious oAECI (all causality and treatment-related) will be summarized according to worst toxicity grades. In addition, time to onset of the oAECI and time to resolution of the oAECI will be separately summarized with descriptive statistics by each oAECI.

6.2.1.3. Deaths

The number and percentage of participants who died at any time, who died within 28 days of the first dose of study intervention and who died within 90 days after the last dose of study intervention as well as the primary reason for death will be tabulated.

Date and cause of death will be provided in individual participant data listing together with selected dosing information.

In addition, deaths due to COVID-19 may be presented in a separate listing if there is significant impact of COVID-19.

6.2.2. Laboratory Test Abnormalities

The SAS will be used to evaluate laboratory tests.

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle

(Cycle 0, Cycle 1 and cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

An evaluation of drug-induced serious hepatotoxicity (eDISH) plot showing the following laboratory test items will be created:

- Peak serum ALT vs peak total bilirubin
- Peak serum AST vs peak total bilirubin

CCI [redacted]

6.2.3. BOR

The SAS will be used for BOR.

Response rate of CR, OR and CB will be calculated along with two-sided 95% CIs. Disease response will be presented in the form of patient data listings that include, but are not limited to disease response at each visit and best overall response. In addition, progression date, death date, date of the first response, the last disease assessment date and the date of the last contact will be listed. A swimmer plot will also be generated.

6.2.4. PFS

The SAS will be used for PFS.

PFS will be censored on the date of the last adequate disease assessment for participants who do not have an event, on the date of the last adequate disease assessment before the new anticancer therapy for participants who start a new anticancer therapy prior to an event, or on the date of the last adequate disease assessment before the gap for participants with an event after a gap of 2 or more missing disease assessments. Participants who do not have an adequate post-baseline disease assessment will be censored on the first date of the study intervention unless death occurs on or before the time of the second planned disease assessment in which case the death will be considered an event.

A data listing of PFS will be provided. A swimmer plot will be generated. Although a summary table is not planned to be generated due to a small sample size, it may be provided using the Kaplan-Meier method as appropriate.

In addition, duration of follow-up time will be summarized with simple descriptive statistics as well as with the reverse Kaplan-Meier method.

6.2.5. OS

The SAS will be used for OS.

OS for participants not known to have died are censored on the date of the last known alive.

A data listing of OS will be provided. A swimmer plot will be generated. Although a summary table is not planned to be generated due to a small sample size, it may be provided using the Kaplan-Meier method as appropriate.

In addition, duration of follow-up time will be summarized with simple descriptive statistics as well as with the reverse Kaplan-Meier method.

6.2.6. TTR

The SAS will be used for TTR, TTVGPR and TTCR. In TTR summary, participants whose BOR are PD, stable disease (SD), MR or deaths will be excluded. Similarly, participants whose BOR are PD, SD, MR, PR or deaths will be excluded from the summary of TTVGPR, and participants whose BOR are other than sCR/CR will be excluded from the summary of TTCR.

A data listings of TTR, TTVGPR and TTCR will be provided.

6.2.7. DOR

The SAS will be used for DOR. In DOR summary, participants whose BOR are PD, clinical relapse, SD or MR will be excluded.

DOR will be censored on the date of the last adequate disease assessment for participants who do not have an event, on the date of the last adequate disease assessment before the new anticancer therapy for participants who start a new anticancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments.

A data listing of DOR will be provided. A swimmer plot will be generated. Although a summary table is not planned to be generated due to a small sample size, it may be provided using the Kaplan-Meier method as appropriate.

In addition, duration of follow-up time will be summarized with simple descriptive statistics.

6.2.8. PK Analyses

6.2.8.1. PK Concentrations

The PK concentration population will be used to summarize PK concentrations.

The concentrations of elranatamab will be summarized by descriptive statistics (as described in Table 6) by cycle and nominal time. Individual participant and median profiles of the concentration time data will be plotted by cycle using nominal times for only Cycle 0 and Cycle 1. Median profiles will be presented on both linear-linear and log-linear scales.

In addition, plot (linear and log scale) of the predose concentrations by cycle and day within cycle will be provided for each dose, on the same plot, in order to assess the attainment of steady-state.

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

6.2.8.2. PK Parameters

The PK parameter analysis population will be used to summarize PK parameters.

The PK parameters will be summarized descriptively by cycle and will include the set of summary statistics as specified in the table below:

Table 6. PK Parameters to be Summarized Descriptively

Parameter	Summary statistics
AUC_{inf}, AUC_{τ}, C_{min}, C_{max}, CL/F, and V_z/F	N, arithmetic mean, median, coefficient of variation (CV%), standard deviation, minimum, maximum, geometric mean, geometric CV%
$t_{½}$	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum
T_{max}	N, median, minimum, maximum

Presentations for elranatamab concentrations will include:

- A listing of all concentrations sorted by participant ID, cycle and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by each nominal time post-dose, cycle where the set of statistics will include n, mean, median, standard deviation, CV%, minimum, maximum, geometric mean, and geometric CV% and the number of concentrations above the lower limit of quantification.

- Median concentrations against nominal time post-dose by cycle, with all cycles presented on the same plot. Two plots will be generated, so that the concentrations can be presented on linear and logarithmic scales.

- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose.

- For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used

To assess the relationship between the PK parameters and dose, C_{max} and AUC_{τ} will be plotted across cycles on linear scale, and will include individual participants values and the geometric means. Geometric means will have a different symbol than the individual values.

6.2.9. Analysis of Immunogenicity Data

The immunogenicity analysis set will be used to assess immunogenicity data.

For the immunogenicity data, the percentage of participants with ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-baseline will be generated. Any data related to NAb will be similarly summarized. For participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit. The potential impact of immunogenicity on PK and clinical response including PD markers, safety/tolerability and efficacy of ADA will be explored, if warranted by the data.

6.2.10. MRD

The SAS will be used for MRD unless otherwise specified.

The MRD negativity rate will be calculated along with the 2-sided 95% CI as follows:

- MRD negative with confirmed sCR/CR,
- MRD negative based on the subset who achieved confirmed sCR/CR,
- MRD negative based on the subset who achieved confirmed sCR/CR among evaluable participants who have at least one MRD assessment.

CCI [redacted]

CCI [redacted]

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

The SAS and PPS will be used to summarize baseline characteristics, separately. In case these 2 analysis sets are completely the same set, summaries using the PPS may be omitted.

Baseline characteristics such as demographics, prior line of therapy, medical history, disease characteristics (baseline relapse or refractory, baseline cytogenetic risk, IMWG MM Diagnosis Criteria, baseline bone marrow plasma cells, ECOG performance status, extramedullary disease, type of measurable disease at baseline, current disease stage by Revised Multiple Myeloma International Staging System (R-ISS), renal function and liver function) will be tabulated and listed. Further, the following baseline disease characteristics will be summarized by descriptive statistics:

- Time since first diagnosis (months), defined as (date of the first dose of study intervention - date of the first diagnosis) / 30.4375;
- Time since onset of current episode, defined as (date of the first dose of study intervention - date of the onset of current episode) / 30.4375.

6.4.2. Study Conduct and Participant Disposition

The total number of enrolled participants, the number of participants who completed/discontinued the treatment/study and the reason for any premature discontinuation from the treatment/study will be presented. In addition, the number of participants in each analysis set also be provided.

6.4.3. Study Treatment Exposure

The SAS will be used to summarize participant exposure to study intervention.

The following will be summarized:

- Duration of treatment (weeks),
- Number of cycles started per participant,
- Number (%) of participants starting a cycle,
- Total cumulative dose (mg),
- Overall dose intensity (mg/week),
- Overall relative dose (%), and
- Overall relative dose intensity (%).

The duration of treatment will be calculated as follows:

Duration of treatment (weeks) = ((last non-zero dose date) - (first dose date) + 1) / 7.

The total cumulative dose will be calculated as the sum of the actual doses (mg) that the participant received during the study.

The overall dose intensity will be calculated as follows:

Overall dose intensity (mg/week) = (total cumulative dose) / Ceiling(((last zero/non-zero dose date) - (first dose date) + 1) / 7).

In the expression above, "Ceiling" denotes a ceiling function.

The total planned dose is defined as follows:

Total planned dose (mg) =
0.6 × (baseline body weight) +
Sum(Ceiling(((last zero/non-zero QW dose date in a QW interval) - (first QW dose date in the same interval) + 1) / 7) × (body weight used to calculate an actual dose)) +
Sum(Ceiling(((last zero/non-zero Q2W dose date in a Q2W interval) - (first Q2W dose date in the same interval) + 1) / 14) × (body weight used to calculate an actual dose)).

In the expression above, "Sum" denotes a summation. If a participant experiences either a weight loss or gain >10% compared to weight used to calculate a prior dose within a QW/Q2W interval, the interval will be split based on weight used to calculate actual doses. If a participant never receives a Q2W dosing, the third term in the right-hand side of expression will put zero. If a patient continues the study, the latest date of either the last QW dose date or the last Q2W dose date will be replaced by the data cutoff date.

The overall relative dose will be calculated as follows:

Overall relative dose (%) = (total cumulative dose) / (total planned dose) × 100.

The planned duration of treatment is calculated as follows:

Planned duration of treatment (weeks) = ((date of permanent treatment discontinuation or data cutoff date, whichever occurs first) - (first dose date) + 1) / 7.

The overall planned dose intensity (mg/week) will be calculated as follows:

Overall planned dose intensity (mg/week) = (total planned dose) / Ceiling(planned duration of treatment).

Last of all, the overall relative dose intensity will be calculated as follows:

Overall relative dose intensity (%) = (overall dose intensity) / (overall planned dose intensity) × 100.

6.4.4. Concomitant Medications and Nondrug Treatments

The SAS will be used to summarize concomitant medications and non-drug treatments.

Summary of concomitant medications will include the frequency and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category.

Summary of non-drug treatments will include the frequency and percentage of patients by MedDRA preferred term.

6.4.5. Prior Anticancer Therapy

The SAS will be used to summarize prior anticancer therapy.

Prior anticancer drugs will be coded in the WHO Drug coding dictionary and will be summarized by PT. A participant will be counted only once within a given PT, even if he or she received the same medication at different times.

The number and percentage of participants in each of the following anticancer therapy categories will be tabulated:

- Number of prior anticancer therapy lines (descriptive statistics, as well as broken down in categories by the number of prior lines),
- Prior IMiDs and type,
- Prior PI and type,
- Prior anti-CD38 mAb and type,
- Participants who are triple-class exposed,
- Participants who are triple-class refractory,
- Participants who are penta-drug exposed,
- Participants who are penta-drug refractory,
- Participants with prior stem cell transplant and type, and
- Prior BCMA-targeted therapy.

Prior anticancer drug therapy will be summarized as follows based on the number and percentage of participants:

- Best overall response on the last prior anticancer therapy line received, and
- Reason for stopping the last prior therapy.

6.4.6. Subsequent Anticancer Therapy

The SAS will be used to summarize subsequent anticancer therapy.

Subsequent anticancer drug treatment will be coded in the WHO Drug coding dictionary and will be summarized by PT.

Number and percentage of participants with any anticancer therapy after discontinuation of study intervention will be tabulated overall and by type of therapy.

6.5. Safety Summaries and Analyses

6.5.1. Vital Signs

Vital signs (temperature (axillary), BP and pulse rate) and body weight will be presented by data listing.

6.5.2. Electrocardiograms

The analysis of ECG results will be based on participants in the SAS with baseline and on treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for HR using Fridericia's correction (QTcF). Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF. Individual QT (all evaluated corrections) intervals will be listed by time.

The number and percentage of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated:

Table 7. Safety QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	≥450–480	>480–500	>500
Increase from baseline		30–60	>60

In addition, the number and percentage of participants with uncorrected QT values >500 msec will be summarized.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 msec value in appropriate clinical context. However, values from individual tracings

within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time matched baseline triplicate values on Day 1, or the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

6.5.3. Other Safety Data

The SAS will be used to summarize any additional safety data.

Serum/urine pregnancy test results will be presented in the listings.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment. Further, ad-hoc analyses may be performed due to a regulatory submission outside Japan.

8. APPENDICES

Appendix 1. IMWG Response Criteria for MM

All response categories require two consecutive assessments made any time before starting any new therapy. Participants must have measurable disease at enrolment (study entry).

Measurable disease is defined as:

- Serum M-protein ≥0.5 g/dL (5 g/L);
- Urine M-protein ≥200 mg/24 h;
- Serum free light chain (FLC) assay: involved FLC level ≥100 mg/L (10 mg/dL) provided serum FLC ratio is abnormal.

Whenever more than one parameter is used to assess response, the overall assigned level of response is determined by the lower or lowest level of response. Participants will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; participants cannot move to a lower response category.

Table 8. IMWG Response Criteria for MM

Response	IMWG Criteria [a]
Stringent Complete Response (sCR)	• Complete response as defined below plus normal FLC ratio 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). [b] • In patients whereby the only measurable disease is by serum FLC levels, sCR is defined as normal FLC ratio of 0.26 to 1.65 plus absence of clonal cells in bone marrow as defined above.
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. [c] • In patients whereby the only measurable disease is by serum FLC levels, CR is defined as normal FLC ratio of 0.26 to 1.65 plus criteria listed above.
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/24 h. • In patients whereby the only measurable disease is by serum FLC levels, VGPR is defined as a ≥90% decrease in the difference between involved (tumor) and uninvolved (non-tumor) serum FLC levels.

Table 8. IMWG Response Criteria for MM

Response	IMWG Criteria [a]
Partial Response (PR)	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/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 (SPD) [d] 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%–89%. In addition to the above listed criteria, if present at baseline, a 50% reduction in the size (SPD) [d] of soft tissue plasmacytomas is also required.
No Change/Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease.

Progressive Disease (PD)	• Increase of ≥25% from lowest response value in any one or more of the following:
	  • 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 [d] 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 per μL) if this is the only measure of disease

Clinical Relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder; • 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 [d] of the measurable lesion; • Hypercalcemia (>11 mg/dL); • Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-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.

Table 8. IMWG Response Criteria for MM

Response	IMWG Criteria [a]

a. All response categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. To confirm response or PD, two discrete samples are required, and testing cannot be based upon the splitting of a single sample. In the IMWG criteria, CR patients must also meet the criteria for PD shown here to be classified as PD for the purposes of calculating time to progression and progression free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression free survival. Patients will be considered to have PD if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.

b. Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

c. Confirmation with repeat bone marrow biopsy is not required. Careful attention should be given to new positive immunofixation results appearing in patients who have achieved a complete response, when the isotype is different. This probably represents oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.

d. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or dedicated CT scans where applicable. Measurement of tumor size will be determined by the SPD.

Appendix 2. IMWG MRD Criteria

MRD tests should be initiated only at the time of suspected complete response. Confirmation with two consecutive assessments is not required.

Table 9. IMWG MRD Criteria

Response	IMWG Criteria
Sustained MRD-negative[1]	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).
Flow MRD-negative[2]	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (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 two 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 or higher.
Imaging negative 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; MRD = minimal residual disease; NGF = next generation flow cytometry; NGS = next generation sequencing; PET = positron emission tomography; SUV = standardized uptake value.

1. Sustained MRD negativity, when reported, should also annotate the method used (eg, sustained sequencing MRD-negative).
2. Bone marrow multiparametric flow cytometry should follow NGF guidelines. The reference NGF method is an eight color two tube approach, which has been extensively validated. The two tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The complete eight color method should use a lyophilized mixture of antibodies. Five million cells should be assessed. The method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	antidrug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical
AUC_{last}	concentration versus time curve
BCMA	B-cell maturation antigen
BMA	bone marrow aspirate
BLQ	below the limit of quantification
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C0D1	Cycle 0 Day 1
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CB	clinical benefit
CD38	cluster of differentiation 38
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
CR	complete response
CRP	c-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
DILI	drug induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response

Abbreviation	Term
ECG	Electrocardiogram
eDISH	evaluation of drug-induced serious hepatotoxicity
FLC	free light chain
HBV	hepatitis B virus
HCV	hepatitis C virus
ICANS	immune effector cell-associated neurotoxicity
IFN	interferon
IL	interleukin
IMID	immunomodulatory drug
IMWG	International Myeloma Working Group
ISR	injection site reactions
LDH	lactate dehydrogenase
LLQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MTD	maximum tolerated dose
NAb	neutralizing antibodies
NC	not calculated
NCI	National Cancer Institute
ND	not done
NGS	next-generation sequencing
NS	no sample
oAECI	other adverse events of clinical interest
OR	overall response
OS	overall survival
PD	pharmacodynamics
PD	progressive disease
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetics
PPS	per protocol analysis set
PR	partial response
PT	preferred term
PT	prothrombin time

Abbreviation	Term
PT/INR	prothrombin time-international normalized ratio
PTT	partial thromboplastin time
QTcF	corrected QT (Fridericia method)
R-ISS	Revised Multiple Myeloma International Staging System
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
sCR	stringent complete response
SD	stable disease
sIL-2R	soluble interleukin-2 receptor
SMQ	standardized MedDRA queries
SOC	system organ class
$t_{½}$	terminal elimination half life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
TTR	time to response
TTCR	time to complete response
TTVGPR	time to very good partial response
VGPR	very good partial response
V_z/F	apparent volume of distribution during terminal phase
WBC	white blood cell