Protocol C1071003

AN OPEN-LABEL, MULTICENTER, NON-RANDOMIZED PHASE 2 STUDY OF ELRANATAMAB (PF-06863135) MONOTHERAPY IN PARTICIPANTS WITH MULTIPLE MYELOMA WHO ARE REFRACTORY TO AT LEAST ONE PROTEASOME INHIBITOR, ONE IMMUNOMODULATORY DRUG AND ONE ANTI-CD38 ANTIBODY

Statistical Analysis Plan
(SAP)

Version: 9

Date: 26 October 2022

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1. VERSION HISTORY

This SAP for study C1071003 is based on the protocol amendment 9 dated 29 July 2022 and to incorporate regulatory input.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 19 November 2020	Original 07 October 2020	N/A	N/A
2 30 March 2021	Amendment 2 14 February 2021	Regulatory input	• Section 3.5, definition of on-treatment period is updated. • Section 4: added two analyses sets for interim analyses and update definition of enrolled • Section 5.1.1: updated target ORR and power • Section 5.1.2: Clarified the scenario of crossing efficacy boundary for Cohort A • Section 5.2.5: updated the criteria for change in dosing schedule • Section 6.1.1: clarified types of PD in BOR derivations rules, analyses for CCR (sCR+CR), VGPR or better (sCR+CR+VGPR) are added • Section 6.4.2: Updated PRO analyses to be reported separately • Section 6.5: added subset analysis by ECOG PS • Section 6.6.1.1: removed age <18 for consistency with the updated inclusion criteria and added ethnicity; moved ECOG PS to Section 6.6.1.3 • Section 6.6.3: added cycle summary of study intervention exposure; updated the criteria for change in dosing schedule; added summary of breakdown of dose interruptions; removed total number of cycle started • Section 6.6.4: added summary of pre-medication • Section 6.7.1.1: added potential subset analysis of AESI by premedication in cycle 1 • Section 6.7.5 removed summary of QTcB and its definition; removed algorithm for change from baseline and multiple measurements

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Section 7: added interim safety assessments • Appendix 1: Added abbreviation for E-DMC • Study intervention has replaced study treatment across the document
3 29 June 2021	Amendment 6 30 May 2021	Regulatory Input	• Section 7: added interim safety assessments for GBS related, peripheral neuropathy/IR neurological events • Sections 3.5 and 6.7.2, the safety reporting period after • last dose of study intervention has been increased to 90 days. • Elranatamab has replaced PF-06863135 in the SAP • QTcF has been corrected. • Interim analysis set populations (for both cohort A and B) were further defined • Section 5.2.5: updated definition of cycle • Section 6.7.1: updated that TEAEs leading to dose interruptions and reductions will be based on the information collected on the exposure CRF. • EORTC QLQ CIPN20 added as PRO outcome • Update imputation rules for AE start/stop dates • Add summary of peripheral neuropathy, neurological examination, tocilizumab and steroids use for patients with CRS; • Additional subgroup analyses are added for sex, race, organ function, and penta refractory group. • Section 6.1.3 Additional analyses of BOR is added • Section 6.7.1.2 Other adverse event of clinical interest is added. • Analyses type is added in section 2.2 summary table • Details for safety endpoints were moved to section 3.5

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Summary of tocilizumab/ steroids usage for participants with CRS • Table 2 is updated to include PD in scenario 3,7,11,15, and 19 • Appendix 2 of list of cytopenias is added
4 20 October 2021	Amendment 6 30 May 2021	Blinded Data Review	• Clarified throughout that PD is confirmed PD for BOR, PFS, and DOR. • Section 6.1.1 Exact 95% CIs is added for BOR. • Section 6.1.3 Agreement rate (n, %) and Agreement for BOR (n, %) between BICR and investigator will be summarized by cohort. • Sections 6.2.3 and 6.2.4 Remove censoring for inadequate baseline for PFS and DOR to align with IMWG guidance. • Section 6.2.6 Add that Duration of follow- up will be summary with descriptive and with reverse Kaplan – Meier method. • Section 6.2.8 MRD negative rate is updated; sustained MRD negative and duration of MRD negative are updated in section 6.4.1. • Section 6.6.5 Transplant is added for subsequent anticancer therapy. • Section 6.7.1 AE by SOC and PT will be sorted by alphabetical order for SOC and by descending order of frequency, and AE grade presentation. • Cytopenias will be summarized in clusters. • Section 6.7.1.1 update AESI symptom for CRS, ICANS, Peripheral Neuropathy, and ICE scores. Peripheral Neuropathy is moved to AESI instead of oAECI. • Section 6.7.3 lab data for liver function at anytime are added; details of derive several CTCAE terms are provided. • Creatinine clearance calculation is added. • Section 6.7.5 QTcF will be derived and QTcF categories are updated by CTC.

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Section 6.6.3 Treatment duration, dose delay, dose intensity, and relative dose are updated. • Section 7.1.1 Disclosure IA results is clearly defined and updated. • Section 7.1.2 Grade 5 CRS and ICANS updated.
5 07 January 2022	Amendment 8 23 December 2021	Regulatory Input	• Section 3.4 Use last measurable pre-dose assessment for baseline for efficacy. • Sections 5.1.1, 5.1.2 The total number of planned participants was revised from 150 to 180 participants allowing for more robust datasets. Power/sample size calculations reverted back to be based on the exact method. Interim analyses (IA) revised to include a more robust data set (increased N from 60 to 90 for Cohort A) and added efficacy IA for Cohort B. IAs to be based on actual number with adequate follow-up at time of IA. The follow-up period for final analysis was revised. • Section 6.1.1 Align with IMWG and allow no minimum gap for confirmation of response as long as done with separate sample. • Section 6.1 Descriptive analysis for DOR follow-up added. • Section 6.2 Added time to VGPR and CR and defined MRD evaluable. • Section 6.2 Added if EMD at baseline, response cannot be confirmed until initial post-baseline EMD assessment. • Section 6.2 Clarified only adequate PK samples will be included in the analyses. • Section 6.5 Added EOS reason may be derived from EOT reason. • Section 6.6 Added clustering for hematologic AEs, injection site reactions and secondary malignancies as oAECI, deaths within 30 days of first dose, data handling rules for efficacy related labs, QTcF will be derived only. • Section 7.1 Updated the posterior probability threshold of ≥90% to ≥80% for Grade 3-4 CRS/ICANS and

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			Grade 4 treatment related nonhematologic for the interim safety assessments.
6 04 April 2022	Amendment 8 23 December 2021	Blinded Data Review	• Section 6.1 Added analyses for derived response for BICR and investigator. • Section 6.2 Added analyses for biochemical response. • Section 6.4 Clarified which responses for EMD participants require a post-baseline EMD assessment, remove landmark sMRD analyses.
7 14 April 2022	Amendment 8 23 December 2021	External environment (align with evolving MM landscape)	• Added key secondary endpoint ORR by BICR baseline EMD status for Cohort A. • Updated total enrolled participants.
8 08 July 2022	Amendment 8 23 December 2021	Blinded Data Review	• Added modifications to protocol section. • Section 6.2 Added time-to-event COVID-19 analyses. • Section 6.5 Added Cohort B specific subset analyses. • Section 6.6 Added Hypogammaglobulinemia as oAECI.
9 26 October 2022	Amendment 9 29 July 2022	Regulatory Input	• Clarified the final efficacy analysis is based on the final analysis evaluable set (same as the safety analysis set).

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1071003. 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.

Any deviations from this analysis plan will be described in the Clinical Study Report (CSR).

This study has two cohorts: Cohort A will enroll participants who are naïve to BCMA-directed therapies, and Cohort B will enroll participants who have prior exposure to BCMA-directed therapies. The planned interim analysis and final analysis of the primary endpoint for the respective cohort will include all data up to a data cutoff date which will be determined by the criteria as outlined in Section 5.1. If a cohort is stopped at its interim analysis, this interim analysis will be considered the final analysis of the primary endpoint for the cohort. All summaries and analyses associated with a planned analysis will include all data pertaining to visits/assessments performed up to and including the data cutoff date in the respective cohort.

Additional analyses of the non-efficacy data may be performed for publication and review. Additional analyses of the efficacy data may be provided per regulatory agency request/agreement.

As this is an open-label non-randomized study, the treatment is unblinded on participant level. However, the aggregate/cumulative efficacy data summary by cohort should be unavailable to the study team and the external investigators until the database snapshot for the primary analysis.

2.1. Modifications to the Analysis Plan Described in the Protocol

- Added key secondary endpoint ORR by BICR baseline EMD status for Cohort A.
- Updated total enrolled participants.
- Added final analysis evaluable set which is the same as the safety analysis set.

2.2. Study Objectives, Endpoints, and Primary Estimand

Type	Objectives	Endpoints
Primary		
Efficacy	• To determine the efficacy of Elranatamab in Cohort A and Cohort B	• ORR by BICR per IMWG.
Key Secondary		
Efficacy	• To determine additional efficacy of Elranatamab in Cohort A	• ORR by BICR baseline EMD status per IMWG.
Secondary		
Efficacy	• To determine additional efficacy of Elranatamab in Cohort A and Cohort B	• DOR by BICR and investigator per IMWG. • CRR by BICR and investigator per IMWG. • ORR by investigator per IMWG. • DOCR by BICR and investigator per IMWG. • PFS by BICR and investigator per IMWG. • OS. • TTR by BICR and investigator per IMWG. • MRD negativity rate (central lab) per IMWG.
Safety	• To determine the safety and tolerability of Elranatamab	• AEs and laboratory abnormalities as graded by NCI CTCAE v5.0. • Severity of CRS and ICANS assessed according to ASTCT criteria.[1]
PK	• To evaluate the PK of Elranatamab	• Pre- and postdose concentrations of Elranatamab.
Immunogenicity	• To evaluate the immunogenicity of Elranatamab	• ADAs and NAbs against Elranatamab.

Type	Objectives	Endpoints
Exploratory		
Efficacy	• To explore additional efficacy of Elranatamab in Cohort A and Cohort B	• sMRD-negativity, DOMRD negativity, and biochemical response rate.
Biomarker	• To explore the relationship between Elranatamab and the biology of the participant's MM	• Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens.
	• To explore correlations between Elranatamab exposure and efficacy, safety and biomarker endpoints, if data allow	• Selected PK, efficacy, safety and biomarker endpoints.
PRO	• To assess the impact of elranatamab on patient-reported symptoms and functioning	• EORTC QLQ-C30 and MY20. • EORTC QLQ CIPN20. • EQ-5D. • PGIS/PGIC.
	• To collect healthcare resource use data	• Hospitalizations, including length of stay, ICU admissions, transfusions, infections and outpatient visits.

Primary Estimand: The treatment effect of elranatamab on objective response rate (ORR) as assessed by blinded independent central review (BICR) per the International Myeloma Working Group (IMWG) criteria.[2] The estimand has the following attributes:

- Population: Relapsed/refractory multiple myeloma (RRMM) participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least one dose of study intervention.

- Variable: Objective response defined as confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) according to the IMWG criteria based on BICR assessment, from the date of first dose until the first documentation of confirmed progressive disease (PD), death or start of new anticancer therapy, whichever occurs first.

- Intercurrent events: All data collected after an intercurrent event of subsequent anticancer therapy will be excluded except if required to confirm PD. All response assessments regardless of gaps in disease assessments will be considered. Participants who do not have a post-baseline disease assessment due to early PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience PD, or stop disease assessments for any reason prior to achieving an objective response will be counted as non-responders in the assessment of objective response.

- Population-level summary measure: Objective response rate (ORR) defined as the proportion of participants in the analysis population with an objective response and 2-sided 95% confidence interval (CI) for ORR.

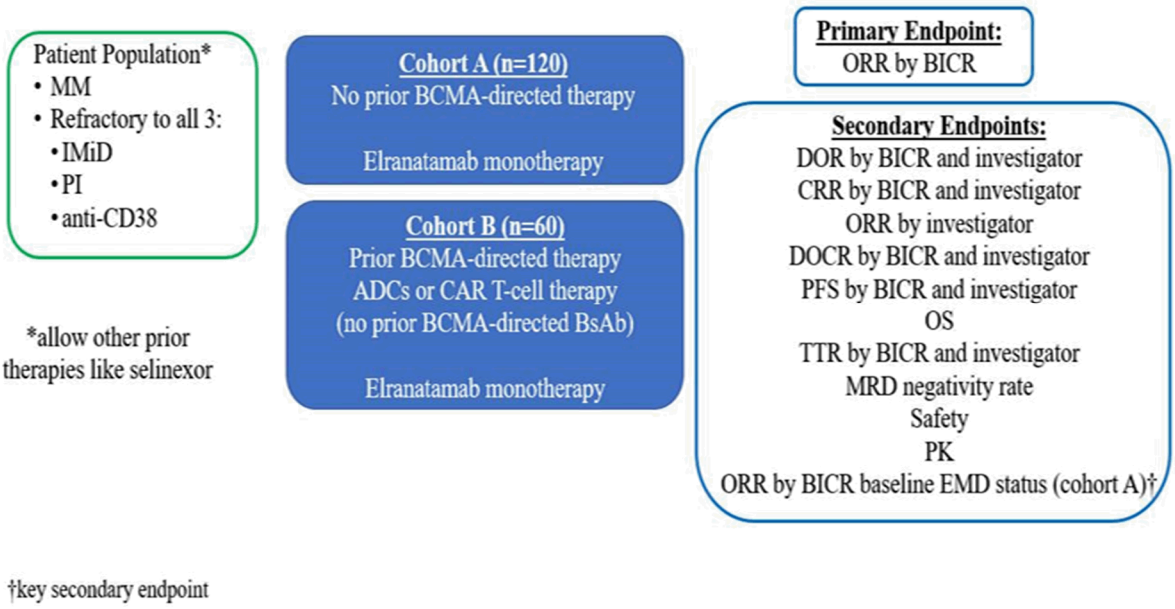
The key secondary estimand for ORR by BICR baseline extramedullary disease (EMD) status per IMWG for Cohort A is the same as the primary estimand except performed separately for participants with and without EMD at baseline per BICR.

2.3. Study Design

Study C1071003 is an open-label, multicenter, non-randomized, Phase 2 study to evaluate the efficacy and safety of elranatamab in RRMM participants who are refractory to at least one PI, one IMiD, and one anti-CD38 mAb. To determine the effects of prior BCMA-directed therapy on the response to elranatamab monotherapy, this study will enroll 2 independent and parallel cohorts, one with participants who are naïve to B-cell maturation antigen (BCMA)-directed therapies (Cohort A) and the other with participants who have been previously exposed to BCMA-directed therapy (Cohort B). The primary objective for each independent cohort will be to determine the efficacy (ie, ORR) of elranatamab as assessed by BICR, as defined by IMWG.

A schematic of the study design is presented in Figure 1.

Figure 1. Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

ORR by BICR is defined as the proportion of participants with an objective response by BICR per IMWG criteria.

Objective response is defined as having a best overall response (BOR) of confirmed sCR, CR, VGPR or PR per IMWG criteria. BOR will be assessed programmatically based on reported timepoint responses by BICR recorded at evaluation time points from the date of

first dose until confirmed disease progression, death or start of new anticancer therapy, whichever occurs first.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Objective Response Rate by BICR Baseline EMD Status

ORR by BICR baseline EMD status for Cohort A is defined the same as the primary endpoint except separately for participants with and without EMD at baseline per BICR.

3.2.1.2. Objective Response Rate by Investigator

ORR by investigator is defined as the proportion of participants with an objective response per IMWG criteria as assessed by investigator.

3.2.1.3. Complete Response Rate

Complete response rate (CRR) is defined as the proportion of participants with a BOR of confirmed sCR/CR per IMWG criteria.

CRR by BICR and CRR by investigator will be summarized separately.

3.2.1.4. Duration of Response

Duration of response (DOR) is defined, for participants with an objective response per IMWG criteria, as the time from the first documentation of objective response that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first.

DOR by BICR and DOR by investigator will be summarized separately.

3.2.1.5. Duration of Complete Response

Duration of complete response (DOCR) is defined, for participants with a sCR/CR per IMWG criteria, as the time from the first documentation of sCR/CR that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first.

DOCR by BICR and DOCR by investigator will be summarized separately.

3.2.1.6. Progression-free Survival

Progression-free survival (PFS) is defined as the time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause, whichever occurs first.

PFS by BICR and PFS by investigator will be summarized separately.

3.2.1.7. Overall Survival

Overall survival (OS) is defined as the time from the date of first dose until death due to any cause.

3.2.1.8. Time to Response

Time to response (TTR) is defined, for participants with an objective response per IMWG criteria, as the time from the date of first dose to the first documentation of objective response that is subsequently confirmed.

TTR by BICR and TTR by investigator will be summarized separately.

3.2.1.9. Minimal Residual Disease Negativity Rate

Minimal Residual Disease (MRD) (assessed by central lab) negativity rate is the proportion of participants with negative MRD per IMWG sequencing criteria by bone marrow aspirate (BMA) from the date of first dose until confirmed PD, death or start of new anticancer therapy, whichever occurs first.

3.2.2. Safety Endpoints

- Adverse events (AEs) and laboratory abnormalities as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

- Cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS) graded according to ASTCT criteria.[1]

3.2.3. Pharmacokinetic Endpoints

- Pre- and post-dose concentrations of elranatamab.

3.2.4. Immunogenicity Endpoints

- ADAs and NAbs against elranatamab.

3.3. Exploratory Endpoints

3.3.1. Additional Efficacy

- Sustained MRD (sMRD) negativity and duration of MRD (DOMRD) negativity.

3.3.2. Translational Oncology Biomarkers

- Measurements of biomarkers, consisting of DNA, RNA, protein or defined cell types, resulting from analyses of peripheral blood and/or tumor tissue biospecimen obtained at baseline, on treatment and/or at end-of-study.

3.3.3. Patient-reported Outcomes

- Patient-reported outcomes (PROs) are measured using the following instruments:

    - European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients core module (EORTC QLQ-C30): EORTC QLQ-C30 is a well-known, reliable and valid self-administered questionnaire used in oncology trials.[3,4] The QLQ-C30 contains 30 items and is grouped into five functional

scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/quality of life (QoL) scale. The questionnaire uses 4-point Likert scales with responses from "not at all" to "very much" to assess all functioning and symptoms items and two 7-point Likert scales for overall health and overall QoL. Responses to all items are then converted to a 0 to 100 scale using a standard scoring algorithm. Higher scores on the functional scales represent higher levels of functioning. Higher scores on the global health status/QoL scale represent higher health status/quality of life. Higher scores on symptom scales/items represent more extreme symptoms.

- European Organization for Research and Treatment of Cancer Multiple Myeloma module (EORTC QLQ-MY20): The QLQ-MY20 is a myeloma-specific module developed by the EORTC group specifically to assess quality of life in patients with multiple myeloma. It contains 20 items which use 4-point Likert scales, and are grouped into 2 functional scales (future perspective, body image) and 2 symptom scales (disease symptoms, side effects of treatment).[5]

- EuroQol EQ-5D (EQ-5D): The EQ-5D is a general health questionnaire consisting of 2 parts. The first part is a 5-item questionnaire designed to assess health status in terms of a single index value. It consists of 5 descriptors of current health state (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); participants are asked to rate each state on a three-level scale (1=no problem, 2=some problem, and 3=extreme problem). Published weights are available for converting the EQ-5D index to a single summary score ranging from -0.594 to 1, with low scores representing a higher level of dysfunction and 1 representing perfect health. The second part consists of a visual analogue scale: the EQ-VAS. The EQ-VAS records the participant's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

- Patient global impression of disease severity (PGIS)/patient global impression of change (PGIC): The PGIS is a single-item PRO designed to assess participant's overall impression of disease severity at a given point in time. The PGIC is a single-item PRO designed to assess the participant's overall sense of whether there has been a change in their disease since starting treatment. The PGIS and PGIC can be employed as anchors in responder analyses of other PRO instruments, to help interpret clinically meaningful changes in scores.

- European Organization for Research and Treatment of Cancer - chemotherapy-induced peripheral neuropathy (EORTC QLQ-CIPN20): The EORTC QLQ-CIPN20 is a module developed by the EORTC group to assess chemotherapy-induced peripheral neuropathy.[9] It contains 20 items which can be grouped into a sensory subscale (9 items), motor subscale (8 items) and autonomic subscale (3 items).

3.3.4. Healthcare Resource Utilization

- Hospitalizations, including length of stay, ICU admissions, transfusions, infections, and outpatient visits.

3.4. Baseline Variables

Start and end dates of study intervention:

The date of first dose (start date) of study intervention is the earliest date of nonzero dosing of the study drug.

The date of last dose of study intervention is the latest date of nonzero dosing of the study drug.

Definition of baseline:

No windowing will be applied when defining baseline. For example, the protocol requires safety assessments to be performed within 28 days prior to first dose; however, values outside this window will not be excluded when determining baseline assessments. Any deviations from the protocol specified window will be documented as protocol deviations. A separate definition of adequate baseline will be provided for disease assessment related efficacy endpoints.

For all endpoints, the last (measurable for efficacy) assessment performed on or prior to the date of the first dose of study intervention will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing. The screening EMD assessment will serve as the baseline assessment unless it is repeated by C1D1.

Participants who start treatment and discontinue from the study on the same day may have 2 different sets of data collected on Study Day 1 (one during study and one in the End of Treatment [EOT] visit). Data reported at the EOT visit are not eligible for baseline selection.

3.5. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)]. Anticancer therapy includes drug therapy, stem cell transplant, and radiation with curative intent; the start of new anticancer therapy after the first dose of study intervention is derived as outlined in Section 5.2.6. Adverse events occurring on the same day as the first dose of study intervention will be considered to have occurred during the on-treatment period. All other assessments which occur on the same day as the first dose of study intervention will be considered baseline assessments (see Section 3.4 for the definition of baseline).

Safety data collected after the on-treatment period as described above will be listed but not summarized.

3.5.1. Adverse Events

An adverse event is considered treatment-emergent relative to study intervention if the adverse event start date is during the on-treatment period (including on the date of first dose).

AEs will be as characterized by type, severity, timing, seriousness, and relationship to study intervention.

AEs (except CRS and ICANS) will be graded by the investigator according to the NCI CTCAE version 5.0. CRS and ICANS will be graded by the investigator according to the ASTCT criteria.[1] All AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs leading to dose interruption or dose reduction will be derived from the exposure CRF (dose adjustment reason as adverse event and actual dose taken of 0 for interruption and >0 for reduction) and then linked programmatically to the adverse event CRF by the AE identifier.

3.5.2. Laboratory Data

Hematology and chemistry results will be programmatically graded according to the NCI CTCAE version 5.0 for relevant parameters. A shift summary of baseline grade by maximum postbaseline grade will be presented. Parameters which cannot be graded will be summarized relative to the normal range (ie, normal range high or normal range low). Additional details are provided in Section 6.7.3.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following analysis sets are defined:

Defined Analysis Set	Description
Safety Analysis Set	The safety analysis set in each cohort will include all enrolled participants in the respective cohort who received at least one dose of study intervention. This will be the primary analysis population for evaluating participant characteristics, treatment administration/compliance and safety endpoints.
Final Analysis Evaluable Set	The final analysis evaluable set in each cohort will include all enrolled participants in the respective cohort who received at least one dose of study intervention. This will be the primary analysis population for evaluating efficacy endpoints. This is the same as the safety analysis set thus only the “safety analysis set” terminology will be used.
Interim Analysis Evaluable Set A	The interim analysis evaluable analysis set A will include the first 90 enrolled participants who received at least one dose of study intervention in Cohort A. This will be the primary analysis population for evaluating efficacy endpoints at the interim analysis for Cohort A.

Interim Analysis Evaluable Set B	The interim analysis evaluable analysis set B will include the first 30 enrolled participants who received at least one dose of study intervention in Cohort B. This will be the primary analysis population for evaluating efficacy endpoints at the interim analysis for Cohort B.
PK Analysis Set	The PK analysis set is a subset of the safety analysis set and will include participants who have at least one postdose concentration measurement.
Immunogenicity Analysis Set	The immunogenicity analysis set is a subset of the safety analysis set and will include participants who have at least one sample tested for ADA.
Biomarker Analysis Set	The biomarker parameter analysis set in each cohort is a subset of the safety analysis set and will include participants who have at least one baseline biomarker assessment. Analysis sets will be defined separately for biomarkers based on blood, saliva, and bone marrow samples.
PRO Analysis Set	The PRO analysis set in each cohort will include all participants in the safety analysis set who completed a baseline (last PRO assessment prior to or on the first dose of study intervention) and at least one post-baseline PRO assessment.
Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and was assigned to treatment. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.	

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

This study has two cohorts: Cohort A will enroll participants who are naïve to BCMA-directed therapies, and Cohort B will enroll participants who have prior exposure to BCMA-directed therapies. The primary objective of this study is to determine the efficacy in Cohort A and Cohort B with respect to ORR by BICR, as defined by IMWG.

In Cohort A, the study will test the null hypothesis that the ORR by BICR as defined by IMWG is ≤30% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >30%. In Cohort B, the study will test the null hypothesis that the ORR by BICR as defined by IMWG is ≤15% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >15%.

The sample size for Cohort A and Cohort B was calculated to provide adequate power for testing the statistical hypotheses regarding the primary endpoint of ORR independently in the two cohorts using a two-stage design based on exact binomial distribution. A total of 120 participants enrolled and treated in Cohort A provides approximately 98% power to detect a true ORR by BICR of 48% to reject the null hypothesis, with a 1-sided significance level of 0.025. Similarly, a total of 60 participants enrolled and treated in Cohort B provides

approximately 91% power to detect a true ORR by BICR of 34% to reject the null hypothesis, with a 1-sided significance level of 0.025.

At the time of the SAP amendment, 31% of Cohort A had EMD at baseline. If the null hypothesis for ORR by BICR is rejected for Cohort A, the key secondary endpoint of ORR by BICR for those without EMD at baseline will be tested in a hierarchical fashion using the gatekeeping procedure that the ORR is ≤38% with a 1-sided significance level of 0.025. If the null hypothesis for ORR by BICR for those without EMD at baseline is rejected for Cohort A, the key secondary endpoint of ORR by BICR for those with EMD at baseline will be tested in a hierarchical fashion using the gatekeeping procedure that the ORR is ≤12% with a 1-sided significance level of 0.025.

An interim analysis for both futility (non-binding) and efficacy will be conducted on ORR by BICR for Cohort A based on the first 90 participants enrolled and treated in that cohort, and for Cohort B based on the first 30 participants enrolled and treated in that cohort. Each respective interim analysis will occur no earlier than the point at which all early responders (ie, those who respond within the first 3 post-baseline assessments) among the participants to be included have had their responses confirmed.

5.1.2. Decision Rules

An interim analysis for both futility (non-binding) and efficacy will be conducted for the primary endpoint for Cohort A and Cohort B. At the time of the interim analysis, the testing rule based on an exact binomial test will depend on the actual number of participants included in the analysis for each cohort with sufficient follow-up.

At the time of the SAP amendment, enrollment had exceeded the 120 Cohort A and 60 Cohort B participants. At the time of the final analysis, the testing rule based on an exact binomial test will depend on the exact number of participants enrolled and treated in each cohort, respectively. Operating characteristics (Type I and Type II error) were calculated using the exact binomial distribution based on the current enrollment (see below). It can be noted that the futility and efficacy stopping boundaries for both cohorts at the interim analysis are equivalent to what would be induced if using the rho family beta-spending boundary with parameter = 3 and the rho family alpha-spending boundary with parameter = 5, respectively, when testing the results with an exact binomial test.

At the interim analysis for each cohort, accrual may be stopped for further evaluation due to futility; otherwise, the cohort will proceed as planned to the final analysis, and all ongoing participants will continue with scheduled visits per the schedule of activities in the protocol.

At the time of the SAP amendment, 94 Cohort A participants were initially dosed at least 4 months prior to the data cutoff and will be included in the interim analysis. The interim analysis will include a few participants with EMD at baseline who have insufficient follow-up for confirmed response. No interim analysis will be performed for Cohort B participants as not enough participants have adequate follow-up since Cohort B has a higher incidence of EMD at baseline compared to Cohort A. The boundaries at the final analysis for Cohort B do not change if no interim analysis is performed.

Cohort A: Operating Characteristics				
	Futility Criteria (responders/patients)	**Efficacy Criteria (responders/patients)**	**Cumulative alpha spent***	**Cumulative beta spent****
Interim Analysis	≤33/94	≥41/94	0.0036	0.0078
Final Analysis	≤47/123	≥48/123	0.0207	0.0204

* Cumulative alpha spent calculated assuming the null ORR of 0.30.

** Cumulative beta spent calculated assuming the target ORR of 0.48.

Cohort B: Operating Characteristics				
	Futility Criteria (responders/patients)	**Efficacy Criteria (responders/patients)**	**Cumulative alpha spent***	**Cumulative beta spent****
Interim Analysis	≤3/30	≥13/30	0.0002	0.0027
Final Analysis	≤15/64	≥16/64	0.0248	0.0471

* Cumulative alpha spent calculated assuming the null ORR of 0.15.

** Cumulative beta spent calculated assuming the target ORR of 0.34.

The final analysis of each cohort will be conducted once all participants have had at least 2 post-baseline response assessments or have otherwise discontinued response assessments within the first 2 months of treatment.

5.2. General Methods

Unless otherwise specified, disposition, baseline, concomitant medications, study intervention exposure data, and safety data will be summarized by cohort and with both cohorts combined. Efficacy data will be summarized by cohort only.

5.2.1. Data Handling After the Cutoff Date

Data after the cutoff date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations except to derive last contact date.

5.2.2. Pooling of Centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The ‘center’ factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants enrolled at each center.

5.2.3. Analyses to Assess the Impact of COVID-19 Pandemic

The study enrollment may start during the COVID-19 pandemic period. If so, data summaries and analyses may be performed to assess the impact of COVID-19 on the trial population and study data. Details of these summaries and analyses are included in the respective sections.

5.2.4. Definition of Study Day

The study day for assessments occurring on or after the first dose of study intervention (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start date of study intervention + 1.

The study day for assessments occurring prior to the first dose of study intervention (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start date of study intervention.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per participant. The definition for each cycle is driven by study drug elranatamab. Elranatamab is administered on Days 1, 8, 15 and 22 of each 28-day cycle. As described in Protocol Section 6.1.1, if a participant has received QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dosing interval will be changed from QW to Q2W. If the participant subsequently begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to weekly dosing. If the dose interval is changed, cycles should remain the same length (ie, 4-week cycles). In either dosing scenario, the nominal cycle length is 28 days.

- For Cycle 1, the actual cycle starts date is the date each participant receives the first non-zero study intervention;
- For all other cycles, the actual cycle start date for each participant is the earliest start date of dosing in the Cycle X Day 1 visit CRF exposure page;
- For all but the last cycle;
    - Actual cycle stop date is calculated as the start date of the next cycle minus 1 day;
    - Actual cycle duration is calculated from Day 1 of a cycle to the day prior to Day 1 of the next cycle, as follows:

        Actual Cycle Duration (weeks) = (cycle stop date – cycle start date + 1)/7
- For the last cycle, actual cycle duration is based on the actual cycle stop date which is last zero/non-zero dose date + (7 days if on QW or 14 days if on Q2W) – 1 day. If C1D4 is the last visit, cycle stop date is Day 7 if C1D4 occurred by then.

The cycle day will be calculated as:

Cycle day = Date of the assessment/event – cycle start date + 1.

5.2.6. Definition of Start of New Anticancer Therapy

Start date of new anticancer therapy (drug, radiation with curative intent, transplant) is used to determine the end of the on-treatment period (see Section 3.5) and for censoring in efficacy analyses (see Section 6.1).

The start date of new anticancer therapy is the earliest date after first dose date amongst the following:

- Start date of anticancer drug therapy recorded in the 'Next Anticancer Therapy (NXT CNCR)' eCRF pages;
- Start date of radiation therapy recorded in 'Concomitant Radiation' and 'Non-drug Treatments (NXT RAD)' eCRF pages;
- Start date of transplant recorded in 'Transplant details (TRANSPLT)' eCRF page.

When start date of anticancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using the data collected on the eCRF pages described above.

5.2.7. Date of Last Contact

The date of last contact will be derived for participants not known to have died at the data cutoff date using the latest complete date (ie, imputed dates will not be used in the derivation) among the following:

- All assessment dates (eg, blood draws [laboratory, Pharmacokinetics (PK)], vital signs, physical exam, performance status, ECG, Echocardiograms [ECHO]/multigated acquisition [MUGA] scans, disease assessments, etc.);
- Start and stop dates of concomitant therapies including non-drug treatments or procedures;
- Completion dates for PRO Questionnaires;
- Start and end dates of new therapies administered after study intervention discontinuation including systemic therapy, radiation, and surgeries;
- AE start and end dates;
- Last date of contact collected on the 'Survival Status' CRF (do not use date of survival follow-up assessment unless status is 'alive');
- Study intervention start and end dates;
- Date of discontinuation on disposition CRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed or dates when data were entered into the CRF will not be used.

5.2.8. Disease Assessment Date

The Date of Disease Assessment at each nominal timepoint as provided by the investigator on the IMWG response CRF page and by BICR will be utilized for the respective analyses.

5.2.9. Adequate Baseline Disease Assessment

Adequate baseline is defined using the following criteria:

- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and meeting criteria for measurable lesions, and non-missing lesions status at baseline for non-target lesions);
- Baseline lesions must be assessed with an acceptable method of tumor assessment as specified in the protocol (eg, PET/CT, CT or MRI);
- Measurable disease based on IMWG criteria as defined by at least 1 of the following:
  - Serum M-protein $\geq$0.5 g/dL by SPEP;
  - Urinary M-protein excretion $\geq$200 mg/24 hours by UPEP;
  - Serum immunoglobulin FLC $\geq$10 mg/dL ($\geq$100 mg/L) and abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

5.2.10. Adequate Post-baseline Disease Assessment

An adequate disease assessment is defined as an assessment where a time-point response of sCR, CR, VGPR, PR, minimal response (MR), Stable Disease (SD) or PD has been provided. Timepoints where the response is not evaluable or no assessment was performed will not be used for determining the censoring date for time-to-event endpoints including PFS, DOR and DOCR.

5.2.11. Nominal and Unscheduled Visits

For all algorithms and analyses, visit labels as specified on the CRF will be used as the nominal timepoint (ie, assessment will not be slotted).

Unless otherwise specified, unscheduled assessments will not be displayed in summary tables by nominal visit/timepoint. Unscheduled assessments will be used when deriving baseline and worst case on-treatment for safety and PRO analyses (except where noted for baseline ECGs). Additionally, unscheduled assessments will be used for efficacy analyses (eg, defining date of progression/censoring, best overall response, date of last contact).

5.2.12. Standard Deviations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]: (year of given informed consent – year of birth).
- The integer part of the calculated age will be used for reporting purposes.
- Body mass index (BMI) (kg/m^2) = weight (kg)/[height (m)]^2.

For reporting conventions, mean and median should generally be displayed 1 more decimal place than the raw data and standard deviation should be displayed to 2 more decimal places than the raw data. Percentages will be reported to 1 decimal place. The rounding will be performed to the closest integer/first decimal using the common mid-point between the 2 consecutive values. For example, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.13. Analyses for Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation, minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants still present in the study at that visit, unless otherwise specified.

5.2.14. Analyses for Time-to-Event Endpoints

Kaplan-Meier estimates (product-limit estimates) will be presented by cohort together with a summary of associated statistics including the median time with 2-sided 95% CIs. Probabilities of an event at particular timepoint will be estimated with corresponding 2-sided 95% CIs. The CI for the median will be calculated according to Brookmeyer and Crowley, 1982[6] and the CIs for the survival function estimates at particular timepoints will be derived using the log(-log) method.

If a cumulative incidence analysis is performed, the 25th, 50th, and 75th percentiles and probabilities of an event at particular points in time will be estimated from the cumulative incidence curve. Confidence intervals for the estimated probability of an event at a particular timepoint will be generated using the delta method with a log(-log) transformation for the standard error.

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Any imputations will occur at the analysis dataset level. Additionally, in all data listings imputed values will be presented and flagged as imputed.

Missing statistics, eg, when they cannot be calculated, should be presented as 'ND' for not done, 'NR' for not reached or 'NA' for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1. Missing Pharmacokinetic Data

Concentrations below the limit of quantification

For all calculations and figures, all concentrations assayed as below the limit of quantification (BLQ) will be set to zero. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' will be included as a footnote to the appropriate tables and figures. In listings BLQ values will be reported as below limit of quantification ("<LLOQ"), where LLOQ will be replaced with the corresponding value from the analytical assay used.

Deviations, missing concentrations and anomalous values

In summary tables, concentrations will be set to missing if one of the following cases is true:

- A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
- A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

At the discretion of the clinical pharmacologist, summary statistics may not be presented at a particular timepoint if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data. If less than 3 evaluable concentrations or PK parameters at a given timepoint are available, only minimum and maximum will be presented.

5.3.2. Missing ECG Data

For QTc analyses, no values will be imputed for missing data. If 1 or 2 of the triplicate measurements for an ECG parameter are missed, the average of the remaining 2 measurements or the single measurement, respectively, can be used in the analyses. If all triplicate measurements are missing at a timepoint for an ECG parameter, no values will be imputed for this timepoint. If the triplicate needs to be repeated because of an artifact, then the repeated triplicate will be reported on an unscheduled CRF page. Based on a review of the data, these unscheduled assessments may be used in place of the assessments at the nominal time. Data review and consultation with the study team is required to flag these cases.

5.3.3. Handling of Incomplete or Missing Dates

5.3.3.1. Adverse Events

AE Onset Date:

AE Onset Date: If the AE onset date is completely missing, and if the date of first dose is less than AE stop date, then the onset date will be assigned as the date of first dose. Otherwise if the date of first dose is after the AE stop date then the AE onset date will be imputed as the earliest of non-missing AE stop date or informed consent date.

AE Stop Date: If the AE stop date is completely missing then the stop date will be imputed as the latest of the participant withdrawal/completion date, death date, last dose of study intervention, or AE onset date.

5.3.3.2. Exposure

No imputation will be done for the first dose date. Date of the last dose of study intervention, if unknown or partially unknown, will be imputed as follows:

- If the last date of study intervention is completely missing and there is no End of Treatment (EOT) CRF page and no death date, the participant should be considered to be ongoing and use the data cutoff date for the analysis as the last dosing date; or
- If the last date of study intervention is completely or partially missing and there is either an EOT CRF page or a death date available (on or prior to the data cutoff date), then impute this date as the last dose date:
  - = 31DECYYYY, if only Year is available and Year <Year of min (EOT date, death date),
  - = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month <the month of min (EOT date, death date), or
  - = min (EOT date, death date), for all other cases.

5.3.3.3. Date of Death

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing, it will be imputed as the day after the date of last contact;
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death;
  - Missing day and month: January 1st of the year of death.

5.3.3.4. Date of Start of New Anticancer Therapy

Incomplete dates for start date of new anticancer therapy (drug therapy, radiation with curative intent, transplant) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of the on-treatment period. PD date below refers to PD date by investigator assessment. If the imputation results in an end date prior to the imputed start date, then the imputed start date should be set to the end date.

- The end date of new anticancer therapy will be included in the imputations for start date of new anticancer therapy. If the end date of new anticancer therapy is
    - completely missing then it will be ignored in the imputations below;
    - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anticancer therapy;
    - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anticancer therapy.
- For participants who have not discontinued study intervention at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date in the imputations below.
- If the start date of new anticancer therapy is completely or partially missing, then the imputed start date of new anticancer therapy is derived as follows:
    - Start date of new anticancer therapy is completely missing
        - Imputed start date = min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]
    - Only year (YYYY) for start of anticancer therapy is available
        - IF YYYY < Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]

            THEN imputed start date = 31DECYYYY;
        - ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]

            THEN imputed start date = min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]
        - ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]

THEN imputed start date = 01JANYYYY

- Both Year (YYYY) and Month (MMM) for start of anticancer therapy are available

  - IF YYYY = Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy], AND

    MMM < Month of min [max(PD date + 1 day, last dose of study intervention + 1 day), end date of new anticancer therapy]

    THEN imputed start date = DAY (Last day of MMM) MMM YYYY ;

  - ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy], AND

    MMM = Month of min [max(PD date + 1 day, last dose of study intervention + 1 day), end date of new anticancer therapy]

    THEN imputed start date = min [max(PD date + 1 day, last dose of study intervention + 1 day), end date of new anticancer therapy]);

  - ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy], AND

    MMM > Month of min [max(PD date + 1 day, last dose of study intervention + 1 day), end date of new anticancer therapy]

    THEN imputed start date = 01 MMM YYYY;

  - ELSE IF YYYY < Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]

    THEN imputed start date = DAY (Last day of MMM) MMM YYYY;

  - ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]

    THEN imputed start date = 01 MMM YYYY.

5.3.3.5. Other Dates

Imputation methods for other partial dates are as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date;
- If both the day and month are missing, the first day of the year is used;
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively;

- If the date is completely missing, no imputation will be performed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Main Analysis

The primary endpoint is ORR by BICR, defined as the proportion of participants with an objective response by BICR per IMWG criteria.

Estimand strategy: The analysis will consider intercurrent events of start of subsequent anticancer therapy (Section 2.2).

Analysis set: Safety Analysis Set (Section 4).

Intercurrent events and missing data: All data collected after an intercurrent event of subsequent anticancer therapy will be excluded except if required to confirm PD (Table 2). No imputations for missing data will be performed.

Analysis methodology: Point estimates of ORR will be calculated along with corresponding 2-sided exact 95% CIs using the Clopper-Pearson method.[7] The null hypotheses will be tested at 1-sided alpha of 0.025 using an exact binomial test independently in each cohort, and the corresponding 1-sided p-value will be provided separately for Cohort A and Cohort B.

In addition, the frequency (number and percentage) of participants with BOR by BICR in each response category and corresponding 2-sided exact 95% CIs will be summarized: sCR; CR; VGPR; PR; MR; SD; PD; Not evaluable (NE)/unknown.

In addition, the following response categories will be calculated along with corresponding 2-sided exact 95% CIs using the Clopper-Pearson method:

- VGPR or better (sCR + CR + VGPR);
- Clinical benefit (sCR + CR + VGPR + PR + MR).

BOR by BICR will be assessed programmatically based on reported timepoint responses by BICR recorded at evaluation time points from the date of first dose until confirmed disease progression using IMWG response criteria, death or start of new anticancer therapy, whichever occurs first. BOR needs to be confirmed according to IMWG response criteria (Table 2). If a participant meets multiple criteria in determining confirmed BOR, the order of criteria in this table will be used to define the hierarchy. Twenty-eight days is the scheduled gap between the disease assessments however if done on the same day, a different sample is required for confirmation. A confirmatory response assessment may be performed >28 days following the initial response assessment, allowing for a maximum of 1 intervening missing or not evaluable assessment.

The rules for PD confirmation apply to both confirmed PD as BOR and confirmed PD after BOR (for time-to-event analyses), and the PD date is the date of the initial PD assessment.

Table 2. Derivation Rules for Confirmed Best Overall Response per IMWG Response Criteria

Scenario	Timepoint Response at:			BOR
	Assessment 1	Assessment 2	Assessment 3	
1	sCR	sCR		sCR
2	sCR	NE	sCR	
3	CR/VGPR/PR/MR/SD/PD[c]	sCR	sCR	
4	CR	sCR/CR		CR
5	sCR/CR	CR		
6	CR	NE	CR	
7	VGPR/PR/MR/SD/PD[c]	CR	CR	
8	VGPR	sCR/CR/VGPR		VGPR
9	sCR/CR/VGPR	VGPR		
10	VGPR	NE	VGPR	
11	PR/MR/SD/PD[c]	VGPR	VGPR	
12	PR	sCR/CR/VGPR/PR		PR
13	sCR/CR/VGPR/PR	PR		
14	PR	NE	PR	
15	MR/SD/PD[c]	PR	PR	
16	MR	sCR/CR/VGPR/PR/MR		MR
17	sCR/CR/VGPR/PR/MR	MR		
18	MR	NE	MR	
19	SD/PD[c]	MR	MR	
20	SD	No further assessments		SD[a]
21	SD	sCR/CR/VGPR/PR/MR/SD/PD[c]	No further assessments	
22	sCR/CR/VGPR/PR/MR	NE/PD[c] or no further assessment	No further assessments	
23	PD[c]	sCR/CR/VGPR/PR/MR/SD	No further assessments	
24	PD[c]	PD (any reason) including PD after initiation of new anticancer therapy		PD
25	PD[c]	Participant died due to disease before further disease assessment (including death due to		

Scenario	Timepoint Response at:			BOR
	Assessment 1	Assessment 2	Assessment 3	
		disease under study after initiation of new anticancer therapy)		
26	PD[b]	sCR/CR/VGPR/PR/MR/ SD/NE/PD or no further assessments	No further assessments	
27	Death (due to disease under study)			
28	Death (not due to disease under study)			NE
29	NE	No further assessment		
30	NE	NE/PD[c]	No further assessments	
31	PD[c]	NE	No further assessments	

BOR= best overall response; EMD = extramedullary disease; IMWG = International Myeloma Working Group, sCR = stringent complete response, CR = complete response, PR = partial response, VGPR = very good partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

a. SD does not need to be confirmed.

b. PD due to EMD (includes any increased or new lesion), or bone marrow plasma cells does not need to be confirmed.

c. PD due to reasons other than EMD, or bone marrow plasma cells.

Note: category of "No Evidence of Disease" (NED) is not described in the IMWG criteria but is included in the BICR charter to cover uncommon scenarios of no measurable disease at baseline. For any such participants, post-baseline assessment of NED is equivalent to SD.

6.1.2. Sensitivity Analyses

If there are participants who are enrolled but not treated in a cohort, a sensitivity analysis of ORR by BICR in all participants enrolled may be performed in the cohort. In this analysis, the untreated participants will be treated as non-responders.

6.1.3. Additional Analyses of BOR

BICR vs Investigator Assessment:

Table 3 below outlines the possible BOR outcomes by investigator and BICR.

Table 3. Agreement of BOR Outcomes Between Investigator and BICR Assessments

BOR		BICR Assessment							
		sCR	CR	VGPR	PR	MR	SD	PD	NE
Investigator Assessment	sCR	n_{11}	n_{12}	n_{13}	n_{14}	n_{15}	n_{16}	n_{17}	n_{18}
	CR	n_{21}	n_{22}	n_{23}	n_{24}	n_{25}	n_{26}	n_{27}	n_{28}
	VGPR	n_{31}	n_{32}	n_{33}	n_{34}	n_{35}	n_{36}	n_{37}	n_{38}
	PR	n_{41}	n_{42}	n_{43}	n_{44}	n_{45}	n_{46}	n_{47}	n_{48}
	MR	n_{51}	n_{52}	n_{53}	n_{54}	n_{55}	n_{56}	n_{57}	n_{58}

BOR		BICR Assessment							
		sCR	CR	VGPR	PR	MR	SD	PD	NE
	SD	n_{61}	n_{62}	n_{63}	n_{64}	n_{65}	n_{66}	n_{67}	n_{68}
	PD	n_{61}	n_{72}	n_{73}	n_{74}	n_{75}	n_{76}	n_{77}	n_{78}
	NE	n_{81}	n_{82}	n_{73}	n_{84}	n_{85}	n_{86}	n_{87}	n_{88}

$\sum_{i=1}^{8}(n_{ii})$ is the number of agreements on BOR between BICR and Investigator

$\sum_{i,j=1}^{8}(n_{ij})$ for i ≠ j is the number of disagreements on BOR between BICR and Investigator

N= $\sum_{i,j}^{8}(n_{ij})$

The following measures of agreement (n, %) will be calculated for each cohort:

- Agreement rate for BOR = $\sum_{i=1}^{8}(n_{ii})\ /N$;
- Agreement rate for response =$[\sum_{i,j=1}^{4}(n_{ij}) + \sum_{i,j=5}^{8}(n_{ij})]/N$.

Agreement rates are calculated for each metric, the high concordance rate means high agreement between BICR and Investigator.

Agreement (n, %) for BOR between BICR and Investigator will be summarized for each cohort.

ORR before and after the switch to Q2W will be summarized.

6.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed in the Safety Analysis Set by cohort.

6.2.1. Objective Response by BICR baseline EMD Status

ORR by BICR baseline EMD status for Cohort A will be analyzed the same as the primary endpoint except separately for participants with and without EMD at baseline per BICR.

No sensitivity analyses will be performed.

6.2.2. Objective Response Rate by Investigator

Point estimates of ORR by investigator will be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method.[7] The frequency (number and percentage) of participants with BOR by investigator in each response categories will be summarized: sCR; CR; VGPR; PR; MR; SD; PD; NE.

In addition, the following response categories will be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method:

- VGPR or better (sCR + CR + VGPR);

- Clinical benefit (sCR + CR + VGPR + PR + MR).

BOR by investigator will be programmatically assessed based on reported timepoint responses by investigator recorded at evaluation time points from the date of first dose until confirmed disease progression using IMWG response criteria, death or start of new anticancer therapy, whichever occurs first. BOR by investigator needs to be confirmed according to IMWG response criteria (Table 2).

BOR by investigator will be reassessed programmatically based on derived responses per IMWG from the date of first dose until confirmed disease progression using IMWG response criteria, death or start of new anticancer therapy, whichever occurs first. This sensitivity analysis will follow the same rules as the secondary analysis except for deriving response based on the local laboratory and bone marrow data and the individual lesion data provided by the investigator.

6.2.3. Complete Response Rate

CRR is defined as the proportion of participants with a sCR/CR per IMWG criteria.

Point estimates of CRR will be calculated along with corresponding 2-sided exact 95% CIs using the Clopper-Pearson method.[7]

CRR by BICR and CRR by investigator will be summarized separately.

6.2.4. Progression-free Survival

PFS is defined as the time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause, whichever occurs first and will be calculated as follows:

PFS (months) = [date of event or censoring – date of first dose +1] / 30.4375.

PFS will be censored as follows:

- For participants who do not have an event (confirmed PD per IMWG criteria or death due to any cause), censoring will occur on the date of the last adequate disease assessment;

- For participants who start a new anticancer therapy (as defined in Section 5.2.6) prior to an event, censoring will occur on the date of the last adequate disease assessment before the new anticancer therapy;

- For participants with an event after a gap of 2 or more missing disease assessments, censoring will occur on the date of the last adequate disease assessment before the gap;

- Participants who do not have an adequate post-baseline disease assessment will be censored on the date of first dose of study intervention unless death occurs on or before the time of the second planned disease assessment (ie, ≤70 days after the date of first dose) in which case the death will be considered an event.

The censoring and event date options to be considered for the PFS analysis are presented in Table 4. Adequate post-baseline disease assessment are defined in Section 5.2.10.

Table 4. Outcome and Event Dates for PFS Analyses

Scenario	Date of Event/Censoring	Outcome
Progression or death 1. After at most 1 missing or inadequate post-baseline disease assessment or 2. ≤70 days after date of first dose of study intervention	Date of progression or death	Event
Progression or death after 2 or more missing or inadequate disease assessments[a]	Date of last adequate assessment[a] documenting no PD prior to new anticancer therapy or missed disease assessments	Censored
No progression or death		
New anticancer therapy given prior to PD or death		

a. If there are no adequate post-baseline disease assessments prior to confirmed PD or death, then the time without adequate assessment should be measured from the date of first dose of study intervention; if the criteria were met, the censoring will be on the date of first dose of study intervention.

PFS = progression-free survival; PD = progressive disease

Kaplan-Meier estimates (product-limit estimates) will be presented and displayed graphically where appropriate, together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley, 1982.[6]

The PFS rate at 3, 6, 9, 12, 15, 18, and 24 months (and in subsequent 12-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs. The CIs for the survival function estimates at the timepoints defined above will be derived using the log(-log) method according to Kalbfleisch and Prentice[8] (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented along with the overall event and censor rates.

Reasons for censoring will be summarized according to the categories in Table 5. If a participant meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 5. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anticancer therapy before event	Start of new anticancer therapy
2	Event after 2 or more missing or inadequate post-baseline disease assessment after date of first dose	Event after missing or inadequate assessments[a]
3	No event and [withdrawal of consent date ≥ date of first dose or End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [EOS present or disposition page for any EPOCH after screening says participant will not continue into any subsequent phase of the study] and no adequate post-baseline disease assessment	No adequate postbaseline disease assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a.] More than 70 days after last adequate disease assessment.

The PFS time or censoring time and the reasons for censoring will also be presented in a data listing.

PFS by BICR and PFS by investigator will be summarized separately.

If ≥5% of participants have died due to COVID-19 related reasons, these participants will be censored at the time of death and be counted as a competing risk event in a supplementary cumulative incidence analysis.

6.2.5. Duration of Response

DOR is defined, for participants with an objective response per IMWG criteria, as the time from the first documentation of objective response that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. It will be calculated as follows:

DOR (months) = [date of event or censoring – first date of objective response + 1] / 30.4375

The censoring rules for DOR are as described for PFS in Section 6.2.4, except that participants will not be censored for no adequate post-baseline assessment, as only participants with an objective response are included in the analysis of DOR.

If at least 3 participants achieve an objective response and subsequently have an event, DOR will be estimated using the same Kaplan-Meier method as described for PFS in Section 6.2.4 and displayed graphically where appropriate. Otherwise only listings will be provided.

The DOR rate at 3, 6, 9, and 12 months (and in subsequent 6-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

In addition, duration of response follow-up from initial dose and initial response will be summarized with simple descriptive statistics and a swimmer plot for DOR may also be produced.

DOR by BICR and DOR by investigator will be summarized separately.

If ≥5% of responders have died due to COVID-19 related reasons, these participants will be censored at the time of death and be counted as a competing risk event in a supplementary cumulative incidence analysis.

6.2.6. Duration of Complete Response

DOCR is defined, for participants with a sCR/CR per IMWG criteria, as the time from the first documentation of sCR/CR that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. It will be calculated as follows:

DOCR (months) = [date of event or censoring – first date of sCR/CR + 1] / 30.4375

The censoring rules for DOCR are as described for DOR in Section 6.2.5.

If at least 3 participants achieve a sCR/CR and subsequently have an event, DOCR will be estimated using the same Kaplan-Meier method as described for DOR in Section 6.2.5 and displayed graphically where appropriate. Otherwise only listings will be provided.

The DOCR rate at 3, 6, 9, and 12 months (and in subsequent 6-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

DOCR by BICR and DOCR by investigator will be summarized separately.

If ≥5% of responders have died due to COVID-19 related reasons, these participants will be censored at the time of death and be counted as a competing risk event in a supplementary cumulative incidence analysis.

6.2.7. Overall Survival

OS is defined as the time from the date of first dose until death due to any cause and will be calculated in months as follows:

OS (months) = [date of death or censoring – date of first dose +1] / 30.4375

Survival status is expected to be collected irrespective of study intervention discontinuation or participant's request to discontinue study procedures. All participants who have not withdrawn consent for further participation in the study should be followed for survival until the end of the study. OS for participants not known to have died are censored on the date of last known alive.

OS time will be estimated using the same Kaplan-Meier method and displayed graphically as described for PFS in Section 6.2.4. Median OS and 2-sided 95% CI will be provided. The OS rate at 12, 24, and 36 months (and in subsequent 12-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

Frequency (number and percentage) of participants with death events and censoring reasons will be presented by cohort along with the overall event and censor rates. The event and censoring reasons are as follows:

- Death;
- Ongoing and no death;
- Withdrawal of consent;
- Lost to follow-up.

The OS time or censoring time and the reasons for censoring will also be presented in a listing.

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

6.2.8. Time to Response

TTR is defined, for participants with an objective response per IMWG criteria, as the time from the date of first dose to the first documentation of objective response that is subsequently confirmed. For participants with EMD at baseline, MR or better (for those with target plasmacytomas) and CR or better (for those with non-target non-bone EMD only) cannot be confirmed until a post-baseline EMD assessment is performed and the date of confirmed response cannot be prior to the initial EMD assessment date. TTR will be calculated in weeks as follows:

$$\text{TTR (weeks)} = [\text{date of first objective response} - \text{date of first dose} + 1] / 7$$

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

TTR, TTVGPR, and TTCR will be summarized using simple descriptive statistics.

TTR, TTVGPR, and TTCR by BICR and TTR, TTVGPR, and TTCR by investigator will be summarized separately.

6.2.9. Minimal Residual Disease Negativity Rate

MRD negativity rate is defined as the proportion of participants with negative MRD (assessed by central lab) per IMWG sequencing criteria by bone marrow aspirate (BMA) from the date of first dose until confirmed PD, death or start of new anticancer therapy, whichever occurs first.

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

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

- MRD negative with confirmed sCR/CR based on the Safety Analysis Set;
- MRD negative based on the subset who achieved confirmed sCR/CR in the Safety Analysis Set;
- MRD negative based on the subset who achieved confirmed sCR/CR among evaluable patients who have at least one MRD assessment.

Additional subgroups may be summarized if applicable.

6.3. Other Secondary Endpoints

6.3.1. Pharmacokinetic/Pharmacodynamics

Pharmacokinetic analyses will be based on the PK Analysis Set.

A listing of elranatamab concentrations by study visit and timepoint will be generated.

Summary statistics will be provided for pre-dose and post-dose elranatamab concentrations at scheduled visits and nominal timepoints. Values below the limit of quantitation will be treated as zero in the descriptive statistics calculations. For additional details on handling missing and BLQ values, please refer to Section 5.3.1. The summary table will include the number of participants, number of samples with BLQ values, mean, standard deviation, percent coefficient of variation (%CV), median, minimum, maximum, geometric mean, and geometric %CV. For this summary, samples that meet the following conditions will be included:

- For pre-dose samples, have the sample collected before the next dose administration,
- For the 6-hour and 24-hour post-dose samples, have the sample collected within ± 25% of the nominal scheduled time,
- At least 2 consecutive planned doses were administered without interruption or reduction prior to trough sample collection,
    - Ex. C1D8 predose is included in the summary if C1D1 and C1D4 were administered as planned (ie, 12 and 32 mg, respectively),

- Ex. C1D15 predose is included in the summary if C1D4 and C1D8 were administered as planned (ie, 32 and 76 mg, respectively).

Box and Whiskers plots of elranatamab trough concentrations after multiple doses for participants from the PK Analysis Set who meet the conditions stated above will be presented by study visit. The Box and Whiskers plots will be overlaid with geometric means.

In addition, the PK data from this study may be combined with PK data from other studies to develop a population PK model. The correlation between elranatamab exposure parameters and pharmacodynamic biomarker, efficacy and/or safety outcomes will be explored if data allow. Details of these modeling analyses are not within the scope of this SAP and will be described in a separate population PK and exposure response analysis plan.

6.3.2. Immunogenicity

Immunogenicity data will be analyzed in the Immunogenicity Analysis Set. The percentage of participants with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-baseline will be generated. Samples may also be analyzed for the presence of neutralizing antibodies (NAb), and any data 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 pharmacodynamic markers, safety/tolerability and efficacy will be explored, if warranted by the data. This analysis may be reported separately from the CSR.

6.4. Exploratory Endpoints

The following exploratory endpoint analyses may be performed. The non-efficacy results may be presented separately from the main CSR.

6.4.1. Efficacy Analysis

6.4.1.1. Sustained MRD Negativity Rate

Sustained xx-month MRD negativity rate is defined as the proportion of participants with negative MRD per IMWG sequencing criteria and confirmed sCR/CR with at least xx months apart without positive MRD in between, from the date of first dose until confirmed PD, death or start of new anticancer therapy, whichever occurs first, where xx = 6, 12 and 24 months. Sustained xx-month MRD negativity rate will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method.

6.4.1.2. Duration of MRD Negativity

If data permits, DOMRD negativity will be analyzed using Kaplan-Meier method in participants who have achieved negative MRD per IMWG sequencing criteria and confirmed sCR/CR. DOMRD is defined, for participants with negative MRD, as the time from first documentation of negative MRD to the date of first documentation of relapse or death due to any cause, whichever occurs first. Relapse is defined as any one or more of the following criteria:

- Loss of MRD negative state (evidence of clonal plasma cells on 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.

DOMRD negativity will be censored on the date of the last adequate disease assessment for participants who do not have an event (relapse or death), 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.

6.4.2. Biochemical Response Rate

Biochemical BOR will be reassessed programmatically based on derived responses per IMWG from the date of first dose until confirmed disease progression using IMWG response criteria, death or start of new anticancer therapy, whichever occurs first. This exploratory analysis will follow the same rules as the primary analysis except for deriving response based on the local laboratory and bone marrow data and excluding the individual lesion data provided by BICR or investigator.

6.4.3. Biomarker Analysis

Biomarker data including DNA, RNA, protein, metabolites, or defined cell types resulting from analyses of peripheral blood, saliva and/or BM biospecimens will be assessed based on the Biomarker Set.

Exploratory biomarker endpoints will not be reported in CSR, but in a separate biomarker report.

6.4.4. Patient-Reported Outcomes

The following PRO analyses will be performed to support the CSR development. All other PRO analyses described in the study protocol but are not included in this SAP will be described in detail in a separate PRO analysis plan. Analysis of the PRO endpoints except the PRO completion table will be based on the PRO Analysis Set.

All PRO analyses will be carried out for each cohort separately. The PRO analyses will be based on the instruments EORTC QLQ-C30, EORTC QLQ-MY20, EORTC QLQ-CIPN20, EQ-5D index, EQ-5D VAS, and PGIS/ PGIC.

Completion Status

For each cohort at each time point, the number and percentage of participants who completed these instruments will be summarized, as will the reasons for non-completion of these measures. An instrument is considered completed if at least one item was answered by the participant.

EORTC QLQ-C30

This questionnaire contains 30 questions organized into 5 multi-item functional scales, 3 multi-item symptom scales, a global health/quality of life scale, and 6 single item symptom scales. For each of the 15 scales, the results will be summarized using descriptive statistics including mean, standard deviation, 95% CI, median, minimum, maximum at each timepoint. This will be done based on the observed values as well as change from baseline values.

EORTC QLQ-MY20

This questionnaire contains 20 questions organized into 2 functional scales and 2 symptom scales. As with the QLQ-C30, the analysis of the QLQ-MY20 scales will be summarized using descriptive statistics including mean, standard deviation, 95% CI, median, minimum, maximum at each timepoint. This will be done based on the observed values as well as change from baseline values.

EORTC QLQ-CIPN20

This questionnaire contains 20 questions which can be grouped into a sensory subscale (9 items), motor subscale (8 items) and autonomic subscale (3 items). The analysis of the QLQ-CIPN20 subscales will consist of descriptive statistics based on observed values and change from baseline values. Number and percent will be summarized for the item-level responses at each visit.

EQ-5D Index

Analysis of the EQ-5D index will consist of descriptive statistics based on observed values and, separately, based on change from baseline.

EQ-VAS

Analysis of EQ-VAS will consist of descriptive statistics based on observed values and separately, based on change from baseline.

PGIS/PGIC

Analysis of the PGIS and PGIC will be included in the supplementary PRO analysis plan.

6.4.5. Healthcare Resource Utilization

Healthcare resource use data, including hospitalization data (including type of hospitalization, length of stay, ICU admissions), transfusions, infections and outpatient visits may be summarized and listed. Length of first dose (C1D1) and second dose (C1D4) hospitalizations will be summarized.

6.5. Subset Analyses

All the subset analyses will be exploratory; no adjustment for multiplicity will be performed. Analyses will only be performed if there is sufficient sample size. The determination of whether or not there is sufficient sample size will be defined after enrollment is complete and prior to database lock. As a general rule, time to event analyses will not be performed on subgroups unless there are ≥10 events and ≥5% of participants overall within the defined subset and analyses of ORR will only be performed if there are ≥10 participants overall within the defined subset. Deviations from these analyses will be described in the clinical study report.

The following subset analyses will be performed for ORR by BICR based on the Safety Analysis Set:

- Baseline cytogenetics (high risk vs standard risk);
- Baseline bone marrow plasma cells (<50% vs ≥50%);
- Prior stem cell transplant (yes vs no);
- Disease stage (1-2 vs 3);
- Number of prior lines (≤5, >5);
- Type of myeloma (IgG vs non-IgG vs light chain only);
- Age (<65 vs ≥65; <75 vs ≥75);
- Sex (Male vs Female);
- Race (White vs others);
- Renal function (CrCl ≤60 mL/min vs >60 mL/min);
- Liver function normal (AST and total bilirubin ≤ ULN) vs impaired (AST or total bilirubin > ULN);
- Refractory to last therapy (yes vs no);
- Penta refractory (yes vs no);
- ECOG (0 vs 1-2);

- For cohort B, type of prior BCMA-targeted therapy (ADC, CAR-T) and presence of EMD (yes vs no).

ORR in subsets will be presented in a forest plot.

Other subgroups of race may be summarized, if data permits. The subset analyses may also be performed for ORR based investigator assessment.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Analyses of baseline data will be based on the Safety Analysis Set and will be displayed by cohort and overall.

6.6.1.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by number and percentage:

- Gender (male, female);
- Age;
  - 18 to <65; 65 to <75; ≥75;
  - <65 vs ≥65;
  - <75 vs ≥75;
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not Reported, Unknown) and ethnicity (Hispanic, not Hispanic, Not reported);
- Geographic Region (North America, Europe, Asia, Other).

Age (continuous), height (cm), weight (kg), BMI (kg/m^2) will be summarized with descriptive statistics.

6.6.1.2. Medical History

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's SOC and PT from the 'Medical History' CRF page. Each participant will be counted only once within each PT or SOC. Summaries will be ordered by alphabetical SOC and PT in descending order of overall frequency in two cohorts combined. In case of equal frequency, alphabetical order will be used. Separate summaries will be provided for past, present, or either condition.

6.6.1.3. Disease Characteristics

The following baseline disease characteristics will be summarized by number and percentage:

- Current disease stage by Revised Multiple Myeloma International Staging System (R-ISS, Stage I, II, and III, or unknown);
- Eastern Cooperative Oncology Group (ECOG) Performance status (ie, 0, 1, 2);
- Cytogenetics (including high risk vs standard risk);
- Presence of EMD (target lesions vs non-target lesions only excluding bone vs no) by investigator and BICR, separately;
- Number of bone lesions (1-4, vs 5-10, vs >10) for those with non-target bone lesions only;
- Baseline bone marrow plasma cells (<50% vs ≥50%);
- Type of myeloma (IgG vs non-IgG [IgA, IgD, IgE, IgM] vs light chain only [kappa light chain, lambda light chain]);
- Type of measurable disease at baseline (see Section 5.2.9):
  - Serum M-protein;
  - Urine M-protein;
  - Serum free light chain (if not measurable by serum or urine);
- Renal function (CrCl ≤60 mL/min vs >60 mL/min);
- Liver function normal (AST and total bilirubin ≤ ULN) vs impaired (AST or total bilirubin > ULN [including both AST and total bilirubin >ULN]).

The following baseline disease characteristics will be summarized by descriptive statistics :

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

6.6.1.4. Prior Anticancer Therapy

The prior anticancer therapies are collected under the ‘Response to Regimen’ and ‘Prior Transplant Details’ (PRIOR TPLT) eCRF pages.

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

- Participants with prior IMiDs and type (eg, lenalidomide, pomalidomide, or thalidomide);
- Participants with prior PI and type (eg, bortezomib, carfilzomib, ixazomib);
- Participants with prior anti-CD38 mAb and type (eg, daratumumab, isatuximab);
- Participants who are refractory to their last line of therapy;
- Participants who are triple-class refractory (refractory to at least 1 of each type above);
- Participants who are penta-drug exposed (have received at least 2 IMIDs, 2 PIs and 1 anti-CD38);
- Participants who are penta-drug refractory (refractory to 2 IMIDs, 2 PIs and 1 anti-CD38);
- Participants with prior stem cell transplant and type (autologous, allogeneic, or syngeneic);
- For cohort B, type of prior BCMA-targeted therapy (ADC, CAR-T, both).

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

- Number of prior anticancer therapy lines (descriptive statistics, as well as broken down in categories by the number of prior lines);
- Best overall response on the last prior anticancer therapy line received;
- Reason for stopping the last prior therapy.

The prior anticancer drugs will be coded in the WHO Drug coding dictionary and will be summarized based on the number and percentage of participants 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 summary will be sorted in descending order of the overall frequency in two cohorts combined. In case of equal frequency, alphabetical order will be used.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Disposition

The percentages below will be calculated based on the number of participants in the Safety Analysis Set (unless specified otherwise) and summarized by cohort and overall.

- Number of participants enrolled and treated by country and site;
- Number and percentage of participants in each of the analysis sets defined in Section 4 based on all enrolled participants;
- Number and percentage of enrolled participants with study intervention ongoing, discontinued or not given;
- Number and percentage of enrolled participants who discontinued study intervention, overall and by the main reason for discontinuation of study intervention;
- Number and percentage of participants who discontinued follow-up, overall and by the main reason for discontinuation of follow-up. Participants without a follow-up disposition CRF who died, were lost to follow-up, or withdrew consent during treatment will have their treatment discontinuation reason displayed as their follow-up discontinuation reason.

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

6.6.2.2. Protocol Deviations

Potentially important protocol deviations will be compiled prior to database closure and will be summarized by category (n[%]) for the Safety Analysis Set by cohort and overall.

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

6.6.3. Study Intervention Exposure

Exposure will be summarized based on the Safety Analysis Set.

Elranatamab is administered as a subcutaneous injection at 76 mg once every week on Days 1, 8, 15 and 21 of each 28-day cycle. Elranatamab is also administered on C1D4. A minimum of 2 days should be maintained between the 2 step-up priming doses (C1D1 and C1D4) and a minimum of 3 days between C1D4 dose and the first full dose (C1D8); a minimum of 6 days should be maintained between doses thereafter. The dose of elranatamab should be increased to 76 mg on C1D8 as long as the participant meets the criteria listed in Protocol Section 6.6.1. If a participant does not meet these criteria on C1D8, initiation of dosing with 76 mg should be deferred until the criteria are met. In addition, if a participant has received QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval will be changed from QW to Q2W. If the participant subsequently begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to weekly dosing. If the dose interval is changed, cycles should remain the same length (ie, 4-week cycles).

The summary of treatment exposure elranatamab will include the following information:

- Treatment duration (months);

- Number of cycles started per participant (mean, median, min, max);
- Number and percent of participants starting a cycle (any cycle, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, ≥12-<18, ≥18-<24, ≥24 cycles);
- Total cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose (%);
- Overall relative dose intensity (%);
- Number and percent of participants who received 44 mg on the C1D1 visit;
- Number and percent of participants who received 32 mg on the C1D4 visit;
- Number and percent of participants who received 76 mg on the C1D8 visit;
- Number and percent of participants after 6 cycles who switched from QW to Q2W;
- Number and percent of participants, among those switching from QW to Q2W, who switched back to QW.

The treatment duration of elranatamab (in weeks) during the study for a participant is defined as:

Treatment duration (months) = (last dose date – first dose date + 1)/30.4375

The total cumulative dose (mg) of elranatamab is the sum of the actual doses that the participant received during the study; the cumulative dose (mg) of elranatamab per cycle is the sum of the actual doses that the participant received within that cycle (ie, total dose administered [mg]).

Planned treatment duration is needed to calculate dose intensity (DI) and relative dose intensity (RDI). It is defined as follows:

- Planned treatment duration (weeks) = (number of cycles started x 4) - (number of weeks in the last cycle after permanent treatment discontinuation or data cutoff for those on-treatment).

The DI, relative dose (RD), and the RDI will be calculated for each participant overall across all cycles and also for each individual cycle as follows:

- Overall DI (mg/week) = Total cumulative dose (mg)/(last zero/non-zero dose date – first dose date)/7 + (1 if on QW or 2 if on Q2W). If C1D4 is the last visit, duration is 1 week if C1D4 occurred by then;

- Overall Planned DI (mg/week) = Total planned dose (mg)/ Planned treatment duration (weeks);
- Cycle DI (mg/week) = Total cumulative dose for a given cycle (mg)/Actual cycle duration (weeks);
- Cycle Planned DI (mg/week) = Total planned dose for a given cycle (mg)/4 weeks.

The total planned dose for a given cycle is defined as

- Cycle 1: Planned dose (mg/cycle) = 12+32 + 76 × 3
- After Cycle 1:
  - If the participant is on QW dosing schedule for the cycle:

    Planned dose (mg/cycle) = 76 × 4
  - If the participant is on Q2W dosing schedule for the cycle:

    Planned dose (mg/cycle) = 76 × 2

  For last cycle, subtract planned doses after a participant permanently discontinues treatment or data cutoff for those on-treatment.

The total planned dose is the sum of the total planned dose across all cycles.

The RD and RDI are defined as follows:

- Cycle RD (%) = [Total given dose for a given cycle (mg) / Total planned dose for a given cycle (mg)] × 100;
- Overall RD (%) = [Total cumulative dose (mg) / Total planned dose (mg)] × 100;
- Cycle RDI (%) = [Cycle DI (mg/week) / Cycle Planned DI (mg/week)] × 100;
- Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] × 100.

Cycle DI and Cycle RDI will be summarized and plotted vs time (weeks).

6.6.3.1. Dose Reductions, Interruptions, and Delays

A dose reduction is defined as a nonzero dose that is less than the planned and previous non-zero dose. The planned dose is the same as the prior dose except for C1D4 and C1D8.

The number and percentage of participants with at least 1 dose reduction as well as a breakdown of dose reductions (1/2/3/ ≥4) will be summarized by cohort. In addition, the number and percentage of participants with at least 1 dose reduction due to AE will also be summarized.

An interruption is defined as a continuous missed scheduled dose based on the planned dosing frequency (QW or Q2W). The number and percentage of participants with dose interruptions as well as a breakdown of dose interruptions (1/2/3/ ≥4) will be summarized by cohort and overall. In addition, the number and percentage of participants with at least 1 dose interruption due to AE will also be summarized. Percentages will be calculated based on the total number of participants in the Safety Analysis Set.

A dose delay will be derived based on study drug administration date and will be grouped into the following categories based on the deviation of the actual to the planned treatment administration day (relative to the previous treatment administration date):

- No delay;
- 1-3 days delay;
- 4-6 days delay;
- 7 or more days delay (only in the Q2W schedule).

The number and percentage of participants with delayed study drug administration and maximum length of delay, ie, the worst case of delay if participants have multiple dose delays will be summarized by cohort, as applicable.

6.6.4. Concomitant Medications and Nondrug Treatments

The following analyses will be based on the Safety Analysis Set and will be summarized by cohort.

Concomitant medications are medications, other than study medications, which started prior to first dose date of study intervention and continued on during the on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study medications, which are started before the first dose of study intervention.

Prior and concomitant medications will be summarized from the 'General Concomitant Medications' eCRF page. **Pre-medications** required for CRS will also be summarized (for C1D1, C1D4, C1D8, and other) separately from the 'Concomitant Medications – Pre-Medications (PREMED)' eCRF page.

Summary of prior medication and summary of concomitant medications (excluding for CRS prophylaxis) will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification Level 2 and PT. A participant will be counted only once within a given drug class and within a given drug name, even if he or she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by alphabetical ATC class and descending frequency of drug name in a given ATC class by Cohort A. Medications without an ATC classification Level 2 coded term will be summarized under the 'Unavailable ATC classification' category.

Summary of prior and concomitant medications for CRS prophylaxis will include the number and percentage of participants by PT only.

6.6.5. Subsequent Anticancer Therapies

The following analyses will be based on the Safety Analysis Set and will be summarized by cohort.

Number and percentage of participants with any anticancer therapy after discontinuation of study intervention will be tabulated overall and by type of therapy based on the data collected from the 'Next Anticancer Therapy (NXT CNCR)' eCRF pages, 'Non-drug Treatments (NXT RAD)', 'Non-drug Treatments (NXT SURG)', and 'Transplant details (TRANSPLT)' eCRF pages.

Subsequent anticancer drug treatment will be summarized by PT.

6.7. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the Safety Analysis Set by cohort and overall.

6.7.1. Adverse Events

All analyses will be based on treatment emergent adverse events (TEAEs) unless otherwise specified. Treatment emergent is defined in Section 3.5. AEs not considered treatment emergent will be flagged in data listings. Summaries of TEAEs due to COVID-19 may be produced if appropriate.

A high-level summary of adverse events (all causality and treatment-related, separately) will include the number and percent of participants with:

- Any TEAEs;
- Serious TEAEs;
- Grade 3-4 TEAEs;
- Grade 5 TEAEs;
- TEAEs leading to dose interruptions;
- TEAEs leading to dose reductions;
- TEAEs leading to dose interruptions or reductions;
- TEAEs leading to permanent discontinuation of study intervention;
- CRS;

- ICANS;
- Peripheral neuropathy.

Seriousness, toxicity grade, and withdrawal from drug are as reported by the investigator on the adverse event CRF.

An event will be considered treatment-related if the investigator considered the event as related to the study drug or if relationship is missing.

For all the AE summaries by SOC and 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).

Summaries by SOC and PT by alphabetical order for SOC and by descending order of frequency for PT in two cohorts combined will be provided for:

- TEAEs (all causality and treatment-related);
- TEAEs by maximum severity grade (all causality and treatment-related);
- TEAEs with Grade 3-4 (all causality and treatment-related);
- TEAEs leading to death (all causality and treatment-related);
- TEAEs leading to dose interruptions (all causality);
- TEAEs leading to dose reductions (all causality);
- TEAEs leading to dose interruptions or reductions (all causality);

- TEAEs leading to permanent discontinuation of study medication (all causality and treatment-related);
- TEAEs by maximum severity grade before and after the switch to Q2W (all causality);
- Serious TEAEs (all causality and treatment-related).

The following summaries will be provided by PT only (ie, summaries will not include SOC) in descending order of the overall frequency in two cohorts combined:

- Most common TEAEs in either cohort (all causality and treatment-related, separately) by PT and maximum severity grade;
- Most common serious TEAEs in either cohort (all causality) by PT and maximum severity grade.

Each participant will be counted only once within each SOC and PT.

In case a participant has events with missing and non-missing severity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed if an event has been reported only once for a participant and the grade is missing.

6.7.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) includes the following events:

- CRS: PT coded as “cytokine release syndrome” and collected on the AE CRF page;
- ICANS: PT coded as “immune effector cell-associated neurotoxicity syndrome” and collected on the AE CRF page;
- Peripheral neuropathy: Standardized MedDRA Queries (SMQ) Peripheral Neuropathy (narrow and broad excluding PTs included in the Guillain-Barre syndrome SMQ) and Guillain-Barre syndrome SMQ (narrow).

CRS and ICANS will be assessed according to ASTCT criteria. All the analyses will be performed for each individual AESI separately.

For CRS and ICANS, the 4 participants who received 44 mg priming dose will be summarized separately within each summary table.

A high-level summary of each AESI will include the number and percent of participants with, separately:

- Any AESI;
- Serious AESI;

- AESI by maximum toxicity grade;
- Had >1 AESI (for CRS and ICANS only);
    - Note: If there are >1 AESI with different grades between two doses, it will be considered as one event;
- Had ICANS concurrent with CRS (for ICANS only). Note: if both CRS and ICANS occurred between the same two doses they will be considered as concurrent;
- AESI leading to dose interruptions;
- AESI leading to dose reductions;
- AESI leading to dose interruptions or reductions;
- AESI leading to permanent discontinuation of study intervention;
- AESI with outcome as resolved.

In addition, the following summary will be provided with descriptive statistics as well as broken down in categories by the time to onset, resolution, and duration of the AESI:

- Time to onset of the AESI;
- Time to resolution of the AESI;
- Duration of each AESI event.

For CRS and ICANS, time relative to dose (ie, after the first dose, after the second dose, after the third dose, after >3 doses) will also be summarized with descriptive statistics.

A summary of AESI symptoms will be provided as follows. The most severe symptom will be summarized if participants have multiple occurrences of AESI symptoms.

- The CRS symptoms (fever, hypoxia and hypotension) as collected on the 'CRS AE' CRFs will be summarized by symptom grade using frequency counts and percentages;
- The ICANS symptoms as collected on the 'ICANS' CRFs will be summarized using frequency counts and percentages;
- The immune effector cell-associated encephalopathy (ICE) scores as collected on the 'ICE' CRFs will be summarized for those participants with ICANS events based on the total ICE scores as follows:
    - ICE score 10;

- ICE score 7-9;
- ICE score 3-6;
- ICE score 1-2;
- ICE score 0.

In addition, the number and percent of participants with CRS/ICANS who received concomitant medications including tocilizumab/steroids (from Concomitant medications CRF) will be summarized.

For peripheral neuropathy, the following summary will be provided:

- Peripheral neuropathy TEAEs by PT and maximum severity grade (all causality and treatment-related);
- Peripheral neuropathy TEAEs and medical history.

6.7.1.2. Other Adverse Events of Clinical Interest

Other adverse events of clinical interests (oAECIs) include the following events:

- Infections:
  - The MedDRA SOC of Infections and infestations.
- Cytopenias:
  - The MedDRA PTs for cytopenias are defined in Appendix 2.
- Hypogammaglobulinemia:
  - Including the MedDRA PTs: Blood immunoglobulin G decreased, Hypogammaglobulinaemia, Hypoglobulinaemia, Immunoglobulins decreased and Globulins decreased.
- Injection site reactions:
  - The MedDRA HLT of Injection site reactions.
- Secondary malignancies:
  - The MedDRA SOC of Neoplasms Benign, Malignant and Unspecified.

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.

A high-level summary of each of oAECI will be provided including the following, if applicable:

- Any oAECIs;
- Serious oAECIs;
- oAECIs by maximum toxicity grade;
- oAECIs leading to dose interruptions;
- oAECIs leading to dose reductions;
- oAECIs leading to dose interruptions or reductions;
- oAECIs leading to permanent discontinuation of study intervention.

The following summary will be provided for each oAECI, if applicable:

- oAECI by PT and maximum severity grade (all causality and treatment-related);
- Time to onset of the oAECI, time to resolution, and duration of the oAECI with descriptive statistics as well as broken down in categories.

6.7.2. Deaths

The frequency (number and percentage) of participants in the Safety Analysis Set who died at any time, who died within 28 days of the first dose of study intervention, and who died within 90 days after last dose of study intervention as well as the primary reason for death, will be tabulated based on information from the 'Death Details' and 'Survival Follow-Up' CRFs.

Date and cause of death will be provided in individual participant data listing together with selected dosing information (date of first/last administration, dose).

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

6.7.3. Laboratory Data

Laboratory results will be converted to International System of Units (Système International d'unités, SI) units which will be used for applying severity grades and for all summaries.

As described in Section 3.4, baseline will be defined as the last assessment performed on or prior to date of the first dose of study intervention. If there are multiple assessments that meet the baseline definition on the same day without the ability to determine which was truly last, then the worst grade will be assigned as the baseline grade.

Results collected as strict inequalities (eg, >10, <10) will be converted to numeric values adding or subtracting a factor of 0.001. Expressions of the form "≥" or "≤" will be converted to the end point. These numeric values will be evaluated for clinically significant abnormalities, but will not be included in calculations of summary statistics except for efficacy related laboratory results. Additional data handling rules for efficacy related laboratory data will be described in the programming plan.

Additionally, laboratory results will be programmatically classified according to NCI-CTCAE version 5.0 grade as appropriate. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summary statistics the number and percentage of participants corresponding to grades that only include non-quantitative criteria will be displayed as a blank or NA (not assessed) rather than 0. If there is any overlap between grade criteria (eg, CTCAE grading criteria for Creatinine Increased - a value can fall into one range based on comparison to ULN and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

Grade 0 or Outside Toxicity Reference (OTR) is not defined specifically in the CTCAE guidance. However, programmatically this is used as a category to represent those participants who did not meet any of the Grades 1 to 4 criteria. If the laboratory value is evaluable for CTCAE criteria grading (numeric value is present, valid units and ranges are present as required to allow conversion to standard units and grading), and does not qualify for any of the Grade 1-4 criteria for a given lab test, then the value is assigned as Grade 0 or OTR.

Several of the CTCAE terms (including Hypo/Hypercalcemia, Chronic Kidney Disease, and Activated Partial Thromboplastin) can be derived using several laboratory tests (analytes) as follows:

- Hypo/Hypercalcemia – graded by Serum Calcium or Ionized Calcium;
- Chronic Kidney Disease – graded by estimated Glomerular Filtration Rate (eGFR) or Creatinine Clearance;
- Activated Partial Thromboplastin Time Prolonged (aPTT) – graded by Partial Thromboplastin Time (PTT) or activated Partial Thromboplastin Time (aPTT).

For WBC differential counts (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported by the lab and will be graded following the CTCAE guidance.

When only percentages are available (this is mainly applicable for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) × (Differential %value / 100)

If the investigator reports both the absolute and % value for Neutrophils or Lymphocytes from the same laboratory sample date and participant, ONLY the absolute value will be graded. The % value will not be graded in this scenario.

If the % value is converted to the differential absolute count for grading and the LLN for the differential absolute count is not available (only LLN for % is available) then Grade 1 will be assigned if the following conditions are met:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥800/mm^3.
- Neutrophil count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥1500/mm^3.

For calcium, CTCAE grading is based on Corrected Calcium and Ionized Calcium. Corrected Calcium is calculated from Albumin and Calcium as follows:

Corrected Calcium (mg/dL) = measured total calcium (mg/dL) – 0.8 [serum albumin (g/dL)-4]

Creatinine clearance is calculated as follows:

- Male: Creatinine Clearance = ((140 - Age) / (Serum Creatinine)) * (Weight / 0.814);
- Female: Creatinine Clearance (eGFR) = 0.85* ((140 - Age) / (Serum Creatinine)) * (Weight / 0.814);

Note: the SI unit of Serum Creatinine is "micromol/L", the unit of weight is "Kg".

Abnormalities will be described using the worst grade overall. Worst case overall will be determined using laboratory results from scheduled and unscheduled visits. Several laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high

(hyper) values can be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 Hypercalcemia will be classified as a Grade 0 Hypocalcemia. For CTCAE terms that can be derived using one of several laboratory tests, the maximum postbaseline grade for a given participant and CTCAE term will be the maximum across all possible laboratory tests.

Additional laboratory results that are not part of CTCAE will be presented according to the following categories by scheduled timepoint as well as overall: below normal limit, within normal limits, and above normal limits. In the unlikely event that for a given participant, clinically significant abnormalities are noted in both directions (eg, > Upper Limit of Normal (ULN) and < Lower Limit of Normal [LLN]), then both abnormalities are counted.

The following summary tables will be created:

- Shift summary of laboratory parameters during the on-treatment period by maximum CTCAE grade;
- Shift summary of laboratory parameters from ≤ Grade 2 at baseline to ≥ Grade 3 postbaseline;
- Shift summary of laboratory test results with no CTCAE criteria by worst on treatment assessment.

All laboratory test results will be presented in a data listing sorted by participant identifier, laboratory test, and date/time of collection. The CTCAE grades and the classifications relative to the laboratory reference ranges will be presented. Values outside laboratory normal ranges will be flagged where appropriate.

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test results over the ULN will be calculated and classified for these 3 parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized:

- ALT≥3×ULN, ALT≥5xULN, ALT≥10×ULN, ALT≥20×ULN;
- AST≥3×ULN, AST≥5xULN, AST≥10×ULN, AST≥20×ULN;
- (ALT or AST)≥3×ULN, (ALT or AST)≥5×ULN, (ALT or AST)≥10×ULN, (ALT or AST)≥20×ULN;
- TBILI≥2×ULN;

- Concurrent ALT≥3×ULN and TBILI≥2×ULN;
- ALT≥3×ULN and TBILI≥2×ULN at any timepoint;
- Concurrent AST≥3×ULN and TBILI≥2×ULN;
- AST≥3×ULN and TBILI≥2×ULN at any timepoint;
- Concurrent (ALT or AST)≥3×ULN and TBILI≥2×ULN;
- (ALT or AST)≥3×ULN and TBILI≥2×ULN at any timepoint;
- Concurrent (ALT or AST)≥3×ULN and TBILI≥2×ULN and ALP≥2×ULN;
- (ALT or AST)≥3×ULN and TBILI≥2×ULN and ALP≥2×ULN at any timepoint;
- Concurrent (ALT or AST)≥3×ULN and TBILI≥2×ULN and ALP≤2×ULN or missing;
- (ALT or AST)≥3×ULN and TBILI≥2×ULN and ALP≤2×ULN or missing at any timepoint.

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a participant with an elevation of AST≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different cohorts, by graphically displaying:

- Peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN;
- Peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, the following listings of all TBILI, ALT, AST and ALP values will be provided:

- For participants with a postbaseline TBILI≥2×ULN, ALT≥3×ULN or AST≥3×ULN and ALP≤2×ULN or missing at any timepoint;
- For participants with a postbaseline TBILI≥2×ULN, ALT≥3×ULN or AST≥3×ULN and ALP≤2×ULN or missing at the same visit.

6.7.4. Vital Signs

Vital sign data will be listed.

6.7.5. Electrocardiograms

Triplicate ECGs are required at each assessment. ECG assessments reported by the site will include PR, HR, QT, QRS, and QTcF. A mean score is calculated and reported for any replicate measurements having the same nominal visit. All summary statistics, analyses and figures will be based on the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

ECG summaries will include all ECG assessments from the on-treatment period. RR will be derived from HR. QTcF will be programmatically derived from QT and HR using the following formula:

$$QTcF(msec) = QT(msec) / \sqrt[3]{RR(sec)}$$

All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

QTcF will be summarized by maximum on-treatment values using the following categories:

- <450 msec;
- ≥450 msec but ≤480 msec;
- >480 msec but ≤500 msec;
- >500 msec.

Unscheduled assessments will be utilized in addition to planned assessments. Shift tables will be provided for baseline QTcF value versus worst on-treatment value. Additionally, maximum increases from baseline (including scheduled and unscheduled assessments) will be summarized based on the following categories:

- Change >60 msec;
- Change >30 msec but ≤60 msec;
- Change ≤30 msec.

Data listings will contain the means from a triplicate as well as the parameters from each of the 3 ECGs. Note that using the mean value may result in a participant having a measurement that is not represented by an actual ECG.

6.7.6. Neurological Examinations

A shift summary of baseline status by worst status postbaseline will be presented for each subcategory. Shift summaries over time may also be generated.

7. INTERIM ANALYSES

7.1.1. Interim Analysis for Futility and Efficacy

An interim analysis for both futility (non-binding) and efficacy will be conducted on ORR by BICR for Cohort A based on the first 90 participants enrolled (Interim Analysis Evaluable Set A) and treated in that cohort and for Cohort B based on the first 30 participants enrolled and treated in that cohort (Interim Analysis Evaluable Set B). Each respective interim analysis will occur no earlier than the point at which all early responders (ie, those who respond within the first 3 post-baseline assessments) among the participants to be included have had their responses confirmed.

The interim analyses in both cohorts will be based on the primary endpoint of ORR by BICR. The decision rules are described in Section 5.1.2.

The interim analyses will be performed by an independent statistician. Unblinded results from the interim analyses will not be communicated to the Sponsor's clinical team or to any party involved in the study conduct (apart from the independent statistician and E-DMC members) until the E-DMC has determined that either (i) the analysis has crossed the pre-specified boundary for efficacy or (ii) the study needs to be terminated due to any cause. Further details will be described in the E-DMC charter.

The final analyses will be performed by the Sponsor's clinical team.

7.1.2. Interim Safety Assessments

An E-DMC will review cumulative safety data during the study conduct and may make recommendations to alter the conduct of the study. In addition, the incidence of Grade 3-4 CRS, Grade 3-4 ICANS, Grade 4 treatment-related non-hematologic events (excluding CRS and ICANS), Grade 3-4 treatment-related GBS/GB-like AEs, Grade 4 treatment-related peripheral neuropathy/immune-related (IR) neurologic events (excluding ICANS), Grade 3-4 treatment-related motor neuropathy, and Grade 5 events will each be monitored throughout the study. If the number of participants observed to have such identified events exceeds a pre-specified threshold, the study will be placed on a temporary enrollment hold by the sponsor until discussions can be held with the E-DMC. During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. Pending E-DMC assessment, participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the investigator in consultation with the sponsor.

In the event that any criteria for temporary enrollment hold are met, written notification documenting the reason for temporary enrollment hold (or study termination) will be provided by the sponsor to the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study.

The criteria for placing the study on temporary hold for safety reasons are based on Bayesian posterior probabilities. Using a non-informative Beta (0.5, 0.5) prior distribution, if the number of participants observed to have Grade 3-4 CRS results in a posterior probability that the true Grade 3-4 CRS rate exceeding 20% is ≥0.80, the study will be put on a temporary

hold. Separate but similar criteria will be used for participants with Grade 3-4 ICANS and treatment-related Grade 4 non-hematologic events (excluding CRS and ICANS). Table 6 summarizes the minimum number of participants with such identified events that would meet the above criteria.

Table 6. Minimum Number of Participants With Identified Events That Would Prompt Temporary Enrollment Hold

Number of Evaluable Participants (Cohort A + B)	10-13	14-18	19-22	23-26	27-30	31-35	36-39
Minimum number of participants with Grade 3-4 CRS events that would lead to a temporary enrollment hold*	4	5	6	7	8	9	10
Minimum number of participants with Grade 3-4 ICANS events that would lead to a temporary enrollment hold*	4	5	6	7	8	9	10
Minimum number of participants with Grade 4 treatment-related non hematologic events (excluding CRS and ICANS) that would lead to a temporary enrollment hold*	4	5	6	7	8	9	10

Prior distribution: Beta (0.5,0.5)

Criteria for 40 or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 20% is ≥0.80.

Evaluable participants are defined as those who have received at least 1 dose of study treatment having an identified event or those without such an event who have been followed for at least 28 days from first dose.

* The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, if there are 4 participants experiencing the identified AE out of the first 6 evaluable participants, the study will be put on hold). A minimum of 4 events are required to trigger a temporary hold.

The criteria for placing the study on temporary hold for the following safety reasons are based on Bayesian posterior probabilities using a non-informative Beta (0.5, 0.5) prior distribution.

- If the number of evaluable participants observed to have treatment-related Grade 3-4 GBS/GB-like AEs results in a posterior probability that the true rate of such events exceeding 3% is ≥0.80, the study will be put on a temporary hold.

- If the number of evaluable participants observed to have treatment-related Grade 4 sensory neuropathy/other IR neurologic AEs (excluding ICANS) or treatment-related Grade 3-4 motor neuropathy results in a posterior probability that the true rate of such events exceeding 10% is ≥0.80, the study will be put on a temporary hold.

Table 7 summarizes the minimum number of evaluable participants with such identified events that would meet the above criteria.

Table 7. Minimum Number of Participants with Identified Treatment-Related Events That Would Prompt Temporary Enrollment Hold (GBS/GB-like AEs, Peripheral Neuropathy/IR Neurologic AEs)

Number of Evaluable Participants (Cohort A + B)	20-39	40 -64	65-90	91-116	117-144	145-150[a]	
Minimum number of participants with Grade 3-4 treatment-related GBS/GB-like events that would lead to a temporary enrollment hold*	2	3	4	5	6	7	
Number of Evaluable Participants (Cohort A + B)	20-27	28-35	36-43	44-52	53-60	61-69	70-78[b]
Minimum number of participants with Grade 4 treatment-related sensory neuropathy/IR neurologic AE (excluding ICANS) or Grade 3-4 treatment-related motor neuropathy events that would lead to a temporary enrollment hold**	4	5	6	7	8	9	10

Prior distribution: Beta (0.5,0.5)

a. Criteria for 151 or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 3% is ≥0.80.

b. Criteria for 79 or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 10% is ≥0.80.

Evaluable participants are defined as those who have received at least 1 dose of study treatment having an identified event or those without such an event who have been followed for at least 28 days from first dose.

* The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, for GBS/GB-like AEs, if there are 2 participants experiencing the identified AE out of the first 10 evaluable participants, the study will be put on hold). A minimum of 2 events are required to trigger a temporary hold.

** The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, if there are 4 participants experiencing the identified AE out of the first 15 evaluable participants, the study will be put on hold). A minimum of 4 events are required to trigger a temporary hold.

The list of search criteria for IR neurologic AE PT is defined in Appendix 3. Further clinical review is required to determine if a specific event meets the criteria.

In addition, the study will be put on temporary hold if any of the following criteria are met in the safety analysis set of the two cohorts combined:

- 1 Grade 5 event of CRS;
- 1 Grade 5 event of ICANS;
- 1 Grade 5 treatment-related peripheral neuropathy or IR neurologic event;
- Any 2 treatment-related Grade 5 events (excluding CRS, ICANS, and peripheral neuropathy/IR neurologic event).

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9. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time prolonged
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	anatomic Therapeutic Chemical
AUC	area under the curve
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
BCMA	B-cell maturation antigen
BICR	blinded independent central review
BLQ	below the limit of quantitation
BMA	bone marrow aspirate
BMI	body mass index
BOR	best overall response
C#D#	cycle # day # (eg, C1D1 = cycle 1 day 1)
CD#	cluster of differentiation # (eg, CD38)
CI	confidence interval
C_{max}	maximum observed concentration
CR	complete response
CRR	complete response rate
CRF	case report form
CRS	cytokine release syndrome
CSE	clinical summary of efficacy
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DI	dose intensity
DLT	dose limiting toxicity
DMC	data monitoring committee
DOCR	duration of complete response
DOMRD	duration of minimal residual disease
DOR	duration of response
ECG	electrocardiogram

Abbreviation	Term
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
E-DMC	external data monitoring committee
EMD	extramedullary disease
EORTC MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire of Cancer Patients core module
EORTC QLQ-CINP20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire of chemotherapy-induced peripheral neuropathy module
EOS	end of study
EOT	end of treatment
EQ-5D	EuroQoL 5 Dimensions
FLC	free light chain
GBS	Guillain-Barre syndrome
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HLT	high level term
ICANS	immune cell-associated neurotoxicity syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
Ig#	Immunoglobulin (eg, IgM, IgA, etc)
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LOD	limit of detection
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MR	minimal response
MRD	minimal residual disease
MUGA	multigated acquisition
N/A; NA	not applicable; not assessed
NAb	neutralizing antibody
NCI	National Cancer Institute
NE	not evaluable
NED	no evidence of disease
NGS	next generation sequencing
oAECI	other adverse events of clinical interest

Abbreviation	Term
ORR	objective response rate
OS	overall survival
OTR	outside toxicity reference
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcB	corrected QT (Bazzett's method)
QTcF	corrected QT (Fridericia's method)
Q2W	every 2 weeks
QW	every 1 week
RD	relative dose
RDI	relative dose intensity
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SPEP	serum protein electrophoresis
sMRD	sustained minimal residual disease
SMQ	Standardised MedDRA Queries
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse events
T_{max}	time for C_{max}
TTCR	time to complete response
TTR	time to response
TTVGPR	time to very good partial response
ULN	upper limit of normal
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

Appendix 2. List of MedDRA Preferred Terms for Cytopenia

- 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;
- CD4 lymphocytes decreased;
- CD4 lymphocyte percentage decreased;
- Thrombocytopenia;
- Platelet count decreased;
- Platelet production decreased.

Appendix 3. List of MedDRA Preferred Terms for IR neurological AE (including ICANS)

- Altered state of consciousness;
- Aphasia;
- Brain oedema;
- Cognitive disorder;
- Confusional state;
- Consciousness fluctuating;
- Depressed level of consciousness;
- Encephalitis;
- Encephalopathy;
- Immune-mediated encephalopathy;
- Intracranial pressure increased;
- Loss of consciousness;
- Mental status changes;
- Motor dysfunction;
- Neurotoxicity;
- Seizure.