Protocol C1071009
(MAGNETISMM-9)

A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE A DOSING REGIMEN WITH TWO STEP-UP PRIMING DOSES AND LONGER DOSING INTERVALS OF ELRANATAMAB (PF-06863135) MONOTHERAPY IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Statistical Analysis Plan
(SAP)

Version: 3.0

Date: 31 July 2022

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1. VERSION HISTORY

This SAP for study C1071009 is based on the final approved Protocol Amendment 2 (dated 10 June 2022). A tabular summary of changes in earlier versions is in Appendix 2.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
3 15 July 2022	Protocol Amendment 10 June 2022	Updates per Protocol Amendment 2 and be consistent with the analyses on the program level	Section 2.1 and 3.2.2: Revised DLT observation period definition to 28 days starting on the first dose of 116 or 152 mg. • Section 2.2 and 6.7.3, Figure 1: Participants enrolled in Part 1 should be switched to the RP2D identified in Part 2A (116 mg or 152 mg) administered Q4W after 6 cycles if PR or better is persisting for ≥ 2 months. • Section 2.1, 2.2, 5.1.2.2 , 6.1.3 and 6.5.1: Remove MTD. • Section 2.2, 5.1.1.2, 5.1.2.2, and 6.7.3 Clarified the rules to open Part 2C. • Section 3.5.1, 6.7.3.1 and 6.8.1: Updated to indicate that dose reduction of elranatamab below 76 mg is no longer permitted. • Section 5.1.1.2: Added scenarios to BLRM approach. • Section 5.2.6: Added "Transplant" as new anticancer therapy. • Section 6.3.1: Updated analysis on ORR and rules for BOR. Added sensitivity analysis on BOR assessed programmatically based on derived responses per IMWG. • Table 5: Updated the censoring and event date options to be considered for the PFS analysis. • Table 6: Updated PFS Censoring Reasons and Hierarchy. • Section 6.3.7, updated analysis on Time to Response. • Section 6.4.1: Clarified PK/PD analysis. • Section 6.6: Added subset analysis by Prior BCMA-target agent (Yes vs. No). • Section 6.7.1: Updated Baseline Summaries. • Section 6.7.3: Updated analysis on Study Intervention Exposure.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Section 6.8.1: Peripheral neuropathy added as an AESI; added PT for AE analysis. • Section 6.8.3: added derivation rules for Several CTCAE terms from lab tests. • Section 7.2.1: Revised criteria for placing enrollment on a temporary hold. • Section 2.1, 3.2.1 and 6.3.2: Changed name of CCRR and DOCCR to CRR and DOCR, respectively. • Section 3.2.1.8 and 6.3.8: Clarify analysis on MRD negative rate. • CCI [redacted] • Section 6.1: Clarified intercurrent event handling. • Section 4: Clarified DLT Evaluable Set. • Section 6.8.5: Revised threshold for QTcF Assessment.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1071009. 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 CSR.

Study C1071009 is a prospective, open-label, multicenter, non-randomized Phase 1/2 study aimed to evaluate the safety (in particular the rate of Grade ≥2 CRS) of a priming dose regimen that involves premedication and 2 step-up priming doses to be administered within the first week of elranatamab treatment in RRMM participants who are refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb. There is one planned interim analysis for futility, which takes place once 30 participants in Part 1 either complete Cycle 1 of study intervention or discontinued the study intervention prior to the end of Cycle 1. The primary analysis will be conducted once all participants have completed Cycle 1 of study intervention or have otherwise discontinued the study intervention. All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

2.1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Primary			
Safety	• To assess the rate of Grade ≥2 CRS when elranatamab is administered with a dosing regimen of 2 step-up priming doses and premedication in participants with RRMM.	• Grade ≥2 CRS rate during C1.	• The primary estimand is rate of Grade ≥2 CRS during C1 as assessed by ASTCT criteria. It will be estimated based on all enrolled RRMM participants who received at least 1 dose of study intervention regardless of duration on the study treatment.
Secondary			
Safety	• To assess the safety and tolerability of elranatamab at doses >76 mg with a longer dosing interval (>1 week) in order to identify the RP2D (**Part 2A only**).	• Incidence of DLTs during DLT observation period	• The secondary estimand is DLT rate estimate based on data from DLT-evaluable participants during the DLT observation period.

Type	Objectives	Endpoints	Estimands
Safety	• To evaluate the overall safety profile of elranatamab with 2 step-up priming doses and alternative dosing regimens in participants with RRMM.	• Adverse Events as characterized by type, frequency, severity as graded by NCI CTCAE version 5.0, timing, seriousness, and relationship to elranatamab. The severity of CRS and ICANS will be assessed according to ASTCT criteria; • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• Not Applicable.
Efficacy	• To evaluate the anti-myeloma activity of elranatamab with alternative dosing regimens in participants with RRMM.	• ORR and CRR, per IMWG response criteria as determined by investigator; • Time to event endpoints: TTR, DOR, DOCR and PFS per IMWG response criteria as determined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• Not Applicable.
PK	• To evaluate the PK of elranatamab	• Pre- and postdose concentrations of elranatamab.	• Not Applicable.
Immunogenicity	• To evaluate immunogenicity of elranatamab	• Incidence and titers of ADA and NAb against elranatamab.	• Not Applicable.
[redacted]	CCI [redacted]		
[redacted]	[redacted]	[redacted]	[redacted]

Type	Objectives	Endpoints	Estimands
CCI			

2.2. Study Design

Study C1071009 is a prospective, open-label, multicenter, non-randomized Phase 1/2 study aimed to evaluate the safety (in particular the rate of Grade ≥2 CRS) of a priming dose regimen that involves premedication and 2 step-up priming doses to be administered within the first week of elranatamab treatment in RRMM participants who are refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb. All participants in all dosing groups will contribute to the primary objective of the study, ie, assessing the rate of Grade ≥2 CRS during C1, as the same dosing regimen is administered to all treatment groups during the first cycle.

For both Part 1 and Part 2, the first 2 doses of elranatamab on C1D1 and C1D4 will serve as the step-up priming doses and will be administered on an inpatient basis to monitor participants for CRS/ICANS. The dose of elranatamab should be increased to 20 and 76 mg on C1D4 and C1D8, respectively, as long as the participant meets redosing criteria as specified in Section 6.5.1 of the protocol.

In addition, the study will evaluate the overall safety, tolerability, PK, pharmacodynamics, and preliminary anti-myeloma activity of alternative regimens of elranatamab at dose levels >76 mg starting from Cycle 2 with different dosing intervals (QW, Q2W, Q4W) (Part 2), and a regimen of elranatamab full dose of 76 mg QW for 6 cycles followed by Q2W or >76 mg Q4W (Part 1).

The following dosing regimens will be assessed:

- **Part 1: Premedication, 2 step-up priming doses, and full dose 76 mg QW for 6 cycles followed by Q2W and/or RP2D (116 mg or 152 mg) Q4W;**

Part 1 aims to evaluate the overall safety, tolerability, PK, pharmacodynamics, and preliminary anti-myeloma activity of the following regimen:

- **C2 to C6**: elranatamab 76 mg QW;
- **C7 onwards**: elranatamab 76 mg Q2W (for participants with IMWG response of PR or better persisting for ≥2 months on QW).

If after switching to Q2W interval, 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 76 mg QW for the remainder of the study.

- **C7 onwards once the RP2D is identified in Part 2A**: elranatamab RP2D (116 mg or 152 mg) Q4W (for participants with IMWG response of PR or better persisting for ≥2 months on QW or Q2W).

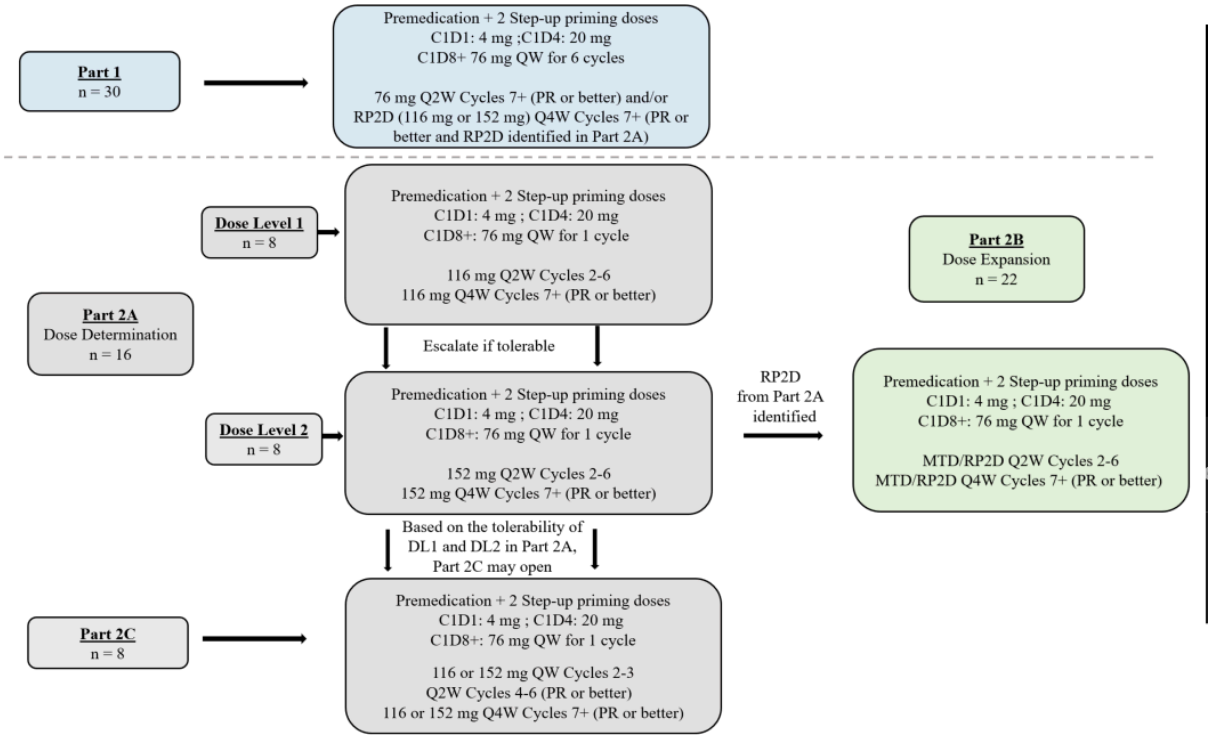
If after switching to Q4W interval; the participant subsequently begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to RP2D (116 mg or 152 mg) Q2W for the remainder of the study.

- **Part 2: Premedication, 2 step-up priming doses, and full dose >76 mg** (ie 116 and 152 mg) **at different dosing intervals.**

  Part 2 aims to evaluate the safety and efficacy of a regimen that includes premedication and a dosing regimen of 2 step-up priming doses (Week 1) followed by full dose >76 mg with different dosing intervals starting from C2. Part 2 includes a dose determination part (Part 2A Dose level 1 and Dose level 2), a dose expansion part (Part 2B), CCI Part 2A dose determination and Part 2C tolerability evaluation will be based on a BLRM approach. The decision to start enrolling participants in a new cohort (Part 2A Dose level 2, Part 2B or Part 2C) will be a joint decision to be determined by the investigators and the sponsor in dose level review meetings.

  - **Part 2A** will evaluate full elranatamab doses >76 mg starting from C2 with a longer dosing interval (>1 week) to determine the potential RP2D to be further evaluated in Part 2B. Approximately 8 participants will be enrolled at each dose level in Part 2A. The potential RP2D identified in Part 2A Dose Level 1 or Dose Level 2 will be further evaluated and confirmed in Part 2B (dose expansion).
  - **Part 2B** will begin once the potential RP2D from Part 2A Dose level 1 or Dose level 2 is selected. Approximately 22 participants will be enrolled to confirm the safety and efficacy of the selected dosing regimen. Approximately a total of 30 participants will be enrolled and treated at the potential RP2D, 8 from Part 2A and 22 from Part 2B.

Figure 1. Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoint is Grade ≥2 CRS rate during Cycle 1, defined as the proportion of participants in the Safety Analysis Set experiencing Grade ≥2 CRS as assessed by ASTCT[1] criteria.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Objective Response Rate

Objective response rate (ORR) is defined as the proportion of participants in the Safety Analysis Set with an objective response per the IMWG response criteria[2] as determined by investigator.

Objective response is defined as having a best overall response (BOR) of confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) per IMWG response criteria.

For all efficacy endpoints per IMWG response criteria, BOR will be assessed programmatically based on investigator reported overall responses recorded at evaluation time points from the date of first dose until confirmed progressive disease (PD), withdrawal of consent, participant lost to follow-up, death or start of new anti-cancer therapy or defined end of study, whichever occurs first.

3.2.1.2. Complete Response Rate

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

3.2.1.3. Duration of Response

Duration of response (DOR) is defined, for participants with an objective response per IMWG criteria as determined by investigator, 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.

3.2.1.4. Duration of Complete Response

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

3.2.1.5. Progression-free Survival

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

3.2.1.6. Overall Survival

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

3.2.1.7. Time to Response

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

3.2.1.8. 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 from the date of first dose until confirmed PD, withdrawal of consent, participant lost to follow-up, death or start of new anticancer therapy or defined end of study, whichever occurs first.

3.2.2. Safety Endpoints

3.2.2.1. DLT Rate (Part 2A and Part 2C only)

Dose limiting toxicity (DLT) rate is defined as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants in the DLT observation period. DLT observation period is Cycle 2 or 28 days starting from the first dose of 116 mg or 152 mg.

3.2.2.2. Adverse Events and Laboratory Parameters

- 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), 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.

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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 the 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 (Section 5.2.9) is be provided for disease assessment related efficacy endpoints.

For all endpoints, the last 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.

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.

Triplicate ECGs are collected at all timepoints except screening (single ECG at screening); therefore, the baseline for ECG measurement is the pre-dose on Cycle 1 Day 1, or the most recent ECG assessment reported prior to the first administration of study drug. Unscheduled assessments will not be included in the calculation of the average. The average of the replicate measurements will be determined after the derivation of the individual parameters at each timepoint.

3.5. Safety Endpoints

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

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

AEs will be 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 according to the ASTCT criteria.[1] All AEs will be coded using the most current version of MedDRA.

TEAEs leading to dose interruption (prior to protocol amendment 2) 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 6.8.3.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Participant Analysis Set	Description
Safety Analysis Set	All enrolled participants who receive at least 1 dose of study intervention.
DLT Evaluable Analysis Set	All enrolled participants in Part 2A and Part 2C, who received the planned 2 doses of 116 mg or 152 mg of study intervention during the DLT observation period or who received at least 1 dose of 116 mg or 152 mg of study intervention and experience DLT(s) during the DLT observation period.
CCI	[redacted]
PK Analysis Set	The PK analysis set is a subset of the safety analysis set and will include participants who have at least 1 postdose concentration measurement.
Immunogenicity Analysis Set	All participants in the safety analysis set who have at least 1 sample tested for ADA.
CCI	[redacted]

Note: "Enrolled" means a participant's, or his or her legally authorized representative'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

5.1.1.1. Primary Endpoint

A Bayesian dual-criterion design[6] will be used to estimate the primary endpoint of the true Grade ≥2 CRS rate during Cycle 1. With this design, the following criteria are defined:

- Bayesian statistical significance: Substantial evidence that the true Grade ≥2 CRS rate exceeds a pre-specified value. For this study, Bayesian statistical significance will be achieved if the posterior probability of the true Grade ≥2 CRS rate exceeding 35% is <10%;

- Clinical relevance: The maximum number Grade ≥2 CRS events threshold that could justify further clinical development. For this study, it is defined as the median of the posterior distribution of the true Grade ≥2 CRS rate is ≤27%.

The analysis will use a Beta-binomial model (binomial sampling for number of Grade ≥2 CRS events and a beta prior distribution). A minimally informative beta prior distribution of the true Grade ≥2 CRS rate will be used. It is assumed a priori that the true mean Grade ≥2 CRS rate is 35%, so the prior distribution will be Beta (0.7, 1.3). Using this prior and based on the dual criteria defined above, approximately 76 participants will be enrolled and treated and a maximum of 20 participants with Grade ≥2 CRS events is allowed to meet the dual criteria in 76 participants. If exactly 20 participants in 76 participants experience Grade ≥2 CRS events, the observed Grade ≥2 CRS rate is 26.3% with median 26.3% and 90% credible interval of (18.7%, 35.0%) based on the posterior distribution.

5.1.1.2. Part 2A and Part 2C

In Part 2A and Part 2C, approximately 8 participants will be enrolled and treated at each dose level to ensure at least 6 DLT evaluable participants (as defined in Section 4) to be evaluated during the DLT observation period. If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants at each dose level.

CCI [redacted]

5.1.2. Decision Rules

5.1.2.1. Primary Endpoint

The study is designed to have an interim analysis for futility and a primary analysis. The interim analysis will be conducted once 30 participants in Part 1 either complete Cycle 1 of study intervention or discontinued the study intervention prior to the end of Cycle 1. The primary analysis will be conducted once all participants have completed Cycle 1 of study intervention or have otherwise discontinued the study intervention.

Table 2 presents the operating characteristics of this 2-stage design, ie, the probability of early trial termination at the interim futility analysis and the probability of observing the critical number of Grade ≥2 CRS (ie, ≤20 participants with Grade ≥2 CRS events in 76 participants) at the primary analysis if the true Grade ≥2 CRS rate is 20%, 21%, 22%, 23%, 27% and 35%, respectively. For example, if the true Grade ≥2 CRS rate = 22%, the probability of stopping the study due to futility at the interim analysis is 0.048, and the probability of observing ≤20 participants with Grade ≥2 CRS rate at the primary analysis is 0.835.

Table 2. Operating Characteristics of Bayesian 2-Stage Dual-Criterion Design

True Grade ≥2 CRS Rate	Prob of Exceeding Futility Boundary at the Interim (R1/N1 ≥11/30)	Prob of GO Decision at the Primary Analysis* (R/N ≤20/76)	Prob of No-GO Decision at the Primary Analysis (R/N >20/76)
20%	0.026	0.919	0.055
21%	0.036	0.882	0.082
22%	0.048	0.835	0.116
23%	0.064	0.779	0.157
27%	0.161	0.488	0.351
35%	0.492	0.065	0.443

* The study does not meet futility criteria at the interim analysis and continues to the primary analysis.
CRS = cytokine release syndrome;
R1 = Number of participants with Grade ≥2 CRS events at the interim futility analysis to stop the study for futility;
N1 = Number of participants at the interim analysis;
R = Number of participants with Grade ≥2 CRS events to meet the dual criteria at the primary analysis;
N = Number of participants at the primary analysis.

At the time of the primary analysis, the critical number of participants with Grade ≥2 CRS events to be observed will be updated based on the actual number of participants enrolled and treated.

5.1.2.2. Part 2A and Part 2C

A BLRM will be utilized for dose determination. The dosing decision and estimation of the RP2D of elranatamab will be guided by the estimation of the posterior probability of DLT in the DLT observation period. Other evidence such as safety data beyond DLT window, clinical activity, PK, and PD data will also be evaluated in determining RP2D.

As this study uses premedication and a dose regimen with 2 step-up priming doses, which were not used in the Phase 1 study of the same compound (C1071001), there is issue of exchangeability between the historical data and the current design. Therefore, weakly informative priors with weighted mixture prior structure are used for the prior distribution of the BLRM parameters.

After each dosing cohort of participants completes the DLT observation period, the posterior distribution for the risk of DLT for each dose level will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals.

- Underdosing: [0, 0.16);
- Target toxicity: [0.16, 0.33);
- Excessive toxicity: [0.33, 1].

Dosing decisions are guided by the EWOC principle.[7] A dose level may only be used for the next dosing cohort of participants if the risk of excessive toxicity ([0.33, 1]) at that dose level is less than 25%.

Table 3 shows some hypothetical dose escalation data scenarios and the corresponding recommendations for the next dose for Part 2A. For example, in Scenario 1, if 1 participant experiences a DLT out of 6 DLT-evaluable participants at 116 mg Q2W dose level, the recommendation is to escalate to the next dose level (152 mg Q2W) with probability of overdosing of 0.083 at 152 mg dose level. In Scenario 3, if 3 participants experience DLTs out of 6 DLT-evaluable participants at 116 mg Q2W dose level, the dose level is deemed too toxic, and the dose finding process will stop with no RP2D identified.

Table 3. Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose

Scenarios	Elranatamab Dose Evaluated (mg;)	D/N	Elranatamab Next Dose (mg)	Pr(TT) at Next Dose	Pr(OD) at Next Dose
1	116 Q2W	1/6	152 Q2W	0.362	0.083
2	116 Q2W	2/6	116 Q2W	0.461	0.161
3	116 Q2W	3/6	N/A	N/A	N/A
4	152 Q2W 116 Q2W	1/6 0/6	152 Q2W	0.199	0.010
5	152 Q2W 116 Q2W	1/6 1/6	152 Q2W	0.408	0.048
6	152 Q2W 116 Q2W	2/6 1/6	152 Q2W	0.555	0.147
7	152 Q2W 116 Q2W	3/6 1/6	116 Q2W	0.582	0.167
8	152 Q2W 116 Q2W	0/6 0/6	152 QW	0.283	0.058
9	152 Q2W 116 Q2W	1/6 1/6	116 QW	0.519	0.188

Abbreviations: D=number of participants with DLT, N=number of DLT-evaluable participants; mg=milligrams; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Q2W=once every two weeks.

5.2. General Methods

Unless otherwise specified, all efficacy analyses and safety analyses will be performed using the Safety Analysis Set. All analyses will be performed by part as follows:

- Part 1;
- Part 2;
  - Part 2A Dose level 1 (if Dose level 2 is identified as RP2D);
  - Part 2A (RP2D) + Part 2B;
  - CCI
- Part 1 and Part 2 Combined.

5.2.1. Data Handling After the Cutoff Date

Data collected 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.

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 randomized 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, disease 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 the study intervention elranatamab. Elranatamab is administered in a 28-day cycle.

- For Cycle 1, the actual cycle start 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 the planned cycle duration and actual cycle stop date is calculated as actual cycle start date + 28 – 1 day.

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) is used to determine the end of the on-treatment period (see Section 3.5) and for censoring in efficacy analyses (see Section 6.3.5).

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)' CRF page;
- Start date of radiation therapy with curative intent recorded in 'Concomitant Radiation' and 'Non-drug Treatments – Follow up Radiation (NXT RAD)' eCRF pages;
- Start date of transplant recorded in 'Transplant details (TRANSPLT)' eCRF page.

When start date of new 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 [safety laboratory, Pharmacokinetics (PK), CCI and immunogenicity], vital signs, physical exam, neurological 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;
- Start and end dates of new therapies administered after study intervention discontinuation including systemic therapy and radiation;
- AE start and end dates;
- Last date of contact collected on the 'Survival Follow-up' 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. Assessment dates after the data cutoff date will not be applied to derive the last contact date.

5.2.8. Disease Assessment Date

The Date of Disease Assessment at each nominal timepoint as provided by the investigator on the IMWG response assessment CRF page 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 >0.5 g/dL by SPEP;
  - Urinary M-protein excretion ≥200 mg/24 hours by UPEP;
  - Serum immunoglobulin FLC ≥10 mg/dL (≥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 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 to 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 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 together with a summary of associated statistics including the median time with 2-sided 95% CIs. Probabilities of an event at particular timepoints will be estimated with corresponding 2-sided 95% CIs. The CI for the median will be calculated according to Brookmeyer and Crowley, 1982[9] and the CIs for the survival function estimates at particular timepoints will be derived using the log(-log) method.[10]

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 time point 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: If the AE onset date is completely missing, and if the date of first dose is earlier 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 first dose date. Date of 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 and 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 intervention 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

The primary analysis will be conducted once all enrolled participants have completed Cycle 1 or have otherwise discontinued the study intervention. At this analysis, the primary endpoint of Grade ≥2 CRS rate during Cycle 1 and the safety endpoints will be evaluated.

For primary completion date reporting purpose (initial CSR), the full scope of the statistical analysis including all the endpoints will be conducted once all participants have been followed for response for at least 6 months or have otherwise discontinued response assessments within the first 6 months of treatment.

The final analysis will be conducted once the last participant enrolled will have been followed for OS for at least 2 years.

6.1. Primary Endpoints

The primary endpoint is Grade ≥2 CRS rate during Cycle 1, defined as the proportion of participants in the Safety Analysis Set experiencing Grade ≥2 CRS as assessed by ASTCT criteria.

Estimand strategy: All data collected after the intercurrent event of treatment discontinuation due to any reason will be excluded in the analysis.

Analysis set: Safety Analysis Set (as defined in Section 4).

Intercurrent events and missing data: The intercurrent event is treatment discontinuation due to any reason. No imputations for missing data will be performed.

Analysis methodology: The median and its corresponding 2-sided 90% credible interval based on the posterior distribution of Grade ≥2 CRS rate will be calculated. In addition, point estimates of Grade ≥2 CRS rate will be calculated along with the 2-sided 90% CIs using the Clopper-Pearson method[8] (exact CI for a binomial proportion).

6.2. Secondary Safety Endpoint

6.2.1. Incidence of DLTs (Part 2A and Part 2C only)

DLT rate during the DLT observation period, which will be calculated as the number of DLT-evaluable participants with DLTs during the DLT observation period divided by the number of DLT-evaluable participants during the DLT observation period. Analyses of DLT will be performed on the DLT Evaluable Analysis Set (as defined in Section 4). DLT rate will be summarized and listed by dose levels.

6.3. Secondary Efficacy Endpoints

6.3.1. Objective Response Rate

ORR is defined as the proportion of participants with an objective response (Section 3.2.1.1) per IMWG response criteria as determined by investigator.

ORR will be analyzed in the Safety Analysis Set. Observed point estimate of ORR will be calculated along with the 2-sided 95% CIs using the Clopper-Pearson method.

The frequency (number and percentage) of participants with BOR by investigator in each response category and corresponding 2-sided 95% confidence interval 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 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 4). 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 required 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 endpoint analyses), and the PD date is the date of the initial PD assessment.

Table 4. Derivation Rules for Confirmed Best Overall Response per IMWG Response Criteria

	Timepoint response at:			
Scenario	**Assessment 1**	**Assessment 2**	**Assessment 3**	**BOR**
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 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) before initiation of new anticancer therapy			
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	

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 new lesion, increased extramedullary or paramedullary lesions, plasmacytomas), or bone marrow plasma cells does not need to be confirmed.
c. PD due to reasons other than EMD, or bone marrow plasma cells.

BOR by investigator will also be assessed 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.

6.3.2. Complete Response Rate

CRR is defined as the proportion of participants with a BOR of confirmed sCR or CR per IMWG criteria as determined by investigator.

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

6.3.3. Duration of Response

DOR is defined, for participants with an objective response per IMWG criteria as determined by investigator, 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. The rules for PD confirmation are described in Table 4.

DOR 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 6.3.5 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 6.3.5 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.

For sensitivity analyses on DOR, if ≥10% of responders have died due to COVID-19 related reasons, these participants will be censored at the time of death.

6.3.4. Duration of Complete Response

DOCR is defined, for participants with a BOR of confirmed sCR or CR per IMWG criteria as determined by investigator, as the time from the first documentation of sCR or CR that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. The rules for PD confirmation are described in Table 4.

DOCR will be calculated as follows:

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

The censoring rules for DOCR are as described for PFS in Section 6.3.5.

If at least 3 participants achieve a BOR of confirmed sCR or CR and subsequently have an event, DOCR will be estimated using the same Kaplan-Meier method as described for PFS in Section 6.3.5 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.

6.3.5. Progression-free Survival

PFS is defined as the time from the date of first dose until confirmed PD per IMWG criteria as determined by investigator or death due to any cause, whichever occurs first. The rules for PD confirmation are described in Table 4.

PFS 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 5. Adequate post-baseline disease assessment are defined in Section 5.2.10, respectively.

Table 5. 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
Neither progression nor death		
New anticancer therapy given prior to PD or death		

a. If there are no adequate post-baseline disease assessments prior to 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.[9]

The PFS rate at 3, 6, 9, 12, 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[10] (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 6. If a participant meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 6. 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.

For the PFS analysis, sensitivity analyses will be performed, if ≥10% of participants have died due to COVID-19 related reasons, these participants will be censored at the time of death.

6.3.6. 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 6.3.5. 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 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.

In addition, OS will be summarized with simple descriptive statistics (mean, standard deviation, minimum, median, and maximum) for duration of follow-up.

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

6.3.7. Time to Response

TTR is defined, for participants with an objective response per IMWG criteria as determined by investigator, 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.

6.3.8. 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 at any time from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first. The rules for PD confirmation are described in Table 4.

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

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;

- CCI [redacted]
- [redacted]

Additional subgroups may be summarized if applicable.

6.4. Other Secondary Endpoints

6.4.1. Pharmacokinetic/Pharmacodynamics

Pharmacokinetic parameter analyses will be based on the PK Analysis Set. No PK parameter is reported.

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 24-hour and 48-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, 4 and 20 mg, respectively);
    - Ex. C1D15 predose is included in the summary if C1D4 and C1D8 were administered as planned (ie, 20 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.

6.4.2. 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.

CCI

CCI

[redacted]

6.6. 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, subset analysis 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 subgroup analyses will be performed for the primary endpoint of Grade ≥2 CRS rate:

- Age (<65 vs ≥65; <75 vs ≥75);
- Sex (Male vs Female);
- Race (White vs Black/African American vs Asian vs Others);
- ADA status (positive vs negative);

  ADA positive participants are those with treatment-emergent ADA, ie, ADA levels are either a) induced or b) boosted with treatment. Those participants with pre-existing ADA at baseline will be classified as ADA ever positive if their ADA levels are boosted after receiving study intervention.

- Organ function at baseline;
  - Liver function: normal (AST and total bilirubin ≤ ULN) vs impaired (AST or total bilirubin > ULN);
  - Renal function: normal (CrCl ≥90 mL/min) vs mild (CrCl 60 - 89 mL/min) vs moderate (CrCl 30 - 59 mL/min).

The following subset analyses may be performed for ORR as determined by investigator:

- Baseline cytogenetics (high risk = Yes vs. No);
- Number of prior therapies (≤4, >4);
- Prior BCMA-target agent (Yes vs. No);
- EMD at baseline (Yes vs. No).

Grade ≥2 CRS rate and ORR in subsets will be presented in a forest plot. Additional subset analysis might also be performed if data permits.

6.7. Baseline and Other Summaries and Analyses

6.7.1. Baseline Summaries

Analyses of baseline data will be based on the Safety Analysis Set.

6.7.1.1. Demographic 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);
- Ethnicity (Hispanic, Not Hispanic, Not reported);
- Geographic Region (North America, Europe, Asia).

Age (continuous), height (cm), weight (kg), BMI (kg/m^2) will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

6.7.1.2. 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 SOC and PT (by alphabetical order for SOC and by descending order of frequency for PT in Part 1 and Part 2 combined). In case of equal frequency, alphabetical order will be used. Separate summaries will be provided for past and present conditions.

6.7.1.3. Disease Characteristics

The following baseline disease characteristics are collected under the "Pre-specified Primary Diagnosis" eCRF page and 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);
- Cytogenetics (standard risk vs high risk);

- Presence of extramedullary disease;
- 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;
- 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).

The following baseline disease characteristics will be summarized by descriptive statistics (mean, median, standard deviation, minimum, and maximum):

- 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, defined as (date of first dose of study intervention– date of onset of current episode) / 30.4375, where date of onset of current episode is the date of the last relapse.

6.7.1.4. Prior Anticancer Therapy

The prior anticancer therapies are collected under the 'Response to Regimen -Prior Cancer Therapy', 'Non-drug Treatments – Prior Radiation Therapy' and 'Transplant Details - Prior' 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, cafilzomib, ixazomib);
- Participants with prior anti-CD38 antibody and type (eg, daratumumab, isatuximab);
- Participants who are refractory to the last line of therapy;

- Participants who are triple-class refractory (refractory to at least 1 IMID, 1 PI and 1 anti-CD38);
- 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).

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 line of anticancer therapy received;
- Reason for stopping the last prior line of anticancer 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 preferred term. A participant will be counted only once within a given preferred term, even if he or she received the same medication at different times. The summary will be sorted in descending order in Part 1 and Part 2 combined. In case of equal frequency, alphabetical order will be used.

6.7.2. Study Conduct and Participant Disposition

6.7.2.1. Disposition

The percentages below will be calculated based on the number of participants in the Safety Analysis Set and summarized as follows:

- 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;
- Number and percentage of enrolled participants with study intervention ongoing, discontinued or not given;
- Number and percentage of enrolled participants who discontinued the study intervention, overall and by the main reason for discontinuation of study intervention;
- Number and percentage of participants who entered follow-up;

- Number and percentage of participants who discontinued follow-up, overall and by the main reason for discontinuation of follow-up.

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

6.7.2.2. Protocol Deviations

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

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

6.7.3. Study Intervention Exposure

Exposure will be summarized based on the Safety Analysis Set.

Elranatamab is administered as a subcutaneous injection. For both Part 1 and Part 2, 2 step-up priming doses regimen will be used during the first cycle as following:

- **C1D1:** Premedication + elranatamab 4 mg;
- **C1D4:** Premedication + elranatamab 20 mg;
- **C1D8:** Premedication + elranatamab 76 mg;
- **C1D15 and C1D22:** elranatamab 76 mg QW.

Starting from Cycle 2, the following dosing regimens will be assessed:

- **Part 1** will evaluate full elranatamab doses at 76 mg QW from Cycle 2 to Cycle 6. Starting from Cycle 7, the dose interval will be changed from QW to Q2W in participants with IMWG response of PR or better persisting for ≥2 month on QW. **Once the RP2D is identified in Part 2A**, the dose interval would also be the elranatamab RP2D (116 mg or 152 mg) Q4W in participants with IMWG response of PR or better persisting for ≥2 months on QW or Q2W.
- **Part 2A** will evaluate full elranatamab doses at 116 mg Q2W (**Dose level 1**) and 152 mg Q2W (**Dose level 2**) from Cycle 2 to Cycle 6. Starting from Cycle 7, the dose interval will be changed from Q2W to Q4W in participants with IMWG response of PR or better persisting for ≥2 month on Q2W.
- **Part 2B** will evaluate the potential RP2D from Part 2A (**Dose level 1** or **Dose level 2**) from Cycle 2 to Cycle 6 at Q2W dosing interval. Starting from Cycle 7, the dose interval will be changed from Q2W to Q4W in participants with IMWG response of PR or better persisting for ≥2 month on Q2W.

- CCI [redacted]

For both Part 1 and Part 2, if, after switching to a less frequent dosing interval, 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 the previous dose interval for the remainder of the study.

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

- Treatment duration (weeks);
- Number of cycles started per participant (mean, median, min, max);
- Number and percent of participants starting a cycle (any cycle, cycle 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, >=12 cycles);
- Total cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose (%);
- Overall relative dose intensity (%);
- Number and percent of responding participants after 6 cycles who switched from QW to Q2W or Q4W (Part 1) or from Q2W to Q4W (Part 2);
- Number and percent of participants, among those switching from QW to Q2W/Q4W (Part 1) or from Q2W to Q4W (Part 2), who switched back to QW/Q2W (Part 1) or Q2W (Part 2).

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

Treatment duration (weeks) = (last dose date – first dose date + 1)/7

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 and intended 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).
- Intended treatment duration (weeks) = (last zero/non-zero dose date – first dose date)/7 + 1 if on QW or 2 if on Q2W, or 4 if Q4W.

  Note: If C1D4 is the last visit and dose is given at this visit, duration is 1 week.

The planned dose for a given cycle is defined as

- Cycle 1: Planned dose (mg/cycle) = 4 + 20 + 76 × 3.
- After Cycle 1:
  - If the participant is on QW dosing schedule for the cycle:

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

    Planned dose (mg/cycle) = Full dose × 2
  - If the participant is on Q4W dosing schedule for the cycle:

    Planned dose (mg/cycle) = Full dose.

  Note: For the 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.

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

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

- Overall DI (mg/week) = Total cumulative dose (mg)/Intended treatment duration (weeks);
- Overall Planned DI (mg/week) = Total planned dose (mg)/Planned treatment duration (weeks);
- Cycle DI (mg/week) = 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 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).

6.7.3.1. Dose Reductions, Interruptions, and Delays

Dose Reduction

A dose reduction is defined as a non-zero dose that is less than the prior dose and less than the planned dose in the protocol.

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. In addition, the number and percentage of participants with at least 1 dose reduction due to AE will also be summarized.

Dose Interruption

An interruption is defined as missing a scheduled dose based on the planned dosing frequency (QW, Q2W or Q4W).

The number and percentage of participants with dose interruptions as well as a breakdown of dose interruptions (1/2/3/ ≥4) will be summarized. 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.

Dose Delay

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 and Q4W 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.

6.7.4. Concomitant Medications and Nondrug Treatments

The following analyses will be based on the Safety Analysis Set.

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 'Prior and Concomitant Medications' eCRF page. Pre-medications required for CRS will also be summarized separately from the 'Pre-Medication Treatment' eCRF page.

Summary of prior medications, concomitant medications (excluding for CRS prophylaxis) and summary of pre-medications will include the number and percentage of participants by ATC Classification Level 2 and preferred term. 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 in descending frequency of ATC class and descending frequency of drug name in a given ATC class in Part 1 and Part 2 combined. In case of equal frequency regarding ATC class (respectively drug name), alphabetical order will be used. 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 preferred term only.

6.7.5. Subsequent Anticancer Therapies

The following analyses will be based on the Safety Analysis Set.

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 preferred term.

6.8. 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.

6.8.1. Adverse Events

All analyses will be based on treatment emergent adverse events (TEAE) 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 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 and PT=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 Part 1 and Part 2 combined) will be provided for:

- Any TEAEs (all causality and treatment-related);
- TEAEs by maximum toxicity 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 intervention (all causality and treatment-related);
- Serious TEAEs (all causality and treatment-related).

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

The following summaries will be provided by PT only (by descending order of frequency in Part 1 and Part 2 combined) for:

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

Each participant will be counted only once within each PT.

In case a participant has events with missing and non-missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed in the event that only 1 event has been reported for a participant and the grade is missing.

6.8.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) include 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 by each individual AESI separately.

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 the two doses, it will be considered as one AESI.
- 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 (for peripheral neuropathy only).

In addition, the following summary will be provided with descriptive statistics (mean, median, standard deviation, minimum, and maximum) as well as broken down in categories by the time to onset and resolution 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 >2 doses) will also be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

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 as collected on the 'CRS AE' CRF 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 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 tocilizumab/ steroids (from Conmed 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 (all causality) and Medical History.

A listing of AESI with supportive information will also be provided.

6.8.1.2. 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 cytopenia are defined in the Appendix (Section 9.1).
- Injection site reactions:
  - The MedDRA HLT of Injection site reactions.
- Hypogammaglobulinemia
  - Including the MedDRA PTs: Blood immunoglobulin G decreased, Hypogammaglobulinaemia, Hypoglobulinaemia, Immunoglobulins decreased and Globulins decreased.

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

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

- 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 oAESI:

- oAECI by PT and maximum severity grade (all causality and treatment-related);
- Time to onset of the oAECI and time to resolution of the oAECI with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

A listing of oAECIs with supportive information will also be provided.

6.8.2. Deaths

The frequency (number and percentage) of participants in the Safety Analysis Set who died at any time and who died within 90 days after last dose of study intervention as well as the primary and secondary 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 (study intervention received, 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.

6.8.3. Laboratory Data

Laboratory results will be converted to International System of Units (Système International d'unités, SI) units which will be used for applying toxicity 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. 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 Upper Limit of Normal (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 Lower Limit of Normal (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 by scheduled timepoint and 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 NCI-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, > ULN and < 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 post-baseline;
- 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 result 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 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.

6.8.4. Vital Signs

Vital sign data will be listed.

6.8.5. Electrocardiograms

Single ECG assessment will be performed at Screening visit and triplicate ECGs are required at all other assessments. ECG assessments reported by the site will include QT, PR, QRS, heart rate 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, except at screening. 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. Fridericia's correction (QTcF) will be programmatically derived from QT and HR using the following formula:

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

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.

7. INTERIM ANALYSES

7.1. Introduction

There are interim safety assessments and an interim analysis for futility planned on this study.

An internal safety review team will review cumulative safety and tolerability data on an ongoing basis for the interim safety assessments and document all decisions in the study TMF.

An interim analysis for futility will be performed on the first 30 participants enrolled and treated in Part 1 to assess the safety of elranatamab in terms of CRS rate using a dose regimen with 2 step-up priming doses. The primary endpoint of Grade ≥2 CRS rate during Cycle 1 will be evaluated at this analysis by the internal core study team and the decisions will be documented in the study TMF. Additional interim analyses may also be performed at other time points for the purpose of safety assessment and/or supporting clinical development.

7.2. Interim Analyses and Summaries

7.2.1. Interim Safety Assessments

An internal safety review team will review cumulative safety data during the study conduct. In addition, the incidence of the following events will each be monitored by the Sponsor throughout the study. The review results and decisions will be documented in the study TMF.

- 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 sensory neuropathy/other IR neurologic AEs (excluding ICANS);
- Grade 3-4 treatment-related motor neuropathy;

- Grade 5 events.

If the number of participants observed to have such identified events exceeds a prespecified threshold, the study will be placed on a temporary enrollment hold by the Sponsor. During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. 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.

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 participants observed to have Grade 3 or 4 CRS results in a ≥0.80 posterior probability that the true Grade 3 or 4 CRS rate exceeds 20%, 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 7 summarizes the minimum number of participants with such identified events that would meet the above criteria.

Table 7. Minimum Number of Participants With Identified Events That Would Prompt Temporary Enrollment Hold (CRS, ICANS, Non-hematologic treatment-related AEs)

Number of Evaluable Participants	10-13	14-18	19-22	23-36	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 greater than or equal to 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 AEs 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. Specifically,

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

Table 8. 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	**20-39**	**40-64**	**65-90**	**-**	**-**	**-**	**-**	**-**	**-**
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	-	-	-	-	-	-
Number of Evaluable Participants	**6-11**	**12-19**	**20-27**	**28-35**	**36-43**	**44-52**	**53-60**	**61-69**	**70-78**
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**	2	3	4	5	6	7	8	9	10

Prior distribution: Beta (0.5,0.5).

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 2 participants experiencing the identified AEs out of the first 4 evaluable participants, the study will be put on hold). A minimum of 2 events are required to trigger a temporary hold.

In addition, the study will be put on temporary hold if any of the following criteria are met:

- 1 Grade 5 event of CRS (by ASTCT criteria);

- 1 Grade 5 event of ICANS (by ASTCT criteria);

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

7.2.2. Interim Analysis for Futility

An interim analysis for futility will be performed to assess the safety of elranatamab in terms of CRS rate using a dose regimen with 2 step-up priming doses. It will be conducted after the 30 participants enrolled and treated in Part 1 have either completed Cycle 1 of study intervention or discontinued the study intervention prior to the end of Cycle 1.

The primary endpoint of Grade ≥2 CRS rate during Cycle 1 will be evaluated at the interim analysis using a futility boundary based on the predictive probability assuming a Beta (0.7, 1.3) prior. More specifically, the study may stop for futility if the predictive probability of observing 20 or fewer participants with Grade ≥2 CRS events in 76 participants at the primary analysis based on the data observed at the interim analysis is less than 10%.

The posterior beta-binomial predictive distribution for the number of participants with Grade ≥2 CRS events in the second stage of the study is as follows:

$$\pi(r_2|\text{IA. r, IA. n}) = \binom{n_2}{r_2} \frac{B(r_2+a+\text{IA.r},b+\text{IA.n-IA.r}+n_2-r_2)}{B(a+\text{IA.r},b+\text{IA.n-IA.r})}$$

where IA.r and IA.n denote the number of participants with Grade ≥2 CRS events and number of participants at the interim analysis, r_2 and n_2 denote the number of participants with Grade ≥2 CRS events and number of participants from the second stage of the study ($n_2 = 46$), and B denotes the Beta function.

The futility boundary based on the posterior predictive distribution can be obtained using the exact method to calculate the probability of observing 20 or fewer participants with Grade ≥2 CRS events in 76 participants at the primary analysis, ie,

$$P(\text{IA. r} + r_2 \leq 20|\text{IA. r, IA. n}) = \sum_{r_2=0}^{20-\text{IA.r}} \pi(r_2|\text{IA. r, IA. n})$$

With 30 participants at the interim analysis, if there are 11 or more participants with Grade ≥2 CRS events, further accrual may be stopped for the study. Otherwise, the study will proceed as planned to the primary analysis as described in Section 6.1.

The interim analysis may also be performed at other time points for the purpose of safety assessment and/or supporting clinical development. The exact futility boundary will be updated prior to the time of the analysis based on the actual number of participants enrolled and treated. Table 9 summarizes the futility boundary in terms of number of participants with Grade ≥2 CRS events at the interim analysis.

Table 9. Futility Boundary (Number of Participants with Grade ≥2 CRS Events) at the Interim Analysis

Number of evaluable participants at the interim analysis	15-17	18-21	22-24	25-27	28-31	32-35	36-38	39-42
Maximum # of participants with Grade ≥2 CRS events at the interim analysis to stop the study for futility	7	8	9	10	11	12	13	14

Table 10 presents the operating characteristics of a few scenarios if the interim futility analysis is performed based on the first 15 participants in the Safety Analysis Set. For example, if 3 participants had Grade ≥2 CRS events in the first 15 participants at the interim analysis, the predictive probability of observing ≤20 participants with Grade ≥2 CRS events in 76 participants at the primary analysis is 75.2%.

Table 10. Predictive Probability at the Primary Analysis with 15 Participants at the Interim Analysis

Scenario	Number of Grade ≥2 CRS Event at the Interim Analysis (N=15)	Predictive Probability [Grade ≥2 CRS Events <= 26.3% (20/76) at the Primary Analysis]
1	2/15	91.3%
2	3/15	75.2%
3	4/15	51.4%
4	5/15	27.8%
5	6/15	11.6%
6	7/15	3.7%

8. REFERENCES

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9. APPENDICES

9.1. Appendix 1: 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;
- Thrombocytopenia;
- CD4 lymphocytes decreased
- CD4 lymphocyte percentage decreased
- CD8 lymphocytes decreased
- CD8 lymphocyte percentage decreased
- Platelet count decreased;
- Platelet production decreased.

9.2. Appendix 2: Version History; Summary of Changes in Earlier Versions

Table 11. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 24 May 2021	Original protocol 28 Mar 2021	N/A	N/A
2 21 July 2021	Protocol Amendment 1 09 June 2021	Updates per Protocol amendment and be consistent with the analyses on the program level	• Section 2.1, Section 3.3.1 and CCI [redacted] • Section 2.2: Study design is updated per protocol amendment 1. • Sections 3.5 and Section 6.8.2: The safety reporting period after last dose of study intervention has been increased to 90 days per protocol amendment. • Section 3.5.1: Updated that TEAEs leading to dose interruptions and reductions will be based on the information collected on the exposure CRF. • CCI [redacted] • Section 5.1.2.1: Updated the operating characteristics of the Bayesian 2-stage design based on the IA with 30 patients in Part 1. • Section 5.2.5: Updated definition of cycle. • Section 5.2.12: Updated age calculation. • Section 6: Added scope and timing of the primary analysis and final analysis. • Section 6.1.: Added estimand strategy. • Section 6.3.1: Additional texts added to clarify confirmatory response assessment timing; Table 4 is updated to include PD in scenario 3, 7, 11, 15 and 19; added additional criteria for PD in scenario 21 and 22. • Section 6.3.5: Updated the censoring rule windowing to 70 days (2 cycles +1 week window per cycle).

Table 11. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Section 6.3.8: Updated MRD negativity will be defined by two thresholds. • Section 6.6: Added subgroup of organ function at baseline. • Section 6.7.1.2: Updated sorting order by SOC and PT. • Section 6.7.1.3: Updated disease characteristics. • Section 6.7.1.4: Added penta refractory summary. • Section 6.7.2.2: Updated protocol deviations to be potentially important PDs. • Section 6.7.3: Updated dosing regimen per protocol amendment 1; added dose reduction/interruption due to AEs will be summarized. • Section 6.8.1: Updated AE summaries per MW input and be aligned with the summaries on the program level. • Section 6.8.1.2: Added Other adverse event of clinical interest. • Section 6.8.3: Added additional language for Liver Function Test summary. • Section 7.2.1: Added safety stopping rule for GBS/GB-like AEs, Peripheral Neuropathy/IR Neurologic AEs. • Section 7.2.2: Updated the IA will be performed based on 30 participants in Part 1; updated Table 10 with 15 participants. • Appendix 1: Added List of cytopenias.

9.3. Appendix 3: List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
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
BLQ	below the limit of quantitation
BLRM	Bayesian logistic regression model
CCI	[redacted]
BMI	body mass index
BOR	best overall response
BP	blood pressure
CRR	complete response rate
CI	confidence interval
C_{max}	maximum observed concentration
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
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
DOCR	duration of complete response
CCI	[redacted]
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
EMD	extramedullary disease

Abbreviation	Term
CCI [redacted]	[redacted]
EOS	end of study
EOT	end of treatment
ICANS	immune cell-associated neurotoxicity syndrome
IMWG	International Myeloma Working Group
LLN	lower limit of normal
LLOQ	lower limit of quantitation
MRD	minimal residual disease
MUGA	multigated acquisition
N/A; NA	not applicable; not assessed
NAb	neutralizing antibody
NCI	National Cancer Institute
NE	not evaluable
NGF	next generation flow cytometry
NGS	next generation sequencing
ORR	objective response rate
OS	overall survival
OTR	outside toxicity reference
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia's method)
RDI	relative dose intensity
RP2D	recommended phase 2 dose
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
CCI [redacted]	[redacted]
SMQ	Standardised MedDRA Queries
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse events

Abbreviation	Term
T_{max}	time for C_{max}
TTR	time to response
ULN	upper limit of normal
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization