Protocol C1071008

A PHASE 1B/2, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF ELRANATAMAB (elranatamab) IN CHINESE PARTICIPANTS WITH MULTIPLE MYELOMA WHO ARE REFRACTORY TO AT LEAST ONE PROTEASOME INHIBITOR, ONE IMMUNOMODULATORY DRUG AND ONE ANTI-CD38 ANTIBODY (TRIPLE-CLASS REFRACTORY MM)

Statistical Analysis Plan
(SAP)

Version: **Amendment 2**

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1. VERSION HISTORY

This statistical analysis plan (SAP) for study C1071008 is based on the final approved protocol amendment 4 dated 17 April 2023.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 11 May 2021	Original 18 Mar 2021	N/A	N/A
Amendment 1 12 Aug 2021	Amendment 1 25 Jun 2021	Updated per protocol amendment and be consistent with the analyses on the program level	1. The criteria for placing the study on temporary hold (specifically related to neuropathy or other IR neurological AEs) were defined. 2. The safety reporting period after last dose of study intervention has been increased to 90 days in Sections 3.5 and 6.6.2. 3. Updated minimum requirement for DLT evaluability in Section 4 and 2.1.1. 4. Additional endpoint of PRO EORTC QLQ CIPN20 was added in Sections 3.2.4 and 6.2.11 5. Updated age calculation in Section 5.2.11 6. Updated MRD negativity will be defined by two thresholds in Section 3.2.1.8 7. Added subset analysis in Section 6.4 8. Added penta refractory in Section 6.5.1.4 9. Replaced all PF-06863135 with elranatamab 10. AESI updated in Section 6.6.1.1 11. Section 6.6.3 added additional language for liver function test summary.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			12. Updated Section 6.6.1 13. Section 6.5.3 dose exposure updated 14. Updated Section 6.5.1.3. Disease characteristics 15. Section 6.2.5 Censoring rule windowing updated to 70 days (2 cycles + 1 week window per cycle); 16. Section 6.1.2: Additional texts added to clarify confirmatory response assessment timing; Table 2 is updated to include PD in scenario 3, 7, 11, 15 and 19; added additional criteria for PD in scenario 21 and 22;
Amendment 2 21 Aug 2023	Amendment 4 17 April 2023		1. Section 5.2.4 last cycle duration definition updated; 2. Section 6.1.2 Table 2 added scenario 23 for BOR SD 3. Section 6.4 updated subset analysis 4. Section 6.5.1.3 updated disease characteristics 5. Section 6.5.3 updated study intervention exposure 6. Section 6.5.4 updated pre-medication summary 7. Section 6.6.1.1 updated AESI analysis 8. Section 6.6.2 updated death reporting period 9. Section 3.5.1 updated that TEAEs leading to dose interruptions and reductions will

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			be based on the information collected on the exposure CRF. 10. Section 6.1.2.1 added analysis for BICR vs investigator regarding BOR assessment 11. Section 2.1 added analyses types 12. Section 9.2. added List of MedDRA Preferred Terms for Cytopenia 13. Section 3.2.1.1 added secondary endpoint Objective Response Rate by BICR Baseline EMD Status 14. Clarified throughout that PD is confirmed PD for BOR, PFS, and DOR. 15. Section 6.1.2 use Clopper-Pearson method to calculate exact CIs 16. Section 6.2.3 and 6.2.5 Remove censoring for inadequate baseline for PFS and DOR to align with IMWG guidance. 17. Section 6.2.6 Add that Duration of follow-up will be summarized descriptively and with reverse Kaplan – Meier method. 18. Section 6.2.8 updated MRD negative rate analysis 19. Section 6.3.1 added exploratory efficacy analysis 20. Section 3.3.1 added exploratory efficacy analysis 21. Section 6.5.5 Transplant is added for subsequent anticancer therapy

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			22. Section 6.6.1 updated including AESI. 23. Section 6.6.3 lab data for liver function at anytime are added; details of derive several CTCAE terms are provided; Creatinine clearance calculation is added 24. Section 6.1.2 Align with IMWG and allow no minimum gap for confirmation of response as long as done with separate sample. 25. Section 6.2.3 Descriptive analysis for DOR follow-up added 26. Section 6.2.7 updated TTR analysis 27. Section 6.5.2.1 Added EOS reason may be derived from EOT reason. 28. Added section 6.6.1.2 other adverse events of clinical interest 29. Section 7.1 Updated the posterior probability threshold of ⩾90% to ⩾80% for Grade 3-4 CRS/ICANS and Grade 4 treatment related nonhematologic for the interim safety assessments. 30. Section 6.2.1 Added analyses for derived response for BICR and investigator. 31. Added Hypogammaglobulinemia as oAECI. 32. Sensitivity analyses added for COVID-19 impact on efficacy endpoints 33. Summary of COVID-19 impact was added.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1071008. 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.

The purpose of the study is to evaluate the safety, pharmacokinetics (PK), pharmacodynamic (PD) and the efficacy of elranatamab in Chinese participants with multiple myeloma who are refractory to at least 1 PI, 1 IMiD and 1 anti-CD38 mAb (triple-class refractory MM).

The study will include 2 parts. Phase 1b part is dose confirmation/safety lead-in to establish the safety of elranatamab (76 mg SC QW with two priming doses of 12 mg and 32 mg SC) in order to confirm the recommended Phase 2 dose (RP2D) in Chinese participants. After the RP2D is confirmed to be safe, the Phase 2 part will be initiated to evaluate the efficacy in Chinese participants. Participants who started from the RP2D in the Phase 1b part will contribute to the efficacy evaluation together with other participants in Phase 2. The primary analysis 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. All summaries and analyses associated with a planned analysis will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

2.1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints
Primary:		
Phase 1b: Safety Phase 2: Efficacy	Phase 1b: • To establish the safety of PF06863135 in order to confirm the RP2D in Chinese participants Phase 2: • To determine the efficacy of elranatamab in Chinese participants with RRMM	Phase 1b: • DLTs observed in Cycle 1 (4 weeks) Phase 2: • ORR by BICR per IMWG
Secondary:		
Efficacy	• To further evaluate the efficacy of elranatamab in Chinese participants with RRMM	• DOR by BICR and investigator per IMWG • CRR by BICR and investigator per IMWG • ORR by investigator per IMWG

Type	Objectives	Endpoints
		• DOCR by BICR and investigator per IMWG • PFS by BICR and investigator per IMWG • OS • TTR by BICR and investigator per IMWG • MRD negativity rate (central lab) per IMWG
Safety	• To determine the safety and tolerability of elranatamab	• Aes and laboratory abnormalities by type, frequency, severity (as graded by NCI CTCAE v5.0), seriousness, and relationship to study therapy. • Severity of CRS and ICANS assessed according to ASTCT criteria[1].
PK	• To evaluate the PK of elranatamab	• PK parameters of elranatamab: C_{max}, T_{max}, AUC_{72} and AUC_{last} • Pre- and post-dose concentrations of elranatamab
Immunogenicity	• To evaluate the immunogenicity of elranatamab	• ADAs and NAbs against elranatamab
PRO	• To assess the impact of elranatamab on patient-reported symptoms and functioning	• EORTC QLQ-C30 and MY20 • EORTC QLQ CIPN20 • EQ-5D
Exploratory:		
Efficacy	• To explore additional efficacy of Elranatamab	• sMRD-negativity • DOMRD negativity
Biomarker	• To explore correlations between elranatamab exposure and efficacy, safety and PD/biomarker endpoints, if data allow	• Selected PK, efficacy, safety and PD/biomarker endpoints
Biomarker	• To explore the relationship between elranatamab and the biology of the participant's MM	• Measurements of biomarkers (DNA, RNA, plasma sBCMA level, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens

2.1.1. Primary Estimand(s)

Primary Estimand in Phase 1b: The safety of elranatamab RP2D measured by DLT rate estimated based on data from DLT-evaluable participants during the DLT observation period (Cycle 1 which is 4 weeks) in Phase 1b. The estimand has the following attributes:

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention in Phase 1b part and either experience DLT(s) during the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who receive less than the minimum requirement of the planned doses of study intervention for reason other than treatment-related toxicity are not evaluable for DLTs. The minimum required exposure for DLT evaluability is 4 out of 5 planned doses of elranatamab during the DLT observation period.

- Variable: Occurrence of DLTs. DLTs are defined in protocol Section 4.3.1

- Intercurrent event(s): All data collected after an intercurrent event of new subsequent anticancer therapy will be excluded. Participants without DLTs who discontinues from treatment and receives less than the minimum requirement of the planned doses of study intervention for reason other than treatment-related toxicity are not evaluable for DLT and will be replaced.

- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants.

Primary Estimand in Phase 2: The treatment effect of elranatamab on ORR as assessed by BICR per the IMWG criteria. The estimand has the following attributes:

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention.

- Variable: objective response defined as confirmed sCR, CR, VGPR and PR according to the IMWG criteria based on BICR assessment, from the date of first dose until the first documentation of PD, death or start of new anticancer therapy, whichever occurs first.

- Intercurrent event(s): All data collected after an intercurrent event of subsequent anticancer therapy will be excluded. All response assessments regardless of gaps in disease assessments will be considered. Data will be collected regardless of discontinuation from treatment. Participants who do not have a post-baseline disease assessment due to early PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience PD or stop

disease assessments for any reason prior to achieving an objective response will be counted as nonresponders in the assessment of objective response.

- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an objective response and 2-sided 90% CI for ORR.

2.2. Study Design

Study C1071008 is an open label, multicenter, non-randomized, Phase 1b/2 study to evaluate the safety, PK, PD, and efficacy of elranatamab in Chinese participants with multiple myeloma (MM) who are refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody (triple-class refractory MM). It includes two parts. Phase 1b part is the dose confirmation/safety lead-in phase to establish the safety profile in order to confirm the RP2D in Chinese participants using DLT. After the RP2D is confirmed to be safe, the participants who started from the RP2D in Phase 1b part will contribute to the efficacy evaluation together with other participants in Phase 2.

The Phase 2 part is a single stage design to evaluate the efficacy and safety in Chinese participants. The primary endpoint in Phase 2 part is ORR by BICR, as defined by IMWG. An independent, external physician with expertise in myeloma will review data from site-sourced components of response assessment and provide response assessment at each post-baseline timepoint according to IMWG criteria, while remaining blinded to investigator-assessed responses.

Additionally, all participants from Phase 1b (6 in total) and approximately 6 participants from Phase 2 will undergo intensive PK sampling to obtain the PK profile of elranatamab at specified timepoints. Sparse PK sampling will also be collected in all participants in the Phase 2 part.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

DLT is the primary endpoint of the Phase 1b part and the observation period for DLT is Cycle 1 (4 weeks). The definition of DLT is provided as in Section 4.3.1 of protocol.

Objective response, defined as confirmed sCR, CR, VGPR and PR according to the IMWG criteria based on BICR assessment, from the date of first dose until confirmed PD, death or start of new anticancer therapy, whichever occurs first, is the primary endpoint of the Phase 2 part.

ORR by BICR is defined as the proportion of participants with an objective response by BICR per IMWG criteria, and will be analyzed in the safety analysis set. The primary analysis of ORR will include participants who started from the RP2D (including the participants from both Phase 1b and Phase 2 parts).

3.2. Secondary Endpoint(s)

3.2.1. Efficacy Endpoints

3.2.1.1. Objective Response Rate (ORR) by Investigator

ORR by investigator is the proportion of participants with an objective response assessed by investigator per IMWG criteria in the safety analysis set.

3.2.1.2. Complete Response Rate (CRR)

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

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

3.2.1.3. Duration of Response (DOR)

DOR is defined, for participants with an objective response per IMWG criteria, as the time from the first documentation of objective response that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. DOR will be censored on the date of the last adequate disease assessment for participants who do not have an event (PD or death due to any cause), on the date of the last adequate disease assessment before the new anticancer therapy for participants who start a new anticancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments.

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

3.2.1.4. Duration of Complete Response (DOCR)

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

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

3.2.1.5. Progression-free Survival (PFS)

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

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

3.2.1.6. Overall Survival (OS)

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

3.2.1.7. Time to Response (TTR)

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

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

3.2.1.8. Minimal Residual Disease (MRD) Negativity Rate

MRD negativity rate is the proportion of participants in the safety analysis set with negative MRD per IMWG criteria by bone marrow aspirate (BMA) from the date of first dose until confirmed PD, death or start of new anticancer therapy, whichever occurs first.

MRD negativity will be defined by threshold of 10^{-5}.

3.2.1.9. Biochemical Response Rate

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

3.2.2. Pharmacokinetic Endpoints

PK parameters of elranatamab: C_{max}, T_{max}, AUC_{72} and AUC_{last}. Pre- and post-dose concentrations ofelranatamab

3.2.3. Immunogenicity Endpoints

ADAs and Nabs against elranatamab

3.2.4. Patient-Reported Outcomes (PROs)

Patient-reported outcomes are measured using following instruments:

- European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients core module (EORTC QLQ-C30): EORTC QLQ-C30 is a well-known, reliable and valid self-administered questionnaire used in oncology trials. The QLQ-C30 contains 30 items and is grouped into five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six

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

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

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

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

3.3. Exploratory Endpoint(s)

3.3.1. Additional efficacy

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

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

DOMRD is defined, for participants with negative MRD, as the time from first documentation of negative MRD to the date of first documentation of relapse or death due to any cause, whichever occurs first.

3.3.2. Translational Oncology Biomarkers

Measurements of biomarkers (DNA, RNA, plasma sBCMA level, protein or defined cell types) resulting from analyses of peripheral blood, and/or BM biospecimens

3.3.3. Pharmacodynamic Endpoint

The endpoint for pharmacodynamics is soluble BCMA (sBCMA).

A whole blood sample, to provide plasma for sBCMA assessment, will be collected at the times specified in the SoA (for predose samples, collection should occur prior to administration of elranatamab on that day). sBCMA levels will be measured in plasma at baseline and at various time points during study treatment, which may enable correlations between sBCMA levels and drug exposure and response.

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 non-zero dosing of the study drug.

The date of last dose of study intervention is the latest date of non-zero dosing of the study drug.

Definition of baseline:

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

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

Triplicate ECGs are collected; therefore, the baseline for each ECG measurement is the average of the pre-dose measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average.

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

3.5. Safety Endpoints

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

On-treatment period is defined as the time from the first dose of study intervention through the minimum of [90 days after last dose, (start day of new anticancer therapy – 1 day)]. Anticancer therapy includes drug therapy, stem cell transplant and radiation with curative intent; the start of new anticancer therapy after the first dose of study intervention is derived as outlined in Section 5.2.5. 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 outside the on-treatment period as described above will be listed but not summarized.

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

3.5.1. Adverse Events

Adverse Events (aEs) as characterized by type, severity, seriousness, and relationship to study intervention.

AEs [except cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS)] will be graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 and coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

Severity of CRS and ICANS will be assessed according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria 1 and coded using the most current version of MedDRA.

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

3.5.2. Laboratory Data

Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE version 5.0) and timing.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Population	Description
Safety Analysis Set	All participants enrolled to study who take at least 1 dose of non-zero study intervention.
DLT Evaluable Analysis Set	All participants enrolled to phase 1b part and who have experienced a DLT in the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who received less than minimum requirement of the planned doses of elranatamab for reason other than treatment-related toxicity are not evaluable for DLTs and will be replaced. The minimum required exposure for DLT evaluability is 4 out of 5 planned doses of elranatamab during the DLT observation period, provided a dose was not missed due to toxicity attributed to study drug.
PK Analysis Set	The PK analysis set is a subset of the safety analysis set and will include participants who have at least one postdose concentration measurement.
PK concentration analysis set	Defined as all participants enrolled and treated who have at least 1 PK concentration in the single-dose and/or multiple-dose PK part.
PK parameter analysis set	Defined as all participants enrolled and treated who have at least 1 of the PK parameters of primary interest in the singledose and/or multiple-dose PK part.
MRD evaluable set	Participants in safety analysis set who has post-baseline assessment and achieves sCR/CR.
Immunogenicity Analysis Set	The immunogenicity analysis set is a subset of the safety analysis set and will include participants who have at least one sample tested for ADA.
Biomarker Analysis Set	The biomarker parameter analysis set is a subset of the safety analysis set and will include participants who have at least one baseline biomarker assessment. Analysis sets will be defined separately for biomarkers based on blood , saliva, and bone marrow aspirate samples.

Population	Description
Pharmacodynamic set	Defined as all participants enrolled and treated who have at least 1 reportable PD concentration.
PRO Analysis Set	The PRO analysis set will include all participants in the safety analysis set who completed a baseline and at least one post-baseline PRO assessment.

Note:"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent 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. Hypothesis and Sample Size

The study includes 2 parts: Phase 1b part and Phase 2 part.

The primary objective of the Phase 1b part is to establish the safety of elranatamab in order to confirm the RP2D in Chinese participants. There will be no formal hypothesis testing in this part. Approximately 6 participants will be enrolled and treated in Phase 1b.

The Phase 2 part will test the null hypothesis (H_0) that the ORR by BICR as defined by IMWG is $\leqslant$30% versus the alternative hypothesis (H_a) that the ORR by BICR as defined by IMWG is >30% using a single-stage design based on the exact binomial distribution. The null hypothesis ORR is based on the results of the DREAMM-2 study[2] and the STORM study[3], which were conducted in similar multiple myeloma populations with respect to prior treatments.

In the FIP Study C1071001, as of data-cutoff date 07 September 2020, there were 15 participants who achieved an objective response among the 20 participants who were treated at dose level $\geqslant$ 215 ug/kg. The ORR was 75% with the 95% exact CI (51%-91%). Therefore, it is assumed that the true ORR with elranatamab will be $\geqslant$51%.

A total of 36 participants will be contributed to the hypothesis testing, which includes the participants enrolled and treated in Phase 2 and those participants who started from the confirmed RP2D in Phase 1b. The sample size will provide 80% power to reject the null hypothesis at a 1-sided significance level of 0.05 assuming the true ORR is $\geqslant$51%. The primary analysis 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.

5.1.2. Decision Rules

At the end of DLT observation period, i.e., Cycle 1 (4 weeks), if the DLT rate is less than 1/3 (0 or 1 participant out of 6), Phase 2 part will be initiated after the DLT observation period is concluded for all enrolled participants in Phase 1b portion. If the DLT rate at the monotherapy RP2D meets or exceeds 1/3, the enrollment will stop until further evaluation of sponsor and investigators, and the following decision will be reflected in a protocol amendment.

Based on the design, at the primary analysis, an observed ORR $\geqslant$44.4% (ie, 16 responders out of the 36 participants) will be needed to reject the null hypothesis, and the cohort has demonstrated that the true ORR exceeds 30%. However, at the time of the analysis, the testing rule will depend on the exact number of participants enrolled and treated.

5.2. General Methods

5.2.1. Data Handling After the Cutoff Date

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

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. Definition of Study Day

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

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

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

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

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

5.2.4. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per participant. The definition for each cycle is driven by study drug elranatamab. Elranatamab is administered on Days 1, 8, 15 and 22 of each 28-day cycle. As described in Protocol Section 6.1.1, if a participant has received QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dosing interval should be changed from QW to Q2W. If the participant subsequently

begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to weekly dosing. If the dose interval is changed, cycles should remain the same length (ie, 4-week cycles). In either dosing scenario, the nominal cycle length is 28 days.

Data that was collected in a visit will be reported according to the visit label. However, data that was not collected in a visit such as log CRF pages (for example AE) or laboratory results that will be provided from the central laboratory, will be assigned to cycles by comparing the date of these assessments to cycles defined below. These cycles are defined according to the visit designator and the dates from the exposure CRF pages.

1. For Cycle X, 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, if the participant received study treatment on that visit (ie, any study drug with dose >0 at that visit);

2. For all but the last cycle,

    a. actual cycle stop date is calculated as the start date of the next cycle minus 1 day;

    b. 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

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

The cycle day will be calculated as:

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

5.2.5. 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.

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 ‘Concomitant Treatment’ eCRF pages with category = “Follow-up Cancer Therapy”;
- Start date of radiation therapy recorded in ‘Radiation Treatment’ and ‘Non-drug Treatments (NXT RAD)’ eCRF pages with Curative intent.

- Start date of transplant recorded in "transplant details" eCRF page.

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

5.2.6. Date of Last Contact

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

- All assessment dates (eg, blood draws [laboratory, Pharmacokinetics (PK)], vital signs, physical exam, performance status, ECG, Echocardiograms [ECHO]/multigated acquisition [MUGA] scans, disease assessments);
- Start and stop dates of concomitant therapies including non-drug treatments or procedures;
- Completion dates for PRO Questionnaires;
- Start and end dates of new therapies administered after study intervention discontinuation including systemic therapy, radiation, and surgeries;
- AE start and end dates;
- Last date of contact collected on the 'Survival 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.

5.2.7. Disease Assessment Date

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

5.2.8. Adequate Baseline Disease Assessment

Adequate baseline is defined using the following criteria:

- All baseline disease assessments must be within 28 days prior to and including the date of first dose;
- 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 serumimmunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65)

5.2.9. 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 DOCCR.

5.2.10. Nominal and Unscheduled Visits

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

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

5.2.11. 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.
- Body mass index (BMI) (kg/m^2) = weight (kg)/[height (m)]^2.

For reporting conventions, mean and median should generally be displayed 1 more decimal place than the raw data and standard deviation should be displayed to 2 more decimal places than the raw data. Percentages will be reported to 1 decimal place. The rounding will be performed to 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.

5.2.12. 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.

5.2.13. 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[4] and the CIs for the survival function estimates at particular timepoints will be derived using the log(-log) method.

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.

Summary statistics will not be presented at a particular timepoint if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

In summary tables of concentration-time profiles, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are not collected, not calculated, or below LLOQ.

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:

The following imputation rules apply if the event is unique for a participant or it is the first of a series of similar events; otherwise, the AE Onset Date will not be imputed:

- If the first active day of study intervention is less than AE stop date, then the onset date will be set to first active day of study intervention;
- Otherwise if the first active day of study intervention is after AE stop date, then set the onset date to the earliest of non-missing AE stop date or informed consent date.

AE Stop Date:

Ongoing events will have the AE Stop Date set to the latest of the subject withdrawal/completion date, death date, last active day of study intervention, or AE Onset date.

Imputation will only occur if event is unique for the participant, or it is the last of a series of similar events; otherwise the Stop Date will not be imputed. Adverse Events are deemed similar if they have the same verbatim term.

Resolved events will have the AE Stop Date set to the 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 treatment 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 treatment 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) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of the on-treatment period. PD date below refers to PD date by investigator assessment. If the imputation results in an end date prior to the imputed start date, then the imputed start date should be set to the end date.

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

THEN imputed start date = 31DECYYYY;

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

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

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

  THEN imputed start date = 01JANYYYY

– Both Year (YYYY) and Month (MM) 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

  MM < 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 MM) MM YYYY ;

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

  MM = 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

  MM > 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 MM 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 MM) MM 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 = 01MMYYYY.

5.3.3.5. Other dates

Imputation methods for other partial dates are as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date;
- If both the day and month are missing, the first day of the year is used;
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively;
- If the date is completely missing, no imputation will be performed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. DLT

Point estimate of DLT rate will be calculated. Adverse events constituting DLTs will be listed.

6.1.2. ORR

6.1.2.1. Primary analysis

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

ORR will be analyzed in the safety analysis set. Point estimates of ORR will be calculated along with corresponding 2-sided exact 90% and 95% CIs using Clopper-Pearson method. The null hypotheses will be tested at 1-sided alpha of 0.05 using exact binomial test.

In addition, the frequency (number and percentage) of participants with BOR by BICR in the following response categories will be summarized: sCR, CR, VGPR, PR, MR, SD, PD, not evaluable (NE), objective response (sCR+CR+VGPR+PR), CCR (sCR+CR), VGPR or better (sCR+CR+VGPR), and clinical benefit response (sCR+CR+VGPR+PR+ MR).

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

Table 2. 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 (due to reasons other than EMD or bone marrow plasma cells)	PD (any reason) including PD after initiation of new anticancer therapy		PD

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

	Timepoint response at:			
25	PD (due to reasons other than EMD, or bone marrow plasma cells)	Participant died due to disease before further disease assessment (including death due to disease under study after initiation of new anticancer therapy)		
26	PD (due to EMD, or bone marrow plasma cells) [b]	sCR/CR/VGPR/PR/MR/ SD/NE/PD or no further assessments	No further assessments	
27	Death (due to disease under study)			
28	Death (not due to disease under study)			NE
29	NE	No further assessment		
30	NE	NE/PD (due to reasons other than EMD or bone marrow plasma cells)	No further assessments	
31	PD [c]	sCR/CR/VGPR/PR/MR/ SD/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.

6.1.2.2. Sensitivity analysis

6.1.2.2.1. Sensitivity analysis 1 to evaluate COVID impact, ie, early discontinuation from treatment/study due to COVID-19 without recovering treatment.

The same analysis as in primary analysis (Section 6.1.2.1) will be all repeated on the below defined sensitivity analysis set 1.

The sensitivity analysis set 1 is defined as all participants in safety analysis set excluding participants who get positive COVID-19 test and resulted treatment interruption within 56 days (inclusive) after Day 1 and followed by discontinuation from treatment/study due to progression or COVID-19 including death due to COVID-19 or with COVID-19 without recovering treatment.

6.1.2.2.2. Sensitivity analysis 2 to evaluate COVID impact, ie, early long term treatment interruption and early discontinuation from treatment/study due to COVID-19.

The same analysis as in primary analysis (Section 6.1.2.1) will be all repeated on below sensitivity analysis set 2.

The sensitivity analysis set 2 is defined as all participants in safety analysis set excluding participants with treatment interruption due to COVID-19 occurring within 56 days (inclusive) after Day 1 and followed by remained interrupted for greater than 28 days before recovering treatment or discontinuation from treatment/study due to COVID-19 including death due to COVID-19 or with COVID-19 without recovering treatment.

6.1.2.3. Additional analyses

6.1.2.3.1. BICR vs Investigator assessment

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

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

BOR		BICR assessment							
		sCR (j=1)	CR (j=2)	VGPR (j=3)	PR (j=4)	MR (j=5)	SD (j=6)	PD (j=7)	NE (j=8)
Investigator assessment	sCR (i=1)	$n_{i,j}$							
	CR (i=2)								
	VGPR (i=3)								
	PR (i=4)								
	MR (i=5)								
	SD (i=6)								
	PD (i=7)								
	NE (i=8)								

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

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

$\sum_{i,j=1}^{8}(n_{i,j})$ = N

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

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

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

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

6.2. Secondary Endpoint(s)

6.2.1. ORR by investigator

Point estimates of ORR by investigator will be calculated along with the 2-sided exact 90% and 95% CIs using the Clopper-Pearson method. The frequency (number and percentage) of participants with BOR by investigator in each response categories will be summarized: sCR; CR; VGPR; PR; MR; SD; PD; NE.

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

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

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

6.2.1.1. Sensitivity analysis

The same sensitivity analyses defined in Section 6.1.2.2 will be conducted for ORR per investigator's assessment.

6.2.2. CRR

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

CRR by BICR and CRR by investigator will be summarized separately

6.2.3. DOR

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

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

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

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

6.2.3.1. Sensitivity analysis

6.2.3.1.1. COVID-19 Imapct

This sensitivity analysis will be on confirmed responders in safety analysis set to evaluate the impact of COVID-19.

In addition to censoring rule defined in Section 6.2.5, and additional censoring rule for COVID-19 as defined in Section 6.2.5.1.1, ie, COVID-19 cenosring for PFS, will also be applied.

A responder who had COVID-19 test positive after first documentation of objective response and leading to permanent discontinuation of study treatment will be censored at the date of first diagnosis of COVID-19.

This analysis is for DOR by BICR and investigator, respectively.

6.2.4. DOCR

If at least 3 participants achieve a CR and subsequently have an event, DOCR will be estimated using the same Kaplan-Meier method as described for DOR in Section 6.2.3 and displayed graphically where appropriate. Otherwise only listings will be provided.

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

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

6.2.5. PFS

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

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

PFS will be censored as follows:

- For participants who do not have an event (confirmed PD per IMWG criteria or death due to any cause), censoring will occur on the date of the last adequate disease assessment;
- For participants who start a new anticancer therapy (as defined in Section 5.2.5) 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 3. Adequate post-baseline disease assessment are defined in Section 5.2.9, respectively.

Table 3. 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 [b]	Date of last adequate assessment [b] documenting no PD prior to new anticancer therapy or missed disease assessments	Censored
No progression or death		
New anticancer therapy given prior to PD or death		

a. If the participant dies ≤ 70 days (within 2 cycles accounting for 3 day visit window) after date of first dose of study intervention and did not initiate any new anticancer therapy, the death is an event with date on the death date.

b. 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 [3].

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[5] (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 4. If a participant meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 4. 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 while on treatment with study intervention; more than 70 days after discontinuing study intervention without PD.

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

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

6.2.5.1. Sensitivity analysis

6.2.5.1.1. COVID-19 Impact

This sensitivity analysis will be on safety analysis set.

In addition to all the censoring rules in Section 6.2.5, a patient will be additionally censored for COVID-19 related early discontinuation from treatment/study. In this analysis, a participant will be censored if the participant discontinues from treatment/study during treatment interruption period caused by positive COVID-19 test after Day 1. Reasons for discontinuation from treatment/study may be, for example, progression, death or withdraw of consent. The date of censoring is the date of first diagnosis of COVID-19.

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

Table 5. PFS Censoring Reasons and Hierarchy for COVID-19 Impact

Hierarchy	Condition	Censoring Reason
1	Discontinues from treatment/study during treatment interruption period caused by positive COVID-19 test after Day 1	Permanent discontinuation due to COVID-19
2	Start of new anticancer therapy before event.	Start of new anticancer therapy
3	Event after 2 or more missing or inadequate post-baseline disease assessment after date of first dose	Event after missing or inadequate assessments [a]
4	No event and [withdrawal of consent date ≥ date of first dose or End of study (EOS) = Participant refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	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
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

b. More than 70 days after last adequate disease assessment while on treatment with study intervention; more than 70 days after discontinuing study intervention without PD.

This analysis is for PFS by BICR and investigator, respectively.

6.2.6. OS

OS time will be estimated using the same Kaplan-Meier method and displayed graphically as described for PFS in Section 6.2.5. 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% CI.

Frequency (number and percentage) of participants with death events and censoring reasons will be presented. The event and censoring reasons are as follows:

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

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

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

If considerable amount of patients died due to COVID-19, sensitivity analysis will be performed by censoring these patients at date of COVID-19 diagonsis.

6.2.7. TTR

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

$$\text{TTR (weeks)} = [\text{date of first objective response} - \text{date of first dose} + 1] / 30.4375$$

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

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

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

6.2.8. MRD Negativity Rate

MRD negativity will be defined by threshold of 10^{-5}.

Point estimates of MRD negativity rate will be calculated along with the 2-sided 95% CIs using the Clopper-Pearsonmethod as follows

- MRD negative with confirmed sCR/CR by BICR based on the Safety Analysis Set;
- MRD negative based on the subset who achieved confirmed sCR/CR in the Safety Analysis Set;

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

6.2.9. Biochemical response rate

This analysis will follow primary analysis of ORR.

6.2.10. Pharmacokinetic Analysis

The PK data will be analyzed using the PK analysis set.

The concentrations of elranatamab will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum maximum, and geometric mean) by cycle, visit, and nominal time.

For participants with intensive PK sampling (Phase 1b and 6 participants from Phase 2), individual concentration-time data of elranatamab following the Cycle 1 Day 1 dose will be analyzed separately using non-compartmental analysis to estimate the PK parameters. The PK parameters estimated will include C_{max}, time to maximum concentration (T_{max}), and area under the concentration-time curve from time zero to time of last measurable concentration (AUC_{last}). Actual sample collection times will be used for the parameter calculations. Individual participant and median profiles of the concentration-time data will be plotted by visit using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

For all participants (phase 1b and phase 2), pre-dose and post-dose trough elranatamab concentrations will be summarized descriptively by cycle and visit.

In addition, the PK/PD data from this study may be used to develop a population PK model. The correlations between elranatamab exposure parameters and pharmacodynamic biomarker, efficacy and/or safety outcomes will be explored if data allows. The results of these modeling analyses will be reported separately from the clinical study report.

6.2.11. Immunogenicity Analysis

For immunogenicity data, the percentage of participants with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and after first dose will be generated. Samples may also be analyzed for the presence of Nab, and any data will be similarly summarized. For participants with positive ADA or Nab, the magnitude (titer), time of onset, duration of ADA or Nab response and respective PK concentration 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.

6.2.12. Patient-reported Outcomes

Analysis of the PRO endpoint will be based on the PRO analysis set.

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

EORTC QLQ-C30.
This questionnaire contains 30 questions organized into 5 multi-item functional scales, 3 multi-item symptom scales, a global health/quality of life scale, and 6 single item symptom scales. For each of the 15 scales, the results will be summarized using descriptive statistics including mean, SD, 95% CI, median, minimum, maximum at each timepoint. This will be done based on the observed values as well as change from baseline values. Figures showing mean scores over time will also be generated.

EORTC QLQ-MY20.
This questionnaire contains 20 questions organized into 2 functional scales and 2 symptom scales. As with C30, the analysis of the MY20 scales will consist of descriptive statistics based on observed values, and descriptive statistics based on change from baseline.

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

EORTC QLQ-CIPN20

This questionnaire contains 20 questions which can be grouped into a sensory subscale (9 items), motor subscale (8 items) and autonomic subscale (3 items). As with QLQ-C30, the analysis of the QLQ-CIPN20 scales will consist of descriptive statistics based on observed values and change from baseline values. Frequency statistics for the item-level responses will also be produced. Figures showing mean scores over time will also be generated.

6.3. Exploratory Endpoints

6.3.1. Efficacy analysis

6.3.1.1. Sustained MRD Negativity Rate

If data permits, sustained MRD negativity rate analysis will performed.

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

6.3.1.2. Duration of MRD negativity

If data permits, DOMRD negativity will be analyzed.

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

- Loss of MRD negative state (evidence of clonal plasma cells on NGS, or positive imaging study for recurrence of myeloma);
- Reappearance of serum or urine M-protein by immunofixation or electrophoresis;
- Development of ⩾5% clonal plasma cells in the bone marrow;
- Appearance of any other sign of progression.

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

6.3.2. Translational Oncology Biomarkers

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

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

6.3.3. Pharmacodynamic Analysis

Results will be summarized using descriptive statistics including mean, SD, 95% CI, median, minimum and maximum.

6.4. Subset Analyses

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

The following subset analyses will be performed for ORR by BICR based on the safety analysis set:

- Baseline cytogenetics (high risk = Yes vs. No);
- Baseline bone marrow plasma cells (<50% vs ⩾50%);
- Baseline extramedullary disease (yes vs no);
- Prior stem cell transplant (Yes vs. No)
- Disease stage (1-2 vs 3);
- Number of prior therapies (≤3, >3);
- Type of myeloma (IgG vs non-IgG vs light chain only);
- Age (<65 vs ≥65; <75 vs ≥75);
- Sex (Male vs Female);
- Renal function (CrCl ≤ 60 ml/min vs > 60 ml/min);
- Penta refractory (yes vs no);
- ECOG (0 vs 1-2).

ORR in subsets will be presented in a forest plot.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Analyses of baseline data will be based on the safety analysis set.

6.5.1.1. 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)
- Eastern Cooperative Oncology Group (ECOG) Performance status

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

BMI (kg/m^2) is computed as weight (kg)/[height (m)]^2.

6.5.1.2. Medical history

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's System Organ Class (SOC) and PT from the 'Medical History' eCRF page. Each participant will be counted only once within each PT or SOC. Summaries will be ordered by primary SOC and PT in descending order of frequency. Separate summaries will be provided for past and present conditions.

6.5.1.3. Disease characteristics

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

- Primary diagnosis;
- Current disease stage by Revised Multiple Myeloma International Staging System (R-ISS, Stage I, II, and III, or unknown);
- Eastern Cooperative Oncology Group (ECOG) Performance status (ie, 0, 1, 2);
- Cytogenetics (high risk = Yes/No/Unknown);
- Presence of EMD (target lesions vs non-target lesions only excluding bone vs no) by investigator and BICR, separately;
- Number of bone lesions (1-4, vs 5-10, vs >10) for those with non-target bone lesions only;
- Baseline bone marrow plasma cells (<50% vs ⩾50%);

- Type of myeloma (IgG vs non-IgG [IgA, IgD, IgE, IgM] vs light chain only [kappa light chain, lambda light chain]);
- Type of Measurable disease at baseline (see Section 5.2.8.):
    - Serum M-protein
    - Urine M-protein
    - Serum free light chain (if not measurable by serum or urine);
- Renal function (CrCl $\leqslant$ 60 mL/min vs > 60 mL/min);
- Liver function normal (AST and total bilirubin $\leqslant$ 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.

6.5.1.4. Prior anticancer therapy

The prior anticancer therapies are collected under the 'Response to Regimen', 'Non-drug Treatments' (PRIOR RAD), and 'Prior Transplant Details' (PRIOR TPLT) eCRF pages.

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

- Participants with at least 1 type of prior anticancer treatment;
- Participants with at least 1 prior anticancer drug therapy;
- Participants with at least 1 prior anticancer radiotherapy;
- Participants with prior ImIDs and type (eg, lenalidomide, pomalidomide, or thalidomide);
- Participants with prior PI and type (eg, bortezomib, cafilzomib);
- Participants with prior anti-CD38 mAb and type (eg, daratumumab, isatuximab);
- Participants who are Triple-class refractory (refractory to at least 1 of each type of ImIDs, PI and anti-CD38 mAb);
- Participants who are penta refractory (refractory to 2 IMIDs, 2 Pis and 1 anti-CD38);

- Participants with prior transplant and type (autologous or allogeneic);

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

- Number of prior anticancer therapy regimens: enumerate and in category of missing/1-3/4-5/>5 ;
- Best overall response on the last prior anticancer therapy regimen received;
- Reason for stopping the last prior therapy.

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

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Disposition

The percentages below will be calculated based on the number of participants in the Safety Analysis Set.

- Number of participants enrolled and treated by 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 study intervention, overall and by the main reason for discontinuation of study intervention;
- Number and percentage of participants who discontinued follow-up, overall and by the main reason for discontinuation of follow-up. Participants without a follow-up disposition CRF who died, were lost to follow-up, or withdrew consent during treatment will have their treatment discontinuation reason displayed as their follow-up discontinuation reason.

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

6.5.2.2. Protocol deviation

Protocol deviations will be compiled prior to database closure and will be summarized by category (n[%]) for the Safety Analysis Set. Categories will be assigned by the study Clinician.

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

6.5.3. Study Intervention Exposure

Exposure will be summarized based on the Safety Analysis Set.

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

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

Elranatamab is administered as a subcutaneous injection at 76 mg once every week on Days 1, 8, 15 and 22 of each 28-day cycle (a minimum of 6 days should be maintained between doses) except the first doses of study intervention for both Phase 1b and Phase 2 will be 12 mg (C1D1) and 32 mg (C1D4), which will serve as priming doses. The dose of elranatamab should be increased to 76 mg on Cycle 1 Day 8 as long as the participant meets the criteria listed in Protocol Section 6.5.1. If a participant does not meet these criteria on Cycle 1 Day 8, initiation of dosing with 76 mg should be deferred until the criteria are met. In addition, if a participant has received QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval will be changed from QW to Q2W. If the participant subsequently begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to weekly dosing. If the dose interval is changed, cycles should remain the same length (ie, 4-week cycles).

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

- Treatment duration (weeks) = (minimum of [last dose date + 7, death date] – first dose date)/7, if the last dose occurred in a cycle with QW dosing;
- Treatment duration (weeks) = (minimum of [last dose date + 14, death date] – first dose date)/7, if the last dose occurred in a cycle with Q2W dosing.

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

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

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

The DI and the RDI will be calculated for each participant overall across all cycles and also for each individual cycle as follows:

- Overall DI (mg/week) = Total cumulative dose (mg)/[treatment duration (in weeks)]. If C1D4 is the last visit, duration is 1 week if C1D4 occurred by then;
- Overall Planned DI (mg/week) = Total planned dose (mg)/(planned treatment duration in weeks)
- Cycle DI (mg/week) = Total cumulative dose for a given cycle (mg)/[actual cycle duration (in weeks)]
- Cycle Planned DI (mg/week) = Total planned dose for a given cycle (mg)/4 weeks

The planned dose by cycle is defined as

Cycle 1:

Planned dose (mg/cycle) = 12 + 32 + 76 × 3

After Cycle 1:

- If the participant is on QW dosing schedule for the cycle:

  Planned dose (mg/cycle) = 76 × 4

- If the participant is on Q2W dosing schedule for the cycle:

  Planned dose (mg/cycle) = 76 × 2

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

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

The relative dose intensity (RDI) for each cycle is defined as the actual dose intensity divided by the planned dose intensity for the cycle and expressed in %.

- 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).

6.5.3.1. Dose Reduction and Interruptions

A dose reduction is defined as a nonzero dose that is less than the prior/planned dose.

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.

An interruption is defined as missing a scheduled dose based on the planned dosing frequency (QW or Q2W). The number and percentage of participants with dose interruptions as well as a breakdown of dose interruptions (1/2/3/ ≥4) will be summarized. Percentages will be calculated based on the total number of participants in the Safety Analysis Set.

6.5.4. 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 'General Concomitant Medications' eCRF page. Pre-medications required for CRS will also be summarized (for C1D1,

C1D4, C1D8, and other) separately from the 'Concomitant Medications - Pre-Medications (PREMED)' eCRF page.

Summary of prior medications and summary of concomitant medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (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 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.

6.5.5. Subsequent anticancer therapies

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

Subsequent anticancer drug treatment will be provided in a data listing with data retrieved from 'Next Anticancer Therapy (NXT CNCR)' eCRF page.

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)' eCRF pages, and 'Transplant details (TPL FUP)' eCRF pages.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations.

6.6.1. Adverse Events

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

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

- Any TEAEs;
- Serious TEAEs;
- TEAEs with CTCAE Grade 3-4;

- Grade 5 TEAEs;
- TEAEs leading to dose interruptions of elranatamab;
- TEAEs leading to dose reductions of elranatamab;
- TEAEs leading to permanent withdrawal of elranatamab;
- TEAEs leading to dose interruptions or reductions;
- CRS;
- ICANS
- Peripheral neuropathy.

Seriousness, severity grade, action taken (interruption, dose reduction, and withdrawal) are as reported by the investigator on the adverse event CRF page.

For all the AE summaries by SOC and PT, or PT only, the following cytopenias will be clustered. Each participant will be counted only once within each SOC and clustered terms. However, the number of total events will be based on the individual PTs.

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

Summaries by SOC and PT by alphabetical order for SOC and by descending order of frequency for PT will be provided for:

- TEAEs (all causality);
- TEAEs by maximum severity grade (all causality);

- TEAEs (treatment-related);
- TEAEs by maximum severity grade (treatment-related);
- TEAEs with Grade 3-4 (all causality);
- TEAEs with Grade 3-4 (treatment-related);
- TEAEs leading to death (all causality);
- TEAEs leading to death (treatment-related);
- TEAEs leading to dose interruption (all causality);
- TEAEs leading to dose reduction (all causality);
- TEAEs leading to dose interruptions or reductions (all causality);
- TEAEs leading to permanent withdrawal of elranatamab (all causality);
- TEAEs leading to permanent withdrawal of elranatamab (treatment-related);
- TEAEs by maximum severity grade before and after the switch to Q2W (all causality);
- Serious TEAEs (all causality);
- Serious TEAEs (treatment-related).

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

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

- Most common TEAEs (all causality and treatment-related, separately) by PT and maximum severity grade (All grades, Grade 3-4 and Grade 5);
- Most common serious TEAEs in either cohort (all causality) by PT and maximum severity grade.

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

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

6.6.1.1. Adverse Events of Special Interest

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

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

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

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

- Any AESIs;
- Serious AESIs;
- AESIs by maximum toxicity grade;
  - Had >1 AESI (for CRS and ICANS only);

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

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

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

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

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

- The CRS symptoms (fever, hypoxia and hypotension) as collected on the 'CRS AE' CRFs will be summarized by symptom grade using frequency counts and percentages;
- The ICANS symptoms as collected on the 'ICANS' CRFs will be summarized using frequency counts and percentages;
- The immune effector cell-associated encephalopathy (ICE) scores as collected on the 'ICE' CRFs will be summarized for those participants with ICANS events based on the total ICE scores as follows:
  - ICE score 10;
  - ICE score 7-9;
  - ICE score 3-6;
  - ICE score 1-2;
  - ICE score 0.

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

For peripheral neuropathy, the following summary will be provided:

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

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

AESI may also be summarized by whether a patient received premedication in cycle 1 as specified in the protocol section 6.8.1 (Yes, No).

6.6.1.2. Other Adverse Events of Clinical Interest

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

- Infections:
  - The MedDRA SOC of Infections and infestations.
- Cytopenias:
  - The MedDRA PTs for cytopenias are defined in Appendix 9.2.
- Hypogammaglobulinemia:
  - Including the MedDRA PTs: Blood immunoglobulin G decreased, Hypogammaglobulinaemia, Hypoglobulinaemia, Immunoglobulins decreased and Globulins decreased.
- Injection site reactions:
  - The MedDRA HLT of Injection site reactions.
- Secondary malignancies:
  - The MedDRA SOC of Neoplasms Benign, Malignant and Unspecified.

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

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

- Any oAECIs;
- Serious oAECIs;

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

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

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

6.6.2. Deaths

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

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

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

6.6.3. Laboratory Data

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

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

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

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

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

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

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

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

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

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

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

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

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

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 CTCAE will be presented according to the following categories by scheduled timepoint as well as overall: below normal limit, within normal limits, and above normal limits. In the unlikely event that for a given participant, clinically significant abnormalities are noted in both directions (eg, > Upper Limit of Normal (ULN) and < Lower Limit of Normal [LLN]), then both abnormalities are counted.

The following summary tables will be created:

- Shift summary of laboratory parameters during the on-treatment period by maximum CTCAE grade;
- Shift summary of laboratory parameters from ≤ Grade 2 at baseline to ≥ Grade 3 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. If the criteria for any of the concurrent analyses above are met for <5 participants based on non-concurrent measurements at any timepoint, the concurrent summaries above will be replaced by summaries based on measurements at any timepoint.

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 createdby 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.

6.6.4. Vital Signs

Vital sign data will be listed.

6.6.5. Electrocardiograms

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

ECG summaries will include all ECG assessments from the on-treatment period. RR will be derived from HR. Fridericia's correction (QTcF) will be based on the values collected on the CRF. QTcF will be derived from QT and HR in case QTcF is missing using the following formula:

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

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

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

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

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

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

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

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is an open-label Phase 1b/2 study, the sponsor may conduct unblinded review of the data during the course of study for the purpose of dose confirmation and safety assessment.

7.1. Interim safety assessments

The sponsor will review cumulative safety data during the study conduct. In addition, the incidence of Grade 3-4 CRS, Grade 3-4 ICANS, and Grade 4 treatment related nonhematologic events (excluding CRS and ICANS), Grade 3-4 treatment-related GBS/GBS-like AEs, Grade 3-4 treatment-related peripheral motor neuropathy, Grade 4 treatment-related peripheral neuropathy/immune-related (IR) neurologic events, and Grade 5 events will each be monitored by the sponsor throughout the study. 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 for sponsor's further assessment. (See Protocol Section 10.1.9). 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.

In the event that any criteria for temporary enrollment hold are met, written notification documenting the reason for temporary enrollment hold (or study termination) will be provided by the sponsor to the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study (see also Protocol Section 10.1.9).

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 3-4 CRS results in a posterior probability that the true Grade 3-4 CRS rate exceeding 20% is > 0.80, the study will be put on a temporary hold. Separate but similar criteria will be used for participants with Grade 3-4 ICANS and treatment-related Grade 4 non-hematologic events (excluding CRS and ICANS). Table 6 summarizes the minimum number of participants with such identified events that would meet the above criteria.

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

Number of Evaluable Participants (Phase 1b + 2)	6	7-9	10-13	14-18	19-22	23-26	27-30	31-35
Minimum number of participants with Grade 3-4 CRS events that would lead to a temporary enrollment hold	2	3	4	5	6	7	8	9
Minimum number of participants with Grade 3-4 ICANS events that would lead to a temporary enrollment hold	2	3	4	5	6	7	8	9
Minimum number of participants with Grade 4 treatment-related non hematologic events (excluding CRS and ICANS) that would lead to a temporary enrollment hold	2	3	4	5	6	7	8	9

Prior distribution: Beta (0.5,0.5)

Criteria for 36+ or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 20% is ≥ 0.80.

Evaluable participants are defined as those 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 2 participants experiencing the identified AE out of the first 6 evaluable participants, the study will be put on hold).

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

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

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

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

Number of Evaluable Participants (Phase1b+2)	17-36 [a]				
Minimum number of participants with Grade 3-4 treatment-related GBS/GB-like adverse events that would lead to a temporary enrollment hold*	2				
Number of Evaluable Participants (Phase1b+2)	6-11	12-19	20-27	28-35	36 [b]
Minimum number of participants with Grade 4 treatment-related sensory neuropathy /other 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

Prior distribution: Beta (0.5,0.5)
a.Criteria for 36+ or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 3% is $\geq$0.80.
b.Criteria for 36+ or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 10% is $\geq$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 2 participants experiencing the identified AE out of the first 17 evaluable participants, the study will be put on hold). Before the number of evaluable participants reaches 17, if there are 2 participants experience the identified AE then the study will be put on temporary hold. In other words, as long as 2 participants with identified AE are observed the study will be put on temporary hold regardless of the number of evaluable participants at the time.
** 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 AE out of the first 5 evaluable participants, the study will be put on 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,
- 1 Grade 5 event of ICANS,
- 1 Grade 5 treatment-related peripheral neuropathy or IR neurologic event,

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

8. COVID-19 IMPACT

The analysis of impact of COVID-19 on efficacy endpoints have been incorporated in associated sensitivity analysis for corresponding endpoint in Section 6.

As an AE, in addition to be included in safety summary as other AE's, COVID-19 will be as well particularly summarized at least as following to reflect its impact on study conduct:

1. Number of patients with positive COVID-19 test,
    - Total number of infected patients
    - Number of infected patients by cycle
    - Number of patients inffected by COVID-19 categorized by once, twice and more than twice.
2. Discontinuation due to COVID-19 or COVID-related AE,
3. COVID-19 related protocol deviations,
4. Death due to COVID-19,
5. Dose interruption due to COVID-19,
    - Number of interruptions
    - Cumulative interruption duration.

9. REFERENCES

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10. APPENDICES

10.1. List of Abbreviations

Abbreviation	Term
ADA	Anti-drug antibody
AE	adverse event
ASTCT	American society for transplantation and cellular therapy
BLQ	below the limit of quantitation
BICR	Blinded independent central review
BP	blood pressure
CCRR	Cumulative complete response rate
CI	confidence interval
CR	Complete response
CRS	Cytokine release syndrome
CSR	clinical study report
CTCAE	Common terminology criteria for adverse events
DLT	Dose-limiting toxicity
DOR	Duration of response
DOCCR	Duration of cumulative complete response
ECG	Electrocardiogram
EOT	End of treatment
EMD	Extramedullary disease
ICANS	Immune cell-associated neurotoxicity syndrome
IMWG	International myeloma working group
IR	Immune-related
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minimal response
MRD	Minimal residual disease
N/A	not applicable
Nab	Neutralizing antibody
ND	Not done
NE	Not evaluable
NR	Not reached
NCI	National cancer institute
ORR	Objective response rate
OS	Overall survival
PD	Progression disease
PFS	Progression free survival
PK	pharmacokinetic(s)
PR	Partial response

Abbreviation	Term
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RP2D	Recommended phase 2 dose
RR	respiratory rate
RRMM	Relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sBCMA	Soluble BCMA
sCR	Stringent complete response
SD	Stable disease
SOC	System organ class
TTR	Time to response
ULN	upper limit of normal
VGPR	Very good partial response

10.2. List of MedDRA Preferred Terms for Cytopenia

Cytopenia;

Bicytopenia;

Pancytopenia;

Full blood count decreased;

Bone marrow failure;

Myelosuppression;

Red blood cell count decreased;

Haematocrit decreased;

Haemoglobin decreased;

Anaemia;

Normochromic anaemia;

Normocytic anaemia;

Normochromic normocytic anaemia;

Leukopenia;

Agranulocytosis;

Granulocytopenia;

Granulocyte count decreased;

White blood cell count decreased;

Neutropenia;

Neutrophil count decreased;

Neutrophil percentage decreased;

Band neutrophil count decreased;

Band neutrophil percentage decreased;

Cyclic neutropenia;

Metamyelocyte count decreased;

Lymphopenia;

Lymphocyte count decreased;

Lymphocyte percentage decreased;

CD4 lymphocytes decreased;

CD4 lymphocyte percentage decreased;

Thrombocytopenia;

Platelet count decreased;

Platelet production decreased.