Protocol C1071004
(MAGNETISMM-4)

PHASE 1B/2, OPEN LABEL UMBRELLA STUDY OF ELRANATAMAB (PF-06863135), A B CELL MATURATION ANTIGEN (BCMA) CD3 BISPECIFIC ANTIBODY, IN COMBINATION WITH OTHER ANTI-CANCER TREATMENTS IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 18 March 2021

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1. VERSION HISTORY

This SAP for study C1071004 is based on the protocol amendment v1.0 (dated 14 February 2021).

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 18 Mar 2021	Amendment 1.0 14 Feb 2021	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C1071004. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

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

C1071004 study protocol utilizes an umbrella study design. Combinations of PF-06863135, as a backbone therapy, with other anti-cancer therapies will be included in the protocol as sub-studies. Each sub-study is a stand-alone study including a Phase 1b and Phase 2 part. All the analyses will be performed independently for each sub-study.

The following sub-studies are included in this version of the SAP:

- Sub-study A (PF-06863135 + nirogacestat)

The planned interim analysis and the primary analysis for each sub-study will include all data up to a data cutoff date. For Part 2, the interim analysis for futility is planned after the first 25 participants are treated and followed for 2 post-baseline disease assessments in each sub-study. 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 in each sub-study. All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

2.1. Study Objectives, Endpoints, and Estimands

Phase 1b

Primary Objective	Primary Endpoints	Applicable Sub-study
To assess safety and tolerability of PF-06863135 in combination with other anti-cancer therapies in participants with RRMM in order to select a RP2D(s) for the combination	• DLTs during DLT observation period.	• Sub-study A
Secondary Objectives	**Secondary Endpoints**	**Applicable Sub-study**
To evaluate the overall safety profile	• AEs as characterized by type, frequency, severity as graded by NCI CTCAE version 5.0, timing, seriousness, and relationship to PF-06863135 in combination with other anti-cancer therapies. The severity of CRS and ICANS will be assessed according to ASTCT criteria;[1] • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• Sub-study A
To evaluate anti-myeloma activity of PF-06863135 in combination with other anti-cancer therapies	• ORR and CCRR, per IMWG response criteria as determined by investigator; • Time to event endpoints: TTR, DOR, DOCCR and PFS per IMWG response criteria as determined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• Sub-study A
To evaluate the PK of PF-06863135 given alone and in combination with other anti-cancer therapies. Additionally, PK of the combination partner will be	• PK parameters of PF-06863135: Cmax, Tmax, AUClast after PF-06863135 administration alone as a priming dose; • Pre- and post-dose concentrations of PF-06863135 in combination with other anti-cancer therapies;	• Sub-study A

evaluated when administered with PF-06863135	• Trough serum concentrations of the combination partner at selected cycles.	
To evaluate immunogenicity of PF-06863135 and combination partner(s) as applicable.	• Incidence and titers of ADA and NAb against PF-06863135 or combination partner(s) as applicable.	• Sub-study A
Exploratory Objectives	**Exploratory Endpoints**	**Applicable Sub-study**
To explore the relationship between PF-06863135 and combination partners and the biology of the participant's MM.	• Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens.	• Sub-study A
To explore correlations between PF-06863135 exposure and efficacy, safety, and biomarker endpoints, if data allow.	• Selected PK, efficacy, safety, and biomarker endpoints.	• Sub-study A

Phase 2

Primary Objectives	**Primary Endpoints**	**Applicable Sub-study**
To assess the clinical efficacy of PF-06863135 in combination with other anti-cancer therapies.	• ORR per IMWG response criteria as determined by investigator.	• Sub-study A
Secondary Objectives	Secondary Endpoints	Applicable Sub-study
To determine additional efficacy outcomes of PF-06863135 in combination with other anti-cancer therapies.	• CCRR per IMWG criteria as determined by investigator; • Time to event endpoints: TTR, DOR, DOCCR and PFS per IMWG response criteria as determined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• Sub-study A

To further characterize the overall safety profile and tolerability of PF-06863135 in combination with other anti-cancer therapies.	• AEs as characterized by type, frequency, severity as graded by NCI CTCAE, version 5.0, timing, seriousness, and relationship to PF-06863135 in combination with other anti-cancer therapies. The severity of CRS and ICANS will be assessed according to ASTCT criteria;[1] • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• Sub-study A
To evaluate PK of PF-06863135 at the RP2D in combination with other anti-cancer therapies. Additionally, to collect PK data of combination partner data when administered with PF-06863135.	• Trough concentrations of PF-06863135 and combination partners in selected cycles.	• Sub-study A
To evaluate immunogenicity of PF-06863135 and combination partner(s) as applicable.	• Incidence and titers of ADA and NAb against PF-06863135 or combination partner(s) as applicable.	• Sub-study A
Exploratory Objectives	**Exploratory Endpoints**	**Applicable Sub-study**
To assess the impact of PF-06863135 on patient-reported symptoms and health-related quality of life.	• EORTC QLQ-C30 and MY20.	• Sub-study A
To explore the relationship between PF-06863135 and combination partners and the biology of the participant's MM.	• Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens.	• Sub-study A
To explore correlations between PF-06863135 exposure and efficacy, safety and biomarker endpoints, if data allow.	• Selected PK, efficacy, safety and biomarker endpoints.	• Sub-study A

2.1.1. Estimands (All Sub-studies)

Phase 1b

Primary Estimand: Dose-limiting toxicity (DLT) rate estimated based on data from DLT-evaluable participants during the DLT observation period (35 days from Cycle 0 Day 1 through Cycle 1 Day 28 ie, the 1-week period after the priming dose of PF-06863135 on Cycle 0 Day 1, plus 4 weeks of combination study intervention that begins on Cycle 1 Day 1). The estimand has the following attributes:

- Population: Relapsed/refractory multiple myeloma (RRMM) participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who receive at least 1 dose of the study intervention in the Phase 1b part of the study 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 each investigational product for reason other than treatment-related toxicity are not evaluable for DLTs. The minimum required exposure for DLT evaluability of PF-06863135 and the combination partner agent in the DLT observation period is specified in Section 4.

- Variable: Occurrence of DLTs during the DLT observation period.

- 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.

Phase 2

Primary Estimand: the treatment effect of PF-06863135 in combination with other partner agent on objective response rate (ORR) per the International Myeloma Working Group (IMWG) criteria as determined by investigator. 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 stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) per IMWG response criteria as determined by investigator, from the date of first dose until the first documentation of progressive disease (PD), death or start of new anti-cancer therapy.

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

PD, or stop disease assessments for any reason prior to achieving an objective response will be counted as non-responders.

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

2.2. Study Design

This is a prospective, open-label, multi-center, parallel group, Phase 1b/2 umbrella study to evaluate safety, efficacy, PK, and pharmacodynamics of PF-06863135 in combination with other anti-cancer therapies in participants with RRMM. Each sub-study will be conducted independently, as new agents may be included in the future in additional sub-studies within the framework of this protocol.

Each combination will be assessed individually in 2 study parts:

- A Phase 1b part to evaluate the safety, tolerability, and select a recommended dose and regimen for the combination (combination RP2D).

- A Phase 2 part to further evaluate the efficacy and safety of the combination.

Phase 1b Design:

The number of participants to be enrolled in each sub-study in Phase 1b will depend on the number of dose levels evaluated and the number of participants treated at each dose level. Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment (number of participants to be enrolled in the next cohort) decisions will be based on a Bayesian logistic regression model (BLRM) approach.

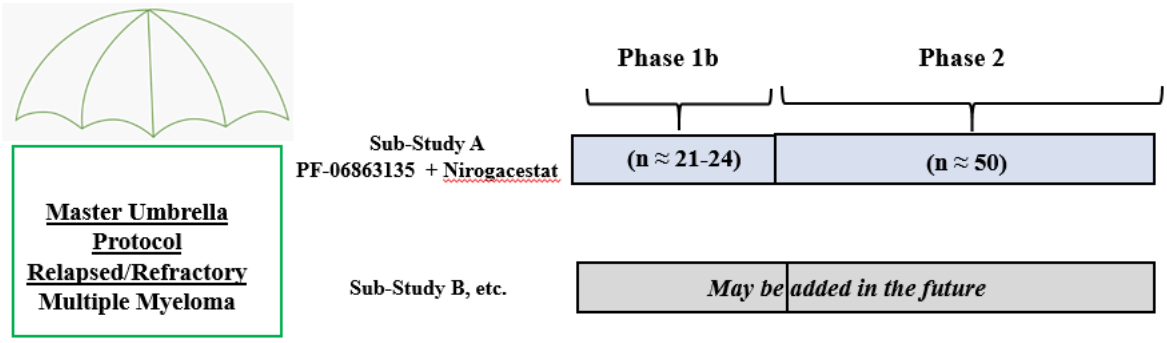
The Phase 1b part of the study will use an escalation approach to determine the RP2D of PF-06863135 when administered in combination with other anti-cancer therapies.

Phase 2 Design:

Phase 2 will begin once the combination RP2D from the Phase 1b is selected. Approximately 50 participants will be enrolled in each sub-study in the Phase 2 part to assess anti-tumor activity and safety of PF-06863135 in combination with other anti-cancer therapies.

Each combination will proceed independently to Phase 2 to further evaluate the safety and anti-tumor activity.

Figure 1. Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Phase 1b

The primary endpoint of the Phase 1b part of each sub-study is the DLTs during the DLT observation period, which is the first 35 days from Cycle 0 Day 1 through Cycle 1 Day 28 of study intervention.

3.1.2. Phase 2

The primary endpoint in the Phase 2 part of each sub-study is ORR per IMWG response criteria, defined as the proportion of participants with an objective response per IMWG response criteria as determined by investigator.

Objective response is defined as having a best overall response (BOR) of confirmed sCR, CR, VGPR or PR.

For all efficacy endpoints per IMWG response criteria, BOR will be assessed based on reported overall responses recorded at evaluation time points from the date of first dose until the first documentation of PD, death or start of new anti-cancer therapy, whichever occurs first.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Cumulative Complete Response Rate

Cumulative complete response rate (CCRR) is defined as the proportion of participants with a cumulative complete response (CCR).

CCR is defined as having a BOR of confirmed sCR or CR per IMWG criteria as determined by investigator, from the date of first dose until the first documentation of PD, death or start of new anticancer therapy.

3.2.1.2. Duration of Response

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

3.2.1.3. Duration of Cumulative Complete Response

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

3.2.1.4. Progression-free Survival

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

3.2.1.5. Overall Survival

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

3.2.1.6. Time to Response

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

3.2.1.7. Minimal Residual Disease Negativity Rate

Minimal Residual Disease (MRD) (assessed by central lab) negativity rate is the proportion of participants with negative MRD per IMWG sequencing criteria by bone marrow aspirate (BMA) at any time after first dose.

3.2.2. Safety Endpoints

Adverse Events (AEs) will be characterized by type, severity, timing, 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.

Laboratory abnormalities will be characterized by type, severity (as graded by NCI CTCAE version 5.0) and timing. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

3.2.3. Pharmacokinetic Endpoints

Phase 1b

- PK parameters of PF-06863135: C_{max}, T_{max}, AUC_{last} after PF-06863135 administration alone as a priming dose;
- Pre- and post-dose concentrations of PF-06863135 in combination with other anti-cancer therapies;
- Trough serum concentrations of the combination partner at selected cycles.

Phase 2

- Trough concentrations of PF-06863135 and combination partners in selected cycles.

3.2.4. Immunogenicity Endpoints

Phase 1b

- Incidence and titers of ADA and NAb against PF-06863135 or combination partner(s) as applicable.

3.3. Exploratory Endpoints

3.3.1. Translational Oncology Biomarkers

- Measurements of biomarkers (DNA, RNA, protein, metabolites or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens.

3.3.2. Patient-Reported Outcomes (Phase 2 Only)

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

- European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients core module (EORTC QLQ-C30): EORTC QLQ-C30 is a well-known, reliable and valid self-administered questionnaire used in oncology trials.[3,4] The QLQ-C30 contains 30 items and is grouped into five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/quality of life (QoL) scale. The questionnaire uses 4-point Likert scales with responses from "not at all" to "very much" to assess all functioning and symptoms items and two 7-point Likert scales for overall health and overall QoL. Responses to all items are then converted to a 0 to 100 scale using a standard scoring algorithm. Higher scores on the functional scales represent higher levels of functioning. Higher scores on the

global health status/QoL scale represent higher health status/quality of life. Higher scores on symptom scales/items represent more extreme symptoms.

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

3.4. Baseline Variables

Start and end dates of study intervention:

The date of first dose (start date) of study intervention in a combination therapy is the earliest date of the first nonzero dose date/time for each of the study drugs.

The date of last dose of study intervention in a combination therapy is the latest date of the last nonzero dose date for each of the study drugs.

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 assessment performed on or prior to the date of the first dose of study intervention will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing.

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

Triplicate ECGs are collected at all timepoints except screening (single ECG at screening); therefore, the baseline for ECG measurement is the pre-dose on Cycle 0 Day 1, or the most recent ECG assessment reported prior to the first administration of study drug. Unscheduled assessments will not be included in the calculation of the average. The average of the replicate measurements will be determined after the derivation of the individual parameters at each timepoint.

3.5. Safety Endpoints

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

On-treatment period is defined as the time from the first dose of study intervention through the minimum of [28 days after last dose, (start day of new anticancer therapy – 1 day)]. Anticancer therapy includes drug therapy and radiation with curative intent; the start of new anticancer therapy after the first dose of study intervention is derived as outlined in Section 5.2.6. Adverse events occurring on the same day as the first dose of study intervention will be considered to have occurred during the on-treatment period. All other assessments which occur on the same day as the first dose of study intervention will be considered baseline assessments (see Section 3.4 for the definition of baseline).

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

3.5.1. Adverse Events

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

3.5.2. Laboratory Data

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

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Participant Analysis Set	Description
DLT-Evaluable Analysis Set	The DLT-evaluable analysis set will include all enrolled participants who receive at least 1 dose of the study intervention in the Phase 1b part of the study and either experience DLT(s) or complete the DLT observation period without DLT. Participants without DLTs who receive less than the minimum requirement of the planned doses of each IP for reason other than treatment-related toxicity are not evaluable for DLTs. The DLT observation period is 35 days from Cycle 0 Day 1 through Cycle 1 Day 28.

	The minimum required exposure for DLT evaluability is defined as follows: • For PF-06863135 (all sub-studies): 4 out of 5 planned doses during the DLT observation period. Participants must be able to receive the full dose on Cycle 1 Day 1 (-1/+3 dosing window) and not require any dose reductions during the DLT observation period; • For nirogacestat (sub-study A): at least 75% of the planned doses and not require any dose reductions during the DLT observation period.
Safety Analysis Set	The safety analysis set will include all enrolled participants who received at least 1 dose of study intervention.
PK Analysis Set	The PK analysis set will include all participants in the safety analysis set who have at least 1 post-dose concentration measurement. The PK parameter analysis set will include all participants in the safety analysis set who have at least one of the PK parameters of interest for PF-06863135.
Immunogenicity Analysis Set	The immunogenicity analysis set will include all participants in the safety analysis set who have at least 1 sample tested for ADA.
Biomarker Analysis Set	The biomarker analysis set will include all participants in the safety analysis set who have at least 1 baseline biomarker assessment. Analysis sets will be defined separately for biomarkers based on blood, and bone marrow samples.
PRO Analysis Set	The PRO analysis set will include all participants in the safety analysis set who completed a baseline (last PRO assessment prior to or on the first dose of study intervention) and at least 1 post-baseline PRO assessment.

Note: "Enrolled" means a participant who is assigned to study intervention in IRT.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

5.1.1.1. Phase 1b

The primary objective in the Phase 1b part of the study is to assess safety and tolerability of PF-06863135 in combination with the combination partner agent in order to select a RP2D for the combination therapy. There is no statistical hypothesis for the Phase 1b part of the study. A BLRM will be utilized for dose escalation of PF-06863135.

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Sample Size Estimation

A minimum of 2-6 DLT-evaluable participants (as defined in Section 4) will be treated at each dose level of PF-06863135. The actual number of participants to be enrolled will depend on the number of dose levels evaluated and the number of participants treated at each dose level in each sub-study. Therefore, it cannot be determined in advance.

For sub-study A, it is estimated that approximately 21-24 DLT evaluable participants will be enrolled and treated with PF-06863135 combination which will include at least 6 DLT evaluable participants treated at the PF-06863135 combination MTD/MAD level and at least 9 DLT evaluable participants at the PF-06863135 combination RP2D level.

If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants in the Phase 1b of each sub-study.

5.1.1.2. Phase 2

The primary endpoint in the Phase 2 part of the study is ORR per IMWG response criteria as determined by investigator. No hypothesis significance testing will be performed. Instead a Bayesian dual-criterion design[8] will be used to estimate the true ORR of PF-06863135 in combination with the combination partner agent. With this design, the following criteria are defined:

- Bayesian statistical significance: Substantial evidence that the true ORR exceeds a null value. For the PF-06863135 combination therapies, Bayesian statistical significance will be achieved if the posterior probability of the true ORR ≥65% exceeds 0.95;

- Clinical relevance: The minimum ORR threshold that could justify further development of a combination. For the PF-06863135 combination therapies, it is defined as the median of the posterior distribution of the true ORR exceeding 75%.

The analysis will use a Beta-binomial model (binomial sampling for number of responders and a Beta prior distribution). A minimally informative beta prior distribution of the true ORR will be used. It is assumed a priori that the true mean ORR for a combination is 65%, so the prior distribution will be Beta (1.3, 0.7). Using this prior and based on the dual criteria defined above, approximately 50 participants will be enrolled in the Phase 2 part of each sub-study and a minimum of 38 objective responses are required to achieve the dual criteria in 50 participants. With exactly 38 objective responses in 50 participants, the observed ORR is 76% with median 75.9% and 90% credible interval of (65.3%, 84.7%) based on the posterior distribution.

5.1.2. Decision Rules (all Sub-studies)

5.1.2.1. Phase 1b

Identification of MTD/MAD

The dosing decision and estimation of the MTD/MAD for each combination will be guided by the estimation of the probability of DLT during the DLT observation period. Other evidence such as safety data beyond DLT window, clinical activity, PK, and PD data will also be evaluated in determining RP2D.

Assessment of Participant Risk

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

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

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[redacted]

5.1.2.2. Phase 2

The Part 2 of each sub-study is designed to have an interim analysis for futility and a primary analysis. The interim analysis will be conducted after the first 25 participants are treated and followed for at least 2 post-baseline disease assessments in each sub-study. 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.

Table 2 presents the operating characteristics of this 2-stage design, ie, the probability of early trial termination at the interim futility analysis and the probability of observing the critical number of objective responses (ie, ≥38 objective responses in 50 participants) at the primary analysis if the true ORR ranges from 65% to 90%. Specifically,

- If the true ORR = 65%, the probability of stopping the study due to futility at the interim analysis is 0.533, and the probability of observing critical number of responses at the primary analysis is 0.064.
- If the true ORR = 80%, the probability of stopping the study due to futility at the interim analysis is 0.047, and the probability of observing critical number of responses at the primary analysis is 0.806.

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

True ORR	Prob of Exceeding Futility Boundary at the Interim (R1/N1 <17/25)	Prob of GO Decision at the Primary Analysis* (R/N ≥38/50)	Prob of No-GO Decision at the Primary Analysis* (R/N <38/50)
65%	0.533	0.064	0.403
70%	0.323	0.218	0.459
75%	0.149	0.502	0.349
80%	0.047	0.806	0.147
85%	0.008	0.967	0.025
90%	<0.001	0.999	0.001

* The study does not meet futility criteria at the interim analysis and continues to the primary analysis.
ORR = objective response rate;
R1 = Minimum number of responses required at the interim futility analysis to continue the study;
N1 = Number of participants at the interim analysis;
R = Minimum number of responses required to meet the dual criteria at the primary analysis;
N = Number of participants at the primary analysis.

At the time of the primary analysis, the critical number of objective responses to be observed will be updated based on the actual number of participants enrolled and treated.

Meeting the dual criteria described above will be considered preliminary evidence that the combination therapy may provide clinically meaningful treatment effect in ORR. However, the decision as to whether a combination will be developed further will depend upon the observed results of both the primary and key secondary efficacy endpoints. As a result, exceeding the critical number of objective responses described above may be sufficient, but may not be necessary, for justifying further development of a combination therapy.

5.2. General Methods

Unless otherwise specified, all analyses will be performed for Phase 1b and Phase 2 separately and with the cohort of RP2D in Phase 1b and Phase 2 combined.

For the Phase 1b part of the study, all analyses will be performed by dose level and with all dose levels combined. For sub-study A, participants on Dose levels 1 and 2 escalated to the next higher dose level(s) will be summarized with the dose level originally assigned.

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. Analyses to Assess the Impact of COVID-19 Pandemic

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

5.2.4. Definition of Study Day

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

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

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

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

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

5.2.5. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per participant. The definition for each cycle is driven by study intervention PF-06863135.

The first cycle of PF-06863135 is 35 days from Cycle 0 Day 1 through Cycle 1 Day 28 (the 1-week period after the priming dose of PF-06863135 on Cycle 0 Day 1, plus 4 weeks of combination study intervention that begins on Cycle 1 Day 1). Starting from Cycle 2, PF-06863135 is administered on Days 1, 8, 15 and 22 of each 28-day cycle. As described in Section 12.5.2 of the protocol, if a participant has received QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dosing interval will be changed from QW to Q2W. If the participant subsequently begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to weekly dosing. If the dose interval is changed, cycles should remain the same length (ie, 4-week cycles). In either dosing scenario, the nominal cycle length is 28 days (except Cycle 1 is 35 days).

- 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 intervention on that visit (ie, any study drug with dose >0 at that visit).

- For all but the last cycle:
  - Actual cycle stop date is calculated as the start date of the next cycle minus 1 day;
  - Actual cycle duration is calculated from Day 1 of a cycle to the day prior to Day 1 of the next cycle, as follows:
    - Actual Cycle Duration (weeks) = (cycle stop date – cycle start date + 1)/7.

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

The cycle day will be calculated as:

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

5.2.6. Definition of Start of New Anticancer Therapy

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

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

- Start date of anticancer drug therapy recorded in the '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.

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

5.2.7. Date of Last Contact

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

- All assessment dates (eg, blood draws [laboratory, Pharmacokinetics (PK)], vital signs, physical exam, performance status, ECG, Echocardiograms [ECHO]/multigated acquisition [MUGA] scans, disease assessments);
- 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.

5.2.8. Disease Assessment Date

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

5.2.9. Adequate Baseline Disease Assessment

Adequate baseline is defined using the following criteria:

- All 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 serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

5.2.10. Adequate Post-baseline Disease Assessment

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

5.2.11. Nominal and Unscheduled Visits

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

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

5.2.12. Standard Deviations and Reporting Conventions

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

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25;
  - In case of missing day: Age [years]: (year/month of given informed consent - year/month of birth);
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth).

The integer part of the calculated age will be used for reporting purposes.

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

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

5.2.13. Analyses for Continuous and Qualitative Variables

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

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

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

5.2.14. Analyses for Time-to-Event Endpoints

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median time with 2-sided 95% CIs. Probabilities of an event at particular timepoints will be estimated with corresponding 2-sided 95% CIs. The CI for the median will be calculated according to Brookmeyer and Crowley, 1982[10] 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.

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

5.3.2. Missing ECG Data

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

5.3.3. Handling of Incomplete or Missing Dates

5.3.3.1. Adverse Events

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

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

5.3.3.2. Exposure

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

- If the last date of study intervention is completely missing and there is no End of Treatment (EOT) CRF page and no death date, the participant should be considered to be ongoing and use the data cutoff date for the analysis as the last dosing date; or

- If the last date of study intervention is completely or partially missing and there is either a PF-06863135 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 intervention is set to the analysis cutoff date in the imputations below.

- If the start date of new anticancer therapy is completely or partially missing, then the imputed start date of new anticancer therapy is derived as follows:
  - Start date of new anticancer therapy is completely missing
    - Imputed start date = min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy]
  - Only year (YYYY) for start of anticancer therapy is available
    - IF YYYY < Year of min [max(PD date + 1, last dose of study intervention +1), end date of new anticancer therapy]

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

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

      THEN imputed start date = 01JANYYYY.
  - Both Year (YYYY) and Month (MMM) for start of anticancer therapy are available
    - IF YYYY = Year of min [max(PD date + 1, last dose of study intervention + 1), end date of new anticancer therapy], AND

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

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

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

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

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

THEN imputed start date = 01 MMM YYYY;

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

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

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

  THEN imputed start date = 01 MMM YYYY.

5.3.3.5. Other Dates

Imputation methods for other partial dates are as follows:

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Phase 1b

DLT rate is calculated as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants in the DLT observation period.

Analyses of DLT will be performed on DLT Evaluable Analysis Set. DLT rate will be summarized and listed by dose levels.

6.1.2. Phase 2

The primary endpoint is ORR, defined as the proportion of participants with an objective response (Section 3.1.2) per IMWG response criteria as determined by investigator.

ORR will be analyzed in the Safety Analysis Set. The median ORR and its corresponding 2-sided 90% credible interval based on the posterior distribution will be calculated. In addition, the observed point estimate of ORR will be calculated along with the 2-sided 90% CIs using the Clopper-Pearson method[11] (exact CI for a binomial proportion).

The frequency (number and percentage) of participants with BOR by investigator in the following response categories will be summarized:

- sCR; CR; VGPR; PR; MR; SD; PD; Not evaluable (NE);
- Objective response (sCR + CR + VGPR + PR);
- VGPR or better (sCR + CR + VGPR);
- Clinical benefit response (sCR + CR + VGPR + PR + MR).

BOR will be assessed based on reported timepoint responses by investigator 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 3). If a participant meets multiple criteria in determining confirmed BOR, the order of criteria in this table will be used to define the hierarchy. No minimal time interval is required between the disease assessments, but a different sample is required for confirmation.

Table 3. 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	sCR	sCR	
4	CR	sCR/CR		CR
5	sCR/CR	CR		
6	CR	NE	CR	
7	VGPR/PR/MR/SD	CR	CR	
8	VGPR	sCR/CR/VGPR		VGPR
9	sCR/CR/VGPR	VGPR		
10	VGPR	NE	VGPR	
11	PR/MR/SD	VGPR	VGPR	
12	PR	sCR/CR/VGPR/PR		PR
13	sCR/CR/VGPR/PR	PR		
14	PR	NE	PR	
15	MR/SD	PR	PR	
16	MR	sCR/CR/VGPR/PR/MR		MR
17	sCR/CR/VGPR/PR/MR	MR		

	Timepoint response at:			
Scenario	**Assessment 1**	**Assessment 2**	**Assessment 3**	**BOR**
18	MR	NE	MR	
19	SD	MR	MR	
20	SD	No further assessments		
21	SD	sCR/CR/VGPR/PR/MR/ SD/PD	No further assessments	SD[a]
22	sCR/CR/VGPR/PR/MR	NE/PD or no further assessment	No further assessments	
23	PD (due to reasons other than EMD or bone marrow plasma cells)	PD (any reason) including PD after initiation of new anticancer therapy		
24	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)		PD
25	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	
26	Death (due to disease under study)			
27	Death (not due to disease under study)			
28	NE	No further assessment		
29	NE	NE/PD (due to reasons other than EMD or bone marrow plasma cells)	No further assessments	NE
30	PD (due to reasons other than EMD, or bone marrow plasma cells)	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.

6.2. Secondary Efficacy Endpoints

6.2.1. Cumulative Complete Response Rate

CCRR is defined as the proportion of participants with a CCR per IMWG criteria as determined by investigator.

Point estimates of CCRR will be calculated along with corresponding 2-sided exact 95% CIs using the Clopper-Pearson method.[11]

6.2.2. Progression-free Survival

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

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

PFS will be censored as follows:

- For participants who do not have an event (PD per IMWG criteria or death due to any cause), censoring will occur on the date of the last adequate disease assessment;
- For participants who start a new anticancer therapy (as defined in Section 5.2.6) prior to an event, censoring will occur on the date of the last adequate disease assessment before the new anticancer therapy;
- For participants with an event after a gap of 2 or more missing disease assessments, censoring will occur on the date of the last adequate disease assessment before the gap;
- Participants who do not have an adequate baseline disease assessment or 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, ≤8 weeks after the date of first dose) in which case the death will be considered an event.

The censoring and event date options to be considered for the PFS analysis are presented in Table 4. Adequate baseline disease assessment and adequate post-baseline disease assessment are defined in Section 5.2.9 and Section 5.2.10, respectively.

Table 4. Outcome and Event Dates for PFS Analyses

Scenario	Date of Event/Censoring	Outcome
No adequate baseline assessment	Date of first dose of study intervention	Censored[a]
Progression or death 1. After at most 1 missing or inadequate post-baseline disease assessment or 2. ≤62 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 ≤62 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.[6]

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[12] (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented along with the overall event and censor rates.

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

Table 5. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
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

a. More than 62 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.

6.2.3. Duration of Response

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

$$\text{DOR (months)} = [\text{date of event or censoring} - \text{first date of OR} + 1] / 30.4375$$

The censoring rules for DOR are as described for PFS in Section 6.2.2, except that participants will not be censored for inadequate baseline assessment or for no adequate post-baseline assessment, as only participants with an OR are included in the analysis of 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 6.2.2 and displayed graphically where appropriate. Otherwise only listings will be provided.

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

6.2.4. Duration of Cumulative Complete Response

DOCCR is defined, for participants with a CCR per IMWG criteria as determined by investigator, as the time from the first documentation of CCR that is subsequently confirmed, until PD per IMWG criteria, or death due to any cause, whichever occurs first. DOCCR will be calculated as follows:

DOCCR (months) = [date of event or censoring – first date of CCR + 1] / 30.4375

The censoring rules for DOCCR are as described for DOR in Section 6.2.3.

If at least 3 participants achieve a CCR and subsequently have an event, DOCCR 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 DOCCR rate at 3, 6, 9, and 12 months (and in subsequent 6-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

6.2.5. Overall Survival

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

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

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

OS time will be estimated using the same Kaplan-Meier method and displayed graphically as described for PFS in Section 6.2.2. Median OS and 2-sided 95% CI will be provided. The OS rate at 12, 24, and 36 months (and in subsequent 12-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

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

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

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

6.2.6. Time to Response

TTR is defined, for participants with an OR per IMWG criteria as determined by investigator, as the time from the date of first dose to the first documentation of OR that is subsequently confirmed. TTR will be calculated in weeks as follows:

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

TTR will be summarized using simple descriptive statistics (mean, standard deviation, minimum, median, and maximum).

6.2.7. Minimal Residual Disease Negativity Rate

MRD negativity rate is defined as the proportion of participants with negative MRD (assessed by central lab) per IMWG sequencing criteria at any time after first dose of study intervention.

Point estimates of MRD negativity rate will be calculated along with the 2-sided 95% CIs using the Clopper-Pearson method.[11]

MRD negativity rate will also be summarized among participants who achieved CCR with 2-sided 95% CIs.

If data permits, MRD-negativity status at 1-year, 2-year and 3-year from the time of first documentation of MRD-negativity may be summarized by number and percentage among participants who achieved CCR and MRD negativity.

6.3. Other Secondary Endpoints

6.3.1. Pharmacokinetic/Pharmacodynamics

Pharmacokinetic parameter analyses will be based on the PK Analysis Set.

6.3.1.1. PF-06863135

PK data analyses will include descriptive summary statistics of the predose and postdose serum concentrations, and PK parameters of PF-06863135 for each sub-study by study visit and time point. Box and Whisker plots for predose PF-06863135 concentrations by study visit and PK parameters (C_{max} and AUC_{last}) will be generated. Values below the limit of quantitation for PF-06863135 and other analytes will be treated as zero in the descriptive statistics calculations. For additional details on handling missing and BLQ values, please refer to Section 5.3.1.

In addition, the PK data from this study may be used to develop a population PK model. PK data from this study maybe pooled with other studies for population PK model development. The correlations between PF-06863135 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.

6.3.1.2. Nirogacestat

PK data analyses will include descriptive summary statistics of predose serum concentrations of nirogacestat by study visit and time point. Box and Whisker plots for predose serum concentrations of nirogacestat by study visit will be generated. PK data from this study maybe pooled with other studies for population PK model development. The correlations between nirogacestat 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.

6.3.2. Immunogenicity

Immunogenicity data will be analyzed in the Immunogenicity Analysis Set.

The percentage of participants with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-baseline will be generated. Samples may also be analyzed for the presence of neutralizing antibodies (NAb), and any data will be similarly summarized. For participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit.

The potential impact of immunogenicity on PK and clinical response including pharmacodynamic markers, safety/tolerability and efficacy will be explored, if warranted by the data. This analysis may be reported separately from the CSR.

6.4. Exploratory Endpoints

The following exploratory endpoints analyses may be performed. The results may be presented separately from the main CSR.

6.4.1. Biomarker Analysis

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

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

6.4.2. Patient-Reported Outcomes

The following PRO analyses will be performed to support the CSR development. All other PRO analyses described in the study protocol but are not included in this SAP will be described in detail in a separate PRO analysis plan.

Analysis of the PRO endpoints will be based on the PRO Analysis Set.

Completion Status

The number and percentage of participants who completed these instruments at each time point 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 performed based on the observed values as well as change from baseline values.

EORTC QLQ-MY20

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

6.5. Subset Analyses

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

The following subset analyses will be performed for ORR as determined by investigator for Phase 2 part only based on the Safety Analysis Set:

- Baseline cytogenetics (high vs standard risk);
- Baseline extramedullary disease (yes vs no);
- Disease stage (1-2 vs 3);
- Number of prior therapies (≤4, >4);
- Type of myeloma (IgG vs other);
- Age (<65 vs ≥65; <75 vs ≥75).

ORR in subsets will be presented in a forest plot.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

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

6.6.1.1. 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);
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not Reported, Unknown);
- Ethnicity (Hispanic, Not Hispanic, Not reported);
- Geographic Region (North America, Europe, Asia, Other).

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

6.6.1.2. Medical History

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's SOC and PT from the 'Medical History' CRF page. Each participant will be counted only once within each PT or SOC. Summaries will be ordered by SOC and PT in descending order of overall frequency in Phase 2. In case of equal frequency, alphabetical order will be used. Separate summaries will be provided for past and present conditions.

6.6.1.3. 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 (0, 1);
- Cytogenetics (including high vs standard risk);
- Presence of extramedullary disease;
- Type of myeloma (IgG vs non-IgG or unknown);

- Type of Measurable disease at baseline (see Section 5.2.9):
  - Serum M-protein;
  - Urine M-protein;
  - Serum free light chain.

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.

6.6.1.4. Prior Anticancer Therapy

The prior anticancer therapies are collected under the 'Response to Regimen -Prior Cancer Therapy', 'Non-drug Treatments – Prior Radiation Therapy' and 'Transplant Details - Prior' eCRF pages.

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

- Participants with 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 proteasome inhibitor and type (bortezomib, cafilzomib, ixazomib);
- Participants with prior anti-CD38 antibody and type (daratumumab, isatuximab);
- Participants who are Triple-class refractory (refractory to at least 1 of each type above);
- 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: missing 1/2/3/4/≤4/>4;
- 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 of Phase 2. In case of equal frequency, alphabetical order will be used.

6.6.2. Study Conduct and Participant Disposition

6.6.2.1. Disposition

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

- Number of participants enrolled and treated by country and site;
- Number and percentage of participants in each of the analysis sets defined in Section 4;
- Number and percentage of enrolled participants with study intervention ongoing, discontinued or not given;
- Number and percentage of enrolled participants who discontinued the study intervention, overall and by the main reason for discontinuation of study intervention;
    - Discontinued PF-06863135;
    - Discontinued the combination partner agent (presenting the study drug name in the summary table).
- Number and percentage of participants who entered follow-up;
- Number and percentage of participants who discontinued follow-up, overall and by the main reason for discontinuation of follow-up;
- Number and percent of participants on Dose levels 1 and 2 escalated to the next higher dose level(s) (Phase 1b only).

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

6.6.2.2. Protocol Deviations

Protocol deviations will be compiled prior to database lock 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.

6.6.3. Study Intervention Exposure

Exposure will be summarized based on the Safety Analysis Set.

Exposure to PF-06863135

PF-06863135 is administered as a subcutaneous injection once every week on Days 1, 8, 15 and 21 of each 28-day cycle (a minimum of 6 days should be maintained between doses) except the first dose will be administered on Cycle 0 Day 1, which will serve as a priming dose. The dose interval will be changed from QW to Q2W in participants with a durable response (PR or better persisting for ≥2 months) who received at least 6 cycles of therapy. If the participant subsequently begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to weekly dosing. If the dose interval is changed, cycles should remain the same length (ie, 4-week cycles).

The summary of treatment exposure to PF-06863135 will include the following information:

- Treatment duration (weeks) and planned treatment duration (weeks);
- Number of cycles started per participant (mean, median, min, max);
- Number and percent of participants starting a cycle (any cycle, cycle 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, >=12 cycles);
- Total number of doses received;
- Total cumulative dose (mg);
- Total planned cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall planned dose intensity (mg/week);
- Overall relative dose intensity (%);
- Number and percent of responding participants after 6 cycles who switched from QW to Q2W;

- The duration of PF-06863135 (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 total cumulative dose (mg) of PF-06863135 is the sum of the actual doses that the participant received during the study; the cumulative dose (mg) of PF-06863135 per cycle is the sum of the actual doses that the participant received within that cycle (ie, total dose administered [mg]).

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

> Planned treatment duration (weeks) = 1 (1 week for Cycle 0) + number of cycles started × 4.

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

Overall:

- Overall DI (mg/week) = Total cumulative dose (mg)/[treatment duration (in weeks)];

- Overall Planned DI (mg/week) = Total planned dose (mg)/(planned treatment duration in weeks);

- Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] × 100.

By Cycle:

- Cycle DI (mg/week) = 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;

- Cycle RDI (%) = [Cycle DI (mg/week) / Cycle Planned DI (mg/week)] × 100.

The planned dose by cycle is defined as

Cycle 0:

- Planned dose (mg/cycle) = Priming dose.

After Cycle 0:

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

  Planned dose (mg/cycle) = Full dose × 4.

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

  Planned dose (mg/cycle) = Full dose × 2.

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

Exposure to Nirogacestat (Sub-study A)

Nirogacestat is administered orally twice daily (BID) at 100 mg dose level in 28-day cycle.

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

- Treatment duration (weeks) and planned treatment duration (weeks);
- Total cumulative dose (mg);
- Total planned cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose intensity (%).

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

> Treatment duration (weeks) = (last dose date of nirogacestat - first dose date of nirogacestat + 1)/7

The cumulative dose (mg) of nirogacestat is the sum of the actual dose levels that the participant received during the study (ie, total dose administered [mg]).

The DI and RDI of nirogacestat will be calculated for each participant during the study. The DI (mg/week) of nirogacestat is defined as

> DI (mg/week) = [cumulative dose (mg)]/[treatment duration (weeks)]

The RDI of nirogacestat is defined as the ratio of the DI and planned dose intensity and expressed in %

> RDI (%) = 100× [DI (mg/week)/[7×2×100 (mg/week)].

6.6.3.1. Dose Reductions, Interruptions, and Delays

Dose Reduction

For PF-06863135 and nirogacestat, a dose reduction is defined as a non-zero dose that is less than the prior dose and less than the planned dose in the protocol.

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

Dose Interruption

For PF-06863135, an interruption is defined as missing a scheduled dose based on the planned dosing frequency (QW or Q2W).

For nirogacestat, an interruption is defined as a 0 mg dose administered on 1 or more days. (Note: A dose interruption is not considered a dose reduction).

What follows defines how dose interruptions of nirogacestat will be counted in the case of multiple dose interruptions:

- If an interruption occurs consecutively for at least 2 days due to the same reason, then it will be counted only once (example: If the actual dose on Days 1-3 is 100 mg BID and actual dose on Days 4-5 is 0 mg and dose interruption on Days 4-5 is due to AE, then the total number of dose interruptions is 1).

- If an interruption occurs consecutively for at least 2 days due to different reasons, then it will be counted for each reason (example: If the actual dose on Days 1-3 is 100 mg and actual dose on Days 4-5 is 0 mg and dose interruption on Day 4 is due to AE and dose interruption on Day 5 is due to dosing error, then the total number of dose interruptions is 2).

- If an interruption occurs for more than 1 day due to the same reason, but the days are not consecutive, ie, there is at least 1 dosing day in between, then each dose interruption will be counted as a different occurrence (example: if the actual dose on Days 1, 3, and 5 is 100 mg BID and actual dose on Days 2 and 4 is 0 mg, and dose interruptions on Day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2).

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.

Dose Delay

Section 12.10.2 in the protocol specifies that if PF-06863135 cannot be administered on the planned day, it should be skipped until the next planned dose (ie, if Day 15 dose cannot be administered, the dose should be skipped until Day 22). Therefore, dose delay is not applicable to PF-06863135 per protocol.

Dose delay is not applicable to nirogacestat (sub-study A).

6.6.4. Concomitant Medications and Nondrug Treatments

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

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

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

Summary of prior medications, concomitant medications and summary of pre-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 Phase 2. 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.

6.6.5. 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 'Follow-up Cancer Therapy' 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 'Response to Regimen – Follow-up Cancer Therapy', 'Non-drug Treatments – Follow-up Radiation', 'Follow-up Cancer Surgery' eCRF pages.

6.7. Safety Summaries and Analyses

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

6.7.1. Adverse Events

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

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

- Any TEAE;
- Serious TEAE;
- TEAE with CTCAE Grade 3-4;
- Grade 5 TEAE;
- TEAEs leading to dose interruptions of PF-06863135;
- TEAEs leading to dose interruptions of the combination partner agent (presenting the study drug name in the summary table);
- TEAEs leading to dose reductions of PF-06863135;
- TEAEs leading to dose reductions of the combination partner agent;
- TEAEs leading to withdrawal of PF-06863135;
- TEAEs leading to withdrawal of the combination partner agent;
- TEAEs leading to withdrawal of all study drugs;
- CRS;
- ICANS.

Related TEAEs will be summarized by each individual study drug as follows:

- Related to any study drug;
- Related to PF-06863135;
- Related to the combination partner agent (presenting the study drug name in the summary table).

Seriousness, toxicity grade, action taken (interruption, reduction, and withdraw) are as reported by the investigator on the adverse event CRF.

Summaries by SOC and PT in descending order of the frequency in Phase 2 will be provided for:

- TEAEs (all causality);
- TEAEs by maximum toxicity grade (all causality);
- TEAEs (treatment-related);
- TEAEs by maximum toxicity grade (treatment-related);
- TEAEs leading to death (all causality);
- TEAEs leading to death (treatment-related);
- TEAEs leading to dose interruption of PF-06863135 (all causality);
- TEAEs leading to dose interruption of PF-06863135 (treatment-related);
- TEAEs leading to dose interruption of the combination partner agent (all causality);
- TEAEs leading to dose interruption of the combination partner agent (treatment-related);
- TEAEs leading to dose reduction of PF-06863135 (all causality);
- TEAEs leading to dose reduction of PF-06863135 (treatment-related);
- TEAEs leading to dose reduction of the combination partner agent (all causality);
- TEAEs leading to dose reduction of the combination partner agent (treatment-related);
- TEAEs leading to withdrawal of PF-06863135 (all causality);
- TEAEs leading to withdrawal of PF-06863135 (treatment-related);
- TEAEs leading to withdrawal of the combination partner agent (all causality);
- TEAEs leading to withdrawal of the combination partner agent (treatment-related);
- Serious TEAEs (all causality);
- Serious TEAEs (treatment related).

An event will be considered treatment related if the investigator considered the event related to one or both of study drugs given in combination, or if relationship is missing. Each participant will be counted only once within each SOC and PT.

The following summaries will be provided by PT only (ie, summaries will not include SOC) in descending order of the frequency in Phase 2 for:

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

Each participant will be counted only once within each PT.

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

6.7.1.1. Adverse Events of Special Interest

For all sub-studies, CRS and ICANS are adverse event of special interest (AESI) and will be assessed (including severity assessment) according to ASTCT criteria.[1] Both CRS and ICANS will be collected on the AE CRF page and coded using the most current version of MedDRA. CRS will have the PT coded as “cytokine release syndrome”, and ICANs will have the PT coded as “immune effector cell-associated neurotoxicity syndrome”.

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

- Any AESIs;
- Serious AESIs;
- AESIs with CTCAE Grade 3-4;
- Grade 5 AESIs;
- AESIs leading to dose interruption of PF-06863135 and the combination partner agent;
- AESIs leading to dose reduction of PF-06863135 and the combination partner agent;

- AESIs leading to permanent withdrawal of PF-06863135 and the combination partner agent.

In addition, time to onset of the AESI, and time to resolution of the AESI (in days) will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum).

A summary of AESI symptoms as collected from 'CRS AE', 'ICANS' and 'ICE' CRFs will be provided. Time to onset of the AESI symptoms, and time to resolution of the AESI symptoms (in hours and/or in days as appropriate) will be summarized.

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

6.7.2. Deaths

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

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

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

6.7.3. Laboratory Data

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

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

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

Additionally, laboratory results will be programmatically classified according to NCI-CTCAE version 5.0 grade. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summary statistics the number and percentage of participants corresponding to grades that only include non-quantitative criteria will be displayed as a blank or NA (not assessed) rather than 0. If there is any overlap between grade criteria (eg, CTCAE grading criteria for Creatinine

Increased – a value can fall into one range based on comparison to Upper Limit of Normal (ULN) and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data.

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

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

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

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

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

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

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

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

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

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

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

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

Abnormalities will be described using the worst grade by scheduled timepoint and overall. Worst case overall will be determined using laboratory results from scheduled and unscheduled visits. Several laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high (hyper) values can be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 Hypercalcemia will be classified as a Grade 0 Hypocalcemia. For CTCAE terms that can be derived using one of several laboratory tests, the maximum postbaseline grade for a given participant and CTCAE term will be the maximum across all possible laboratory tests.

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

The following summary tables will be created:

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

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

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

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

- ALT≥3×ULN, ALT≥5xULN, ALT≥10×ULN, ALT≥20×ULN
- AST≥3×ULN, AST≥5xULN, AST≥10×ULN, AST≥20×ULN
- (ALT or AST)≥3×ULN, (ALT or AST)≥5×ULN, (ALT or AST)≥10×ULN, (ALT or AST)≥20×ULN
- TBILI≥2×ULN
- Concurrent ALT≥3×ULN and TBILI≥2×ULN
- Concurrent AST≥3×ULN and TBILI≥2×ULN
- Concurrent (ALT or AST)≥3×ULN and TBILI≥2×ULN
- Concurrent (ALT or AST)≥3×ULN and TBILI≥2×ULN and ALP≥2×ULN
- Concurrent (ALT or AST)≥3×ULN and TBILI≥2×ULN and ALP≤2×ULN or missing

Concurrent measurements are those occurring on the same date.

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

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created by graphically displaying:

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

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

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

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

6.7.4. Vital Signs

Vital sign data will be listed.

6.7.5. Electrocardiograms

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

ECG summaries will include all ECG assessments from the on-treatment period. RR will be derived from HR. Fridericia's correction (QTcF) will be based on the values collected on the CRF.

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.

All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. Data listings will contain the means from a triplicate as well as the parameters from each of the 3 ECGs. Note that using the mean value may result in a participant having a measurement that is not represented by an actual ECG.

7. INTERIM ANALYSES

7.1. Introduction

There are interim safety assessments and an interim analysis for futility planned on each sub-study.

For both Part 1b and Part 2 of each sub-study, an internal safety review team will review safety and tolerability data on an ongoing basis for the interim safety assessments.

For Phase 2 part of each sub-study, an interim analysis for futility will be conducted after the first 25 participants are treated and followed for at least 2 post-baseline disease assessments without holding participant enrollments. The interim analysis will be performed on the primary endpoint of ORR using the methodology described in Section 6.1.1 by the Sponsor. The internal core study team will review and evaluate the efficacy data at the interim futility analysis.

7.2. Interim Analyses and Summaries

7.2.1. Interim Safety Assessments

An internal safety review team will review cumulative safety data during the study conduct. In addition, the incidence of Grade 3-4 CRS, Grade 3-4 ICANS and Grade 4 treatment-related nonhematologic events (excluding CRS and ICANS) will each be monitored throughout the study. If the number of participants observed to have such identified events exceeds a prespecified threshold, the sub-study will be placed on a temporary enrollment hold. During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. Participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the investigator in consultation with the Sponsor.

The criteria for placing the sub-study on temporary hold for safety reasons are based on Bayesian posterior probabilities. Using a non-informative Beta (0.5, 0.5) prior distribution, if the number of participants observed to have Grade 3 or 4 CRS results in a ≥0.90 posterior probability that the true Grade 3 or 4 CRS rate exceeds 20%, the sub-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. Identified Events That Would Prompt Temporary Enrollment Hold

Number of Evaluable Participants	8-11	12-14	15-18	19-22	23-26	27-30	31-34
Minimum number of participants with Grade 3-4 CRS events that would lead to a temporary enrollment hold	4	5	6	7	8	9	10
Minimum number of participants with Grade 3-4 ICANS events that would lead to a temporary enrollment hold	4	5	6	7	8	9	10
Minimum number of participants with Grade 4 treatment-related non-hematologic events (excluding CRS and ICANS) that would lead to a temporary enrollment hold	4	5	6	7	8	9	10

Prior distribution: Beta (0.5,0.5)

Criteria for 35+ or more evaluable participants will be calculated such that the sub-study will be put on temporary hold if the posterior probability that the true event rate exceeds 20% is greater than or equal to 0.90.

Evaluable participants are defined as those having an identified event or those without such an event who have been followed for at least 35 days from first dose.

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

- 1 Grade 5 event of CRS (by ASTCT criteria);
- 1 Grade 5 event of ICANS (by ASTCT criteria);
- 2 Grade 5 events across all other categories (treatment-related Grade 5 non-hematological events [excluding CRS or ICANS], treatment-related Grade 5 hematological events).

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

7.2.2. Interim Analysis for Futility

For Phase 2 part of the study, an interim analysis for futility will be conducted on the first 25 participants enrolled and treated. The primary endpoint of ORR will be evaluated at this analysis using a futility boundary based on the predictive probability. More specifically, a combination may stop for futility if the predictive probability of observing ≥38 objective responses in 50 patients at the primary analysis based on the data observed at the interim analysis is <0.05.

The posterior beta-binomial predictive distribution for the number of responders in the second stage of the study is as follows:

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

where IA.r and IA.n denote the number of responses and number of participants at the interim analysis, r_2 and n_2 denote the number of responses and number of participants from the second stage of the study ($n_2 = 25$), and B denotes the Beta function.

The futility boundary based on the posterior predictive distribution can be obtained using the exact method to calculate the probability of observing ≥38 objective responses in 50 participants at the primary analysis, ie,

$$P(IA.r + r_2 \geq 38 | IA.r, IA.n) = \sum_{r_2=38-IA.r}^{n_2} \pi(r_2 | IA.r, IA.n)$$

With 25 participants at the interim analysis, if there are ≤16 (64%) objective responses observed, further accrual may be stopped for the combination. Otherwise, the study will proceed as planned to the primary analysis as described in Section 5.1.2.2.

The exact futility boundary will be updated prior to the time of the analysis based on the actual number of participants enrolled and treated in each sub-study.

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9. APPENDICES

9.1. Appendix 1: BLRM Design CCI [redacted]

This section provides the details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model CCI [redacted]

Statistical Model

The statistical model for dose-DLT data CCI [redacted]
CCI [redacted]

The monotherapy RP2D of PF-06863135 is 76 mg, which was determined in Study C1071001. In this sub-study, the initial dose level of PF-06863135 will be 4 mg with a priming dose of 4 mg for the first dose. The dose level of nirogacestat will remain at 100 mg BID.

CCI [redacted]

Description of the Meta-Analytic-Predictive Approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies. Let r_{ds} and n_{ds} be the number of participants with a DLT, and the total number of participants, respectively, at dose d in historical trial s ($s = 1, \ldots, \langle S \rangle$). The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

The historical trials are partitioned into $\langle G \rangle$ exchangeability groups, with the exchangeability group membership of historical trial s being represented by $g(s)$. The new trial is assigned to exchangeability group $g(*)$. The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1, \ldots, \langle G \rangle$. Covariance matrix ψ_g is defined by the standard deviations (t_{g1}, t_{g2}), and correlation r (a common value for r is used across all groups). The parameters t_{g1} and t_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets (t_{g1}, t_{g2}) it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

CCI

[redacted]

The MAP prior for single-agent model parameters in the new trial, $(log(\alpha^*), log(\beta^*))$, is the predictive distribution

$$(log(\alpha^*), log(\beta^*)) \,|(r_{ds}, n_{ds} : s = 1, \ldots, \langle S \rangle)$$

Since the predictive distribution is not available analytically, the Markov chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using Just Another Gibbs Sampler (JAGS) version 4.3.0.

CCI

[redacted]

Table 7. Historical Dose Limiting Toxicity Data CCI

CCI	Number of Participants	Number of Participants with DLTs
	6	0
	4	0
	4	0
	4	0
	6	0
	6	0

Abbreviations: CCI DLT=dose limiting toxicity; CCI

CCI Priors for t_{1p} and t_{2p} are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

The prior distributions for the model used for deriving the MAP priors are specified in Table 8.

Table 8. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior CCI

Parameter	Prior distribution
μ_{1p}	N (mean = 0, sd =2)
μ_{2p}	N (mean = 0, sd=1)
CCI	
r_p	Uniform (-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Single Agent Nirogacestat

Dose-DLT data for nirogacestat as presented in Table 9 of the first-in-patient, dose-finding Phase 1 study (Messersmith et al 2015)[6] are used to derive the prior of the single agent logistic parameters for nirogacestat.

Table 9. Historical Dose Limiting Toxicity Data on Nirogacestat

Nirogacestat Dose Level (mg; BID)	Number of Participants	Number of Participants with DLTs
20	3	0
40	3	0
80	3	0
100	6	1
130	3	0
150	6	1
220	6	1
330	2	2

Abbreviations: BID=twice daily; DLT=dose limiting toxicity; mg=milligrams.

CCI [redacted] Priors for t_{1n} and t_{2n} are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

CCI [redacted]

The prior distributions for the model used for deriving the MAP priors are specified in Table 10.

Table 10. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior CCI [redacted]

Parameter	Prior distribution
μ_{1n}	N (mean = 0, sd = 2)
μ_{2n}	N (mean = 0, sd=1)
CCI [redacted]	
r_n	Uniform (-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Prior Distribution for the Interaction Parameter

Based on pharmacometrics assessment the drug-drug interaction between PF-06863135 and nirogacestat is expected to be low, although uncertainty remains. CCI [redacted] The prior for η_{12} is specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses:

CCI [redacted]

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 11. Table 12 illustrates the resulting prior distribution of DLT rate derived from the priors given in Table 11. Based on the available information, the starting dose PF-06863135 = 4 mg satisfies the EWOC criterion.

Table 11. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
PF-06863135 single agent parameters: CCI [redacted]			
$(\log(\alpha_1), \log(\beta_1))$	CCI [redacted]		
Nirogacestat single agent parameters: CCI [redacted]			
$(\log(\alpha_2), \log(\beta_2))$	CCI [redacted]		
Interaction parameter: Normal prior			
η_{12}	CCI [redacted]		

η12: Two-way interaction between PF-06863135 and nirogacestat.
Abbreviations: CCI [redacted]

Table 12. Summary of Prior Distribution of Dose Limiting Toxicity Rates for CCI [redacted] (Sub-study A)

CCI [redacted]	Prior Probabilities that DLT Rate is Within the Interval			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
	0.656	0.249	0.095	0.169	0.156	0.035	0.122	0.698
	0.589	0.269	0.141	0.198	0.185	0.037	0.136	0.812
	0.475	0.284	0.241	0.255	0.232	0.033	0.169	0.913
	0.428	0.269	0.303	0.288	0.256	0.029	0.192	0.945
	0.362	0.209	0.429	0.364	0.308	0.016	0.260	0.988

Abbreviations: DLT=dose limiting toxicity; CCI [redacted]; SD=standard deviation.

Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next cohort of participants is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future participants, EWOC criteria and maximum amount of escalation allows. In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 13 shows some hypothetical dose escalation data scenarios for sub-study A and the corresponding recommendations for the next dose. CCI [redacted]

Table 13. Sub-study A: Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose

Scenarios	CCI	Pr(TT) at Next Dose	Pr(OD) at Next Dose
1		0.246	0.066
2		0.357	0.170
3		0.348	0.186
4		0.376	0.137
5		0.445	0.205
6		0.336	0.112
7		0.161	0.178
8		0.458	0.077
9		0.493	0.184
10		0.478	0.028
11		0.402	0.231

CCI

Abbreviations: BID=twice daily; CCI ; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; CCI

Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated and in each scenario 1000 trials were simulated.

Simulation Scenarios

Several scenarios are considered for sub-study A (Table 14). Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, the true DLT probability equals to mean of prior DLT. Scenarios 2-3 represent an increase in DLT rate compared to Scenario 1.

Table 14. Sub-study A: Dose Limiting Toxicity Rate Scenarios

Scenarios	CCI [redacted]				
1. Mean prior DLT rate	0.169	0.198	0.255	0.288	0.364
2. 30% more toxic than the mean prior DLT rate	0.220	0.257	0.331	0.374	0.473
3. Higher dose is overly toxic	0.169	0.237	0.331	0.432	0.728

* Nirogacestat dose is fixed at 100 mg BID.

Abbreviations: BID=twice daily; CCI [redacted].

Simulation Details

Simulations were performed using R version 3.6.1 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.3.0 to perform the MCMC analyses.

CCI [redacted]

For sub-study A, the starting dose was PF-06863135 4 mg (QW) and nirogacestat 100 mg BID. The maximum number of participants per trial was set to 30. The trial was stopped when the following criteria were met:

- At least 6 participants have been treated at the recommended MTD $\tilde{d}$.
- The dose $\tilde{d}$ satisfies one of the following conditions:
  - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
  - A minimum of 18 participants have been treated in the trial.

The following metrics were assessed in the simulations:

- Percentage of participants receiving dose combination(s) in the target toxicity interval;
- Percentage of participants receiving an overdose;
- Percentage of participants receiving an under dose;
- Probability that recommended MTD at the end of the trial is in the target toxicity interval;
- Probability that recommended MTD is an overdose;
- Probability that recommended MTD is an under dose;
- Percentage of trials stopped without MTD declaration;
- Average sample size.

Simulation Results

Operating characteristics for sub-study A are presented in Table 15. The percentage of trials with a correctly identified MTD ranges from 48.0% to 89.6%. The average sample size is approximately 14 to 18 participants.

Table 15. Sub-study A: Operating Characteristics

Scenarios	Participant Allocation (%)			Prob of Declare MTD (%)			Prob of Stop with no MTD Found (%)	Average Sample Size
	UD	TT	OD	UD	TT	OD		
1. Mean prior DLT rate	24.1	75.9	0	4.3	89.6	0	6.1	18
2. 30% more toxic than the mean prior DLT rate	0	73.7	26.3	0	48.0	29.7	22.3	14
3. Higher dose is overly toxic	0	70.4	29.6	0	52.6	31.5	15.9	15

Abbreviations: MTD=maximum tolerated dose: OD=overdose; TT=target toxicity; UD=under dose.

9.2. Appendix 2: List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	anatomic Therapeutic Chemical
AUC	area under the curve
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
BCMA	B-cell maturation antigen
BLQ	below the limit of quantitation
BLRM	Bayesian logistic regression model
BMA	bone marrow aspirate
BMI	body mass index
BOR	best overall response
BP	blood pressure
CCR	cumulative complete response
CCRR	cumulative complete response rate
CI	confidence interval
Cmax	maximum observed concentration
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DI	dose intensity
DLT	dose limiting toxicity
DOCCR	duration of cumulative complete response
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity

Abbreviation	Term
EORTC MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients core module
EOS	end of study
EOT	end of treatment
EQ-5D	EuroQoL 5 Dimensions
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICANS	immune cell-associated neurotoxicity syndrome
IMWG	International Myeloma Working Group
IOTA	Investigator Overall Tumor Assessment
irAE	immune-related adverse event
IRT	interactive response technology
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LOD	limit of detection
LVEF	left ventricular ejection fraction
MUGA	multigated acquisition
N/A; NA	not applicable; not assessed
NAb	neutralizing antibody
NCI	National Cancer Institute
NE	not evaluable
OR	objective response
ORR	objective response rate
OS	overall survival
OTR	outside toxicity reference
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcB	corrected QT (Bazzett's method)

Abbreviation	Term
QTcF	corrected QT (Fridericia's method)
RDI	relative dose intensity
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse events
T_{max}	time for C_{max}
TTR	time to response
ULN	upper limit of normal
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

Protocol C1071004
(MAGNETISMM-4)

SUB-STUDY A

PHASE 1B/2, OPEN LABEL UMBRELLA STUDY OF ELRANATAMAB (PF-06863135), A B CELL MATURATION ANTIGEN (BCMA) CD3 BISPECIFIC ANTIBODY, IN COMBINATION WITH OTHER ANTI-CANCER TREATMENTS IN PARTICIPANTS WITH MULTIPLE MYELOMA

Statistical Analysis Plan
(SAP)

Version: 2.0

Date: 12 June 2024

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1. VERSION HISTORY

This SAP for study C1071004, Sub-Study A is based on the protocol amendment v8.0 (dated 31 October 2023).

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 18 Mar 2021	Amendment 1.0 14 Feb 2021	N/A	N/A
2 xx June 2024	Amendment 6.0 Amendment 7.0 Amendment 8.0	Bring SAP into alignment with protocol amendments.	Section 2.1 New section from the most recent SAP template for modifications to the protocol. Clarified BLRM dose selection; Section 3.2 Clarified language around efficacy endpoints; Section 3.3.1 sMRD negativity rate and duration of MRD (DOMRD) negativity are added; Section 3.3.3 EORTC QLQ-CIPN20 is added; Clarified DLT observation period to approximately 35 days, C0+C1 throughout; Section 6.6.3 Updated definition of dose intensity to use planned dose; Section 6.6.3.1 Updated exposure analyses to account for CCI and disallowal of participants to switch from Q2W back to QW; Section 6.6.3.2 Account for new nirogacestat doses and schedules in exposure analyses; Section 6.6.3.3 Clarified dose reduction of elranatamab is not permitted; Appendix 2 Added independent BLRM model for the QD nirogacestat schedule in PA8 dose levels 3A, 3B, 4A, 4B.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses for sub-study A of C1071004 umbrella study. C1071004 sub-study A is a prospective, open-label, multi-center, Phase 1b/2 study to evaluate safety, efficacy, PK, and pharmacodynamics of elranatamab in combination with nirogacestat in participants with relapsed/refractory multiple myeloma (RRMM).

The general methodology for summary and statistical analyses that apply to all sub-studies in the umbrella protocol are described in the Master statistical analysis plan (SAP). This SAP provides statistical methodology and analyses that are specific to sub-study A. 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.

For this sub-study, there is one planned interim analysis for futility, which takes place once after the first 25 participants in Phase 2 are treated and followed for 2 post-baseline disease assessments. 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 in this sub-study. All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

2.1. Modifications to the Analysis Plan Described in the Protocol

The dose escalation schema in section 1.2.1 of the Sub-Study A Protocol Amendment 8 does not capture all possible movement allowed by BLRM in combination studies. This SAP clarifies that opening lateral dose levels is possible, such as going from 3A to 4B, as is escalating from 4B to 4A, as long as the dose level to be opened satisfies the EWOC principle.

2.2. Study Objectives, Endpoints, and Estimands

Phase 1b

Type	Objectives	Endpoints	Estimands
Primary			
Safety	• To assess safety and tolerability of elranatamab in combination with nirogacestat in participants with RRMM in order to select a RP2D(s) for the combination	• DLTs during DLT observation period.	• The primary estimand is DLT rate estimate based on data from DLT-evaluable participants during the DLT observation period, which is approximately 35 days from C0D1 through the end of C1.
Secondary			
Safety	• To evaluate the overall safety profile	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to elranatamab in combination with nirogacestat. The severity of CRS and	• N/A

		ICANS will be assessed according to ASTCT criteria (Lee et al, 2019). • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v5.0), and timing.	
Efficacy	• To evaluate anti-myeloma activity of elranatamab in combination with nirogacestat.	• ORR and CRR, per IMWG response criteria as determined by investigator; • Time to event endpoints: TTR, DOR, DOCR and PFS per IMWG response criteria as determined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• N/A
PK	• To evaluate the PK of elranatamab given alone and in combination with nirogacestat. Additionally, PK of nirogacestat will be evaluated when administered with elranatamab	• Pre- and post-dose concentrations of elranatamab; • Trough serum concentrations of nirogacestat at selected cycles.	• N/A
Immunogenicity	• To evaluate immunogenicity of elranatamab in combination with nirogacestat.	• Incidence and titers of ADA and NAb against elranatamab.	• N/A
Exploratory			
Biomarker	• To explore the relationship between elranatamab and nirogacestat and the biology of the participant's MM.	• Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood and/or BM biospecimens.	• N/A
	• To explore correlations between elranatamab exposure and efficacy, safety, and biomarker endpoints, if data allow.	• Selected PK, efficacy, safety, and biomarker endpoints.	• N/A

Phase 2

Type	Objectives	Endpoints	Estimands
Primary			
Efficacy	• To assess the clinical efficacy of elranatamab in combination with nirogacestat.	• ORR per IMWG response criteria as determined by investigator.	• The primary estimand is the treatment effect of elranatamab in combination with nirogacestat on ORR per IMWG response criteria as determined by investigator. It will be estimated based on all enrolled RRMM participants who received at least 1 dose of study intervention. 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. The median and its corresponding 2-sided 90% credible interval of ORR based on the posterior distribution will be calculated.
Secondary			
Efficacy	• To determine additional efficacy outcomes of elranatamab in combination with nirogacestat.	• CRR per IMWG criteria as determined by investigator. • Time to event endpoints: TTR, DOR, DOCR and PFS per IMWG response criteria as determined by investigator, and OS. • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• N/A
Safety	• To further characterize the overall safety profile and tolerability of elranatamab in combination with nirogacestat.	• AEs as characterized by type, frequency, severity as graded by NCI CTCAE, version 5.0, timing, seriousness, and relationship to elranatamab in combination with other anti-cancer therapies. The severity of CRS and ICANS	• N/A

		will be assessed according to ASTCT criteria (Lee et al, 2019). • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v5.0), and timing.	
PK	• To evaluate PK of elranatamab at the RP2D in combination with nirogacestat. Additionally, to collect PK data of nirogacestat when administered with elranatamab.	• Trough concentrations of elranatamab and nirogacestat in selected cycles.	• N/A
Immunogenicity	• To evaluate immunogenicity of elranatamab in combination with nirogacestat.	• Incidence and titers of ADA and NAb against elranatamab.	• N/A
Exploratory			
Biomarker	• To explore the relationship between elranatamab and nirogacestat and the biology of the participant's MM.	• Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, and/or BM biospecimens.	• N/A
	• To explore correlations between elranatamab exposure and efficacy, safety and biomarker endpoints, if data allow.	• Selected PK, efficacy, safety and biomarker endpoints.	• N/A

2.3. Study Design

Sub-study A of C1071004 protocol will evaluate safety, efficacy, PK, and pharmacodynamics of elranatamab in combination with nirogacestat in in participants with RRMM.

The combination will be assessed in 2 parts in the sub-study:

- **Phase 1b** part to evaluate the safety, tolerability, and select a recommended dose and regimen for the combination (combination RP2D).
- **Phase 2** part to further evaluate the efficacy and safety of the combination.

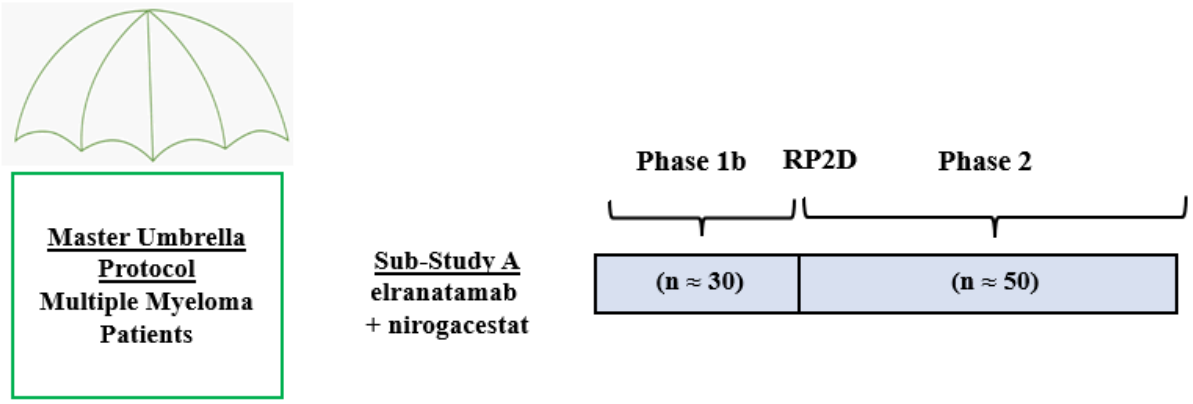
Phase 1b Design:

The number of participants to be enrolled in Phase 1b will depend on the number of dose levels evaluated and the number of participants treated at each dose level. Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment (number of participants to be enrolled in the next cohort) decisions will use an escalation model (BLRM approach) to determine the MTD of elranatamab when administered in combination with nirogacestat.

Phase 2 Design:

Phase 2 will begin once the combination RP2D from the Phase 1b is selected. Approximately 50 participants will be enrolled in the Phase 2 part to assess anti-tumor activity and safety of elranatamab in combination with nirogacestat.

Figure 1. Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

Phase 1b

The primary endpoint of the Phase 1b part is the incidence of DLTs in the DLT-Evaluable Set during the DLT observation period, which is approximately 35 days from C0D1 through the end of C1.

Phase 2

The primary endpoint in the Phase 2 part is ORR per IMWG response criteria, defined as the proportion of participants with an objective response per IMWG response criteria as determined by investigator.

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

For all efficacy endpoints per IMWG response criteria, BOR will be assessed based on reported overall responses recorded at evaluation time points from the date of first dose until

the first documentation of confirmed PD, death or start of new anti-cancer therapy, whichever occurs first.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

For all efficacy endpoints per IMWG response criteria, BOR is assessed based on reported overall responses (per IMWG response criteria (Rajkumar et al, 2014)) recorded at evaluation time points from the date of first dose until the first documentation of confirmed PD, death or start of new anti-cancer therapy, whichever occurs first.
Objective response is defined as having a BOR of confirmed sCR, CR, VGPR, or PR.

3.2.1.1. Complete Response Rate

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

3.2.1.2. Duration of Response

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

3.2.1.3. Duration of Complete Response

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

3.2.1.4. Progression-free Survival

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

3.2.1.5. Overall Survival

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

3.2.1.6. Time to Response

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

3.2.1.7. Minimal Residual Disease Negativity Rate

Minimal Residual Disease (MRD) (assessed by central lab) negativity rate is the proportion of participants with CR or better with negative MRD per IMWG sequencing criteria from the

date of first dose until confirmed PD, death or start of new anticancer first therapy, whichever occurs first.

3.2.2. Safety Endpoints

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

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

3.2.3. Pharmacokinetic Endpoints

Phase 1b

- PK parameters of elranatamab: C_{max}, T_{max}, AUC_{last} after elranatamab administration alone as a priming dose;

- Pre- and post-dose concentrations (free and total) of elranatamab in combination with nirogacestat;

- Trough serum concentrations of nirogacestat at selected cycles.

Phase 2

- Trough concentrations of elranatamab and nirogacestat in selected cycles.

3.2.4. Immunogenicity Endpoints

- Incidence and titers of ADA and NAb against elranatamab.

3.3. Exploratory Endpoints

3.3.1. Translational Oncology Biomarkers Endpoints

- Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens.

- Selected PK, efficacy, safety, and biomarker endpoints

3.3.2. Patient-Reported Outcomes (Phase 2 Only) Endpoints

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

- European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients core module (EORTC QLQ-C30): EORTC QLQ-C30 is a well-known, reliable and valid self-administered questionnaire used in oncology trials.[3,4] The QLQ-C30 contains 30 items and is grouped into five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/quality of

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

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

- European Organization for Research and Treatment of Cancer - chemotherapy-induced peripheral neuropathy (EORTC QLQ-CIPN20): The EORTC QLQ-CIPN20 is a module developed by the EORTC group to assess chemotherapy-induced peripheral neuropathy. [5] It contains 20 items which can be grouped into a sensory subscale (9 items), motor subscale (8 items) and autonomic subscale (3 items).

3.4. Baseline Variables

See Section 3.4 of the master SAP for the definition of baseline variables.

3.5. Safety Endpoints

See Section 3.5 of the master SAP for the definition of the safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

See Section 4 of the master SAP for definitions of analysis sets.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

5.1.1.1. Phase 1b

The primary objective in the Phase 1b part of the study is to assess safety and tolerability of elranatamab in combination with nirogacestat in order to select a RP2D for the combination therapy. There is no statistical hypothesis for the Phase 1b part of the study. A BLRM will be utilized for dose escalation of elranatamab. The dosages of elranatamab and nirogacestat for each dose level are listed in

Table 2. Study Intervention Dose Levels and Administration

Table 2. Study Intervention Dose Levels and Administration

Dose Levels (DL)	Elranatamab	Nirogacestat
1 (starting dose level)	**Priming Dose:** 4 mg C0D1 SC **Full Dose:** 4 mg C1D1 SC, weekly thereafter[b]	100 mg PO **BID** continuous starting on C1D1 until response[a]
2	**2 Step-up Priming Dose:** 4 mg C0D1 SC / 8 mg C0D4 SC **Full Dose:** 12 mg C1D1 SC, weekly thereafter[b]	100 mg PO **BID** continuous starting on C1D1 until response[a]
3	**2 Step-up Priming Dose:** 12 mg C0D1 SC / 32 mg C0D4 SC **Full Dose:** 32 mg C1D1 SC, weekly thereafter[b]	100 mg PO **BID** continuous starting on C1D1 until response[a]
Nirogacestat De-Escalation Levels		
3A	**2 Step-up Priming Dose:** 12 mg C0D1 SC / 32 mg C0D4 SC **Full Dose:** 32 mg C1D1 SC, weekly thereafter[b]	100 mg PO **QD** continuous starting on C1D1 until response[a]
4A	**2 Step-up Priming Dose:** 12 mg C0D1 SC / 32 mg C0D4 SC **Full Dose:** 76 mg C1D1 SC, weekly thereafter[b,c]	100 mg PO **QD** continuous starting on C1D1 until response[a]
3B	**2 Step-up Priming Dose:** 12 mg C0D1 SC / 32 mg C0D4 SC **Full Dose:** 32 mg C1D1 SC, weekly thereafter[b]	50 mg PO **QD** continuous starting on C1D1 until response[a]
4B	**2 Step-up Priming Dose:** 12 mg C0D1 SC / 32 mg C0D4 SC **Full Dose:** 76 mg C1D1 SC, weekly thereafter[b,c]	50 mg PO **QD** continuous starting on C1D1 until response[a]

a. For Dose levels 3A/3B and 4A/4B, nirogacestat will be adjusted to 50 mg QD continuous at time of confirmed VGPR. Once CR (or better) is confirmed, nirogacestat will be permanently discontinued. For all other dose levels, nirogacestat can be continued or adjusted based on this guidance, per investigator discretion. See Section 6.1.1.5.

b. Starting at Cycle 7, if a participant has received QW dosing for at least 6 cycles and PR or better persisting for ≥2 months, dose interval will be changed from QW to Q2W. See Schedule of Activities.

c. For participants on Dose levels 4A and 4B receiving CCI dosing, CCI the dose interval will bechanged to CCI

CCI

CCI

[redacted]

Sample Size Estimation

A minimum of 2-6 DLT-evaluable participants (as defined in Section 4 in the master SAP) will be treated at each dose level of elranatamab. The actual number of participants to be enrolled will depend on the number of dose levels evaluated and the number of participants treated at each dose level. Therefore, it cannot be determined in advance.

It is estimated that approximately up to 30 DLT evaluable participants will be enrolled and treated with elranatamab combination which will include at least 6 DLT evaluable participants treated at the elranatamab combination MTD level and at least 6 DLT evaluable participants at the elranatamab combination RP2D level.

If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants in the Phase 1b of the sub-study.

5.1.1.2. Phase 2

The primary endpoint in the Phase 2 part of the study is ORR per IMWG response criteria as determined by investigator. No hypothesis significance testing will be performed. Instead a Bayesian dual-criterion design[10] will be used to estimate the true ORR of elranatamab in combination with nirogacestat. With this design, the following criteria are defined:

- Bayesian statistical significance: Substantial evidence that the true ORR exceeds a null value. For the elranatamab combination therapies, Bayesian statistical significance will be achieved if the posterior probability of the true ORR ≥65% exceeds 0.95;

- Clinical relevance: The minimum ORR threshold that could justify further development of a combination. For the elranatamab combination therapies, it is defined as the median of the posterior distribution of the true ORR exceeding 75%.

The analysis will use a Beta-binomial model (binomial sampling for number of responders and a Beta prior distribution). A minimally informative beta prior distribution of the true ORR will be used. It is assumed a priori that the true mean ORR for a combination is 65%, so the prior distribution will be Beta (1.3, 0.7). Using this prior and based on the dual criteria defined above, approximately 50 participants will be enrolled in the Phase 2 part of the sub-study and a minimum of 38 objective responses are required to achieve the dual criteria in 50 participants. With exactly 38 objective responses in 50 participants, the observed ORR is 76% with median 75.9% and 90% credible interval of (65.3%, 84.7%) based on the posterior distribution.

5.1.2. Decision Rules

5.1.2.1. Phase 1b

Identification of MTD

The dosing decision and estimation of the MTD/MAD for each combination will be guided by the estimation of the probability of DLT during the DLT observation period. Other evidence such as safety data beyond DLT window, clinical activity, PK, and PD data will also be evaluated in determining RP2D.

Assessment of Participant Risk

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

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

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5.1.2.2. Phase 2

The Phase 2 part of this sub-study is designed to have an interim analysis for futility and a primary analysis. The interim analysis will be conducted after the first 25 participants are treated and followed for at least 2 post-baseline disease assessments in this sub-study. 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.

Table 3 presents the operating characteristics of this 2-stage design, ie, the probability of early trial termination at the interim futility analysis and the probability of observing the critical number of objective responses (i.e., ≥38 objective responses in 50 participants) at the primary analysis if the true ORR ranges from 65% to 90%. Specifically,

- If the true ORR = 65%, the probability of stopping the study due to futility at the interim analysis is 0.533, and the probability of observing critical number of responses at the primary analysis is 0.064.
- If the true ORR = 80%, the probability of stopping the study due to futility at the interim analysis is 0.047, and the probability of observing critical number of responses at the primary analysis is 0.806.

Table 3. Operating Characteristics of Bayesian 2-Stage Dual-Criterion Design

True ORR	Prob of Exceeding Futility Boundary at the Interim (R1/N1 <17/25)	Prob of GO Decision at the Primary Analysis* (R/N ≥38/50)	Prob of No-GO Decision at the Primary Analysis* (R/N <38/50)
65%	0.533	0.064	0.403
70%	0.323	0.218	0.459
75%	0.149	0.502	0.349
80%	0.047	0.806	0.147
85%	0.008	0.967	0.025
90%	<0.001	0.999	0.001

* The study does not meet futility criteria at the interim analysis and continues to the primary analysis.
ORR = objective response rate;
R1 = Minimum number of responses required at the interim futility analysis to continue the study;
N1 = Number of participants at the interim analysis;
R = Minimum number of responses required to meet the dual criteria at the primary analysis;
N = Number of participants at the primary analysis.

At the time of the primary analysis, the critical number of objective responses to be observed will be updated based on the actual number of participants enrolled and treated.

Meeting the dual criteria described above will be considered preliminary evidence that the combination therapy may provide clinically meaningful treatment effect in ORR. However,

the decision as to whether a combination will be developed further will depend upon the observed results of both the primary and key secondary efficacy endpoints. As a result, exceeding the critical number of objective responses described above may be sufficient, but may not be necessary, for justifying further development of a combination therapy.

5.2. General Methods

Unless otherwise specified, all analyses will be performed for Phase 1b and Phase 2 separately and with the cohort of RP2D in Phase 1b and Phase 2 combined.

For the Phase 1b part of the study, all analyses will be performed by dose level and with all dose levels combined.

See Section 5.2 of the master SAP for the detail of the general statistical methods.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Phase 1b

DLT rate is calculated as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants in the DLT observation period.

Analyses of DLT will be performed on DLT Evaluable Analysis Set as defined in Section 4 of the master SAP. DLT rate will be summarized and listed by dose levels. Participants without DLTs who do not receive at least 80% of the planned dose of elranatamab or 75% of the planned dose of nirogacestat are not evaluable for DLT. For calculation of relative dose in the DLT observation period, the denominator (planned dose) for nirogacestat is based on the nominal cycle length of 28 days. For example, for participants assigned 100 mg BID nirogacestat, the planned dosage for the DLT observational period is 100×2×28 = 5600 mg.

6.1.2. Phase 2

The primary endpoint is ORR, defined as the proportion of participants with an objective response (Section 0) per IMWG response criteria as determined by investigator. Participants without documented response will be considered as non-responders.

Primary Estimand: the treatment effect of elranatamab in combination with nirogacestat on ORR per the IMWG criteria as determined by investigator. 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 (Section 0) per IMWG response criteria as determined by investigator.

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

- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an objective response. The median and its corresponding 2-sided 90% credible interval of ORR in the analysis population based on the posterior distribution will be calculated.

Additionally, the observed point estimate of ORR will be calculated along with the 2-sided 90% CIs using the Clopper-Pearson method[13] (exact CI for a binomial proportion).

The frequency (number and percentage) of participants with BOR by investigator in each response category will be summarized: sCR; CR; VGPR; PR; MR; SD; PD; Not evaluable (NE)/unknown.

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

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

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

BOR will be assessed programmatically based on reported timepoint responses by investigator recorded at evaluation time points from the date of first dose until confirmed disease progression, death or start of new anticancer therapy using IMWG response criteria. BOR needs to be confirmed according to IMWG response criteria (Table 4). If a participant meets multiple criteria in determining confirmed BOR, the order of criteria in this table will be used to define the hierarchy. Twenty-eight days is the scheduled gap between the disease assessments after cycle 1. If a confirmation is to be 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.
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.

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

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

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

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

EMD = extramedullary disease; IMWG = International Myeloma Working Group, sCR = stringent complete response, CR = complete response, PR = partial response, VGPR = very good partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.
[a] SD does not need to be confirmed.
[b] PD due to EMD (includes any new lesion, increased extramedullary or paramedullary lesions, plasmacytomas), or bone marrow plasma cells does not need to be confirmed.
[c] PD due to reasons other than EMD, or bone marrow plasma cells.

6.2. Secondary Efficacy Endpoints

6.2.1. Complete Response Rate

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

Point estimates of CRR will be calculated along with corresponding 2-sided exact 95% CIs using the Clopper-Pearson method.[13]

6.2.2. Progression-free Survival

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

PFS will be calculated as follows:

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

PFS will be censored as follows:

- For participants who do not have an event (confirmed PD per IMWG criteria or death due to any cause), censoring will occur on the date of the last adequate disease assessment;
- For participants who start a new anticancer therapy (as defined in Section 5.2.6 in the master SAP) 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 (i.e., ≤70 days after the date of first dose) in which case the death will be considered an event.

The censoring and event date options to be considered for the PFS analysis are presented in Table 5. Adequate post-baseline disease assessment is defined in Section 5.2.10 in the master SAP.

Table 5. Outcome and Event Dates for PFS Analyses

Scenario	Date of Event/Censoring	Outcome
Progression or death 1. After at most 1 missing or inadequate post-baseline disease assessment or 2. ≤70 days after date of first dose of study intervention	Date of progression or death	Event
Progression or death after 2 or more missing or inadequate disease assessments [a]	Date of last adequate assessment [a] documenting no PD prior to new anticancer therapy or missed disease assessments	Censored
Neither progression nor death		
New anticancer therapy given prior to PD or death		

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

PFS = progression-free survival; PD = progressive disease

Kaplan-Meier estimates (product-limit estimates) will be presented and displayed graphically where appropriate, together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley, 1982.[7]

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 [14] (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented along with the overall event and censor rates.

Reasons for censoring will be summarized according to the categories in Table 6. If a participant meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 6. PFS Censoring Reasons and Hierarchy

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

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

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

6.2.3. Duration of Response

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

DOR will be calculated as follows:

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

The censoring rules for DOR are as described for PFS in Section 6.2.2, except that participants will not be censored for no adequate post-baseline assessment, as only participants with an objective response are included in the analysis of DOR.

If at least 3 participants across all dose levels achieve an objective response and subsequently have an event, DOR will be estimated using the same Kaplan-Meier method as described for PFS in Section 6.2.2 and displayed graphically where appropriate. Otherwise only listings will be provided.

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

6.2.4. Duration of Complete Response

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

DOCR will be calculated as follows:

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

The censoring rules for DOCR are as described for DOR in Section 6.2.3.

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

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

6.2.5. Overall Survival

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

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

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

OS time will be estimated using the same Kaplan-Meier method and displayed graphically as described for PFS in Section 6.2.2. Median OS and 2-sided 95% CI will be provided. The OS rate at 12, 24, and 36 months (and in subsequent 12-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

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

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

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

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

6.2.6. Time to Response

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

TTR (weeks) = (date of first objective response – date of first dose + 1) / 7

TTR will be summarized using simple descriptive statistics (mean, standard deviation, minimum, median, and maximum).

6.2.7. Minimal Residual Disease Negativity Rate

MRD negativity rate is defined as the proportion of participants with negative MRD (assessed by central lab) per IMWG sequencing criteria at any time from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first. The rules for PD confirmation are described in Table 4.

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

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

MRD negative based on the subset of MRD evaluable patients (achieve sCR/CR and have at least one MRD assessment

6.3. Other Secondary Endpoints

6.3.1. Pharmacokinetic/Pharmacodynamics

Pharmacokinetic parameter analyses will be based on the PK Analysis Set.

6.3.1.1. Elranatamab

PK data analyses will include descriptive summary statistics of the predose and postdose serum concentrations, and PK parameters of elranatamab by study visit and time point. Box and Whisker plots for predose elranatamab concentrations by study visit and PK parameters (C_{max} and AUC_{last}) will be generated. Values below the limit of quantitation for elranatamab and other analytes will be treated as zero in the descriptive statistics calculations. For additional details on handling missing and BLQ values, please refer to Section 5.3.1 in the master SAP.

In addition, the PK data from this study may be used to develop a population PK model. PK data from this study maybe pooled with other studies for population PK model development. 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.

6.3.1.2. Nirogacestat

PK data analyses will include descriptive summary statistics of predose serum concentrations of nirogacestat by study visit and time point. Box and Whisker plots for predose serum concentrations of nirogacestat by study visit will be generated. PK data from this study maybe pooled with other studies for population PK model development. The correlations between nirogacestat 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.

6.3.2. Immunogenicity

Immunogenicity data will be analyzed in the Immunogenicity Analysis Set.

The percentage of participants with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-baseline will be generated. Samples may also be analyzed for the presence of neutralizing antibodies (NAb), and any data will be similarly summarized. For participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit.

The potential impact of immunogenicity on PK and clinical response including pharmacodynamic markers, safety/tolerability and efficacy will be explored, if warranted by the data. This analysis may be reported separately from the CSR.

6.4. Exploratory Endpoints

6.4.1. Biomarker Analysis

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

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

6.4.2. Patient-Reported Outcomes

The following PRO analyses will be performed to support the CSR development. All other PRO analyses described in the study protocol but are not included in this SAP will be described in detail in a separate PRO analysis plan.

Analysis of the PRO endpoints will be based on the PRO Analysis Set.

Completion Status

The number and percentage of participants who completed these instruments at each time point 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 performed based on the observed values as well as change from baseline values.

EORTC QLQ-MY20

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

EORTC QLQ-CIPN20

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

6.5. Subset Analyses

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

The following subset analyses will be performed for ORR as determined by investigator for Phase 2 part only based on the Safety Analysis Set:

- Baseline cytogenetics (high vs standard risk);
- EMD at baseline (yes vs no);
- Prior stem cell transplant (yes vs no);
- Disease stage (1-2 vs 3);
- Number of prior therapies (≤4, >4);
- Type of myeloma (IgG vsnon-IgG vs light chain only);
- Age (<65 vs ≥65; <75 vs ≥75).

ORR in subsets will be presented in a forest plot. Other subset analyses will be performed as well if deemed clinical meaningful and feasible (sufficient sample size).

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

See Section 6.5.1 of the master SAP for baseline summaries.

6.6.2. Study Conduct and Participant Disposition

See Section 6.5.2 of the master SAP for summaries of study conduct and participant disposition.

6.6.3. Study Intervention Exposure

Exposure will be summarized based on the Safety Analysis Set (SAS). will be calculated based on the total number of participants in SAS.

6.6.3.1. Exposure to Elranatamab

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

- Treatment duration (weeks);
- Number of cycles started per participant (mean, median, min, max);

- Number and percent of participants starting a cycle (any cycle, cycle 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, >=12 cycles);
- Total cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose (%);
- Overall relative dose intensity (%);
- Number and percent of participants after 6 cycles who switched from QW to Q2W;

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

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

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

- Planned treatment duration (weeks) = 1 (1 week for Cycle 0) + number of cycles started × 4 - (number of weeks in the last cycle after permanent treatment discontinuation or data cutoff for those on-treatment).

Intended treatment duration (weeks) = (last zero/non-zero dose date – first dose date)/7 + (1 if on QW or 2 if on Q2W CCI [redacted]). If C0D4 is the last visit, duration is 1 week if C0D4 occurred by then;The planned dose for a given cycle is defined as:

- <u>Cycle 0:</u>
  - Planned dose (mg/cycle) = Planned priming dose(s) per protocol during C0
- <u>After Cycle 0:</u>
  - If the participant is on QW dosing schedule for the cycle:

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

    Planned dose (mg/cycle) = Full dose × 2

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Note: Full dose= 4 ,12, 32, or 76mg depending on DLs. For the last cycle, subtract planned doses after a participant permanently discontinues treatment or data cutoff for those on-treatment.

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

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

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

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

The RD and RDI are defined as follows:

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

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

6.6.3.2. Exposure to Nirogacestat

Nirogacestat is administered in 28-day cycles starting on C1D1. Dose may eventually be reduced or even discontinued if the participant responds well to treatment. The summary of treatment exposure to nirogacestat will include the following information:

- Treatment duration (weeks);
- Total cumulative dose (mg);
- Total planned cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose intensity (%).

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

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

Planned treatment duration, intended treatment duration, planned dose and planned DI is needed to calculate DI and RDI. The planned treatment duration is defined as:

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

- Intended treatment duration (weeks) = (last zero/non-zero dose date – first dose date+1)/7 ;

- Planned dose per cycle (mg/cycle) = total planned daily dose per cycle×28;

Note: 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 total cumulative dose (mg) of nirogacestat is the sum of the dosage that the participant received during the study (ie, total dose administered [mg]).

The overall planned DI is defined as:

- Overall Planned DI (mg/week) = Total planned dose (mg)/(planned treatment duration in weeks).

The overall DI and RDI of nirogacestat will be calculated for each participant during the study.

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

- Overall RD (%) = [Total cumulative dose (mg) / Total planned dose (mg)] × 100;

- Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] × 100.

6.6.3.3. Dose Reductions, Interruptions, and Delays

Dose Reduction

Dose reduction of elranatamab is not permitted.

For nirogacestat, a dose reduction is defined as a non-zero dose that is less than the planned dose in the protocol. For nirogacestat, the number and percentage of participants with at least 1 dose reduction as well as a breakdown of dose reductions (1/2/3/ ≥4) will be summarized by dose cohort (Phase 1b dose escalation part) and Phase 2 part. In addition, the number and percentage of participants with at least 1 dose reduction due to AE will also be summarized. Planned decreases in nirogacestat for participants on dose levels 3A/3B or 4A/4B due to

objective response of confirmed VGPR via 2 consecutive assessments or CR (or better) via bone marrow assessment are not counted as reductions in this analysis.

Dose Interruption

For elranatamab, an interruption is defined as a continuous missed scheduled dose (ie. 0mg dose) based on the planned dosing frequency (QW, Q2W, CCI).

For nirogacestat, an interruption is defined as a 0 mg dose administered on 1 or more days. (Note: A dose interruption is not considered a dose reduction).

What follows defines how dose interruptions of nirogacestat will be counted in the case of multiple dose interruptions:

- If an interruption occurs consecutively for at least 2 days due to the same reason, then it will be counted only once (example: If the actual dose on Days 1-3 is 100 mg BID and actual dose on Days 4-5 is 0 mg and dose interruption on Days 4-5 is due to AE, then the total number of dose interruptions is 1).

- If an interruption occurs consecutively for at least 2 days due to different reasons, then it will be counted for each reason (example: If the actual dose on Days 1-3 is 100 mg and actual dose on Days 4-5 is 0 mg and dose interruption on Day 4 is due to AE and dose interruption on Day 5 is due to dosing error, then the total number of dose interruptions is 2).

- If an interruption occurs for more than 1 day due to the same reason, but the days are not consecutive, ie, there is at least 1 dosing day in between, then each dose interruption will be counted as a different occurrence (example: if the actual dose on Days 1, 3, and 5 is 100 mg BID and actual dose on Days 2 and 4 is 0 mg, and dose interruptions on Day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2).

For each of study treatment, the number and percentage of participants with dose interruptions as well as a breakdown of dose interruptions (1/2/3/ ≥4) will be summarized. In addition, the number and percentage of participants with at least 1 dose interruption due to AE will also be summarized. Percentages will be calculated based on the total number of participants in the Safety Analysis Set.

Dose Delay

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

- No delay;

- 1-3 days delay;

- 4-6 days delay;
- 7 or more days delay (in the Q2W CCI schedule).

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

Dose delay is not applicable to nirogacestat.

6.6.4. Concomitant Medications and Nondrug Treatments

See Section 6.5.4 of the master SAP for summaries of concomitant medications and nondrug treatments.

6.6.5. Subsequent Anticancer Therapies

See Section 6.5.5 of the master SAP for summaries of subsequent anticancer therapies.

6.7. Safety Summaries and Analyses

See Section 6.6 of the master SAP for safety summaries and analyses.

7. INTERIM ANALYSES

7.1. Introduction

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

For both Part 1b and Part 2 of the sub-study, an internal safety review team will review safety and tolerability data on an ongoing basis for the interim safety assessments.

For Phase 2 part of the sub-study, an interim analysis for futility will be conducted after the first 25 participants are treated and followed for at least 2 post-baseline disease assessments without holding participant enrollments. The interim analysis will be performed on the primary endpoint of ORR using the methodology described in Section 6.1.2 by the Sponsor. The internal core study team will review and evaluate the efficacy data at the interim futility analysis.

7.2. Interim Analyses and Summaries

7.2.1. Interim Safety Assessments

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

- Grade 3-4 CRS;

- Grade 3-4 ICANS;
- Grade 4 treatment-related non-hematologic events (excluding CRS and ICANS);
- Grade 3-4 treatment-related GBS/GB-like AEs;
- Grade 4 treatment-related sensory neuropathy/other IR neurologic AEs (excluding ICANS);
- Grade 3-4 treatment-related motor neuropathy;
- Grade 5 events.

If the number of participants observed to have such identified events exceeds a prespecified threshold, the study will be placed on a temporary enrollment hold by the Sponsor. During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. Participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the investigator in consultation with the sponsor.

The criteria for placing the sub-study on temporary hold for safety reasons are based on Bayesian posterior probabilities. Using a non-informative Beta (0.5, 0.5) prior distribution, if the number of participants observed to have Grade 3 or 4 CRS results in a ≥0.80 posterior probability that the true Grade 3 or 4 CRS rate exceeds 20%, the sub-study will be put on a temporary hold. Separate but similar criteria will be used for participants with Grade 3-4 ICANS and treatment-related Grade 4 non-hematologic events (excluding CRS and ICANS). Table 7 summarizes the minimum number of participants with such identified events that would meet the above criteria.

Table 7. Identified Events That Would Prompt Temporary Enrollment Hold

Number of Evaluable Participants	10-13	14-18	19-22	23-26	27-80	31-35	36-39
Minimum number of participants with Grade 3-4 CRS events that would lead to a temporary enrollment hold	4	5	6	7	8	9	10
Minimum number of participants with Grade 3-4 ICANS events that would lead to a temporary enrollment hold	4	5	6	7	8	9	10
Minimum number of participants with Grade 4 treatment-related non-hematologic events (excluding CRS and ICANS) that would lead to a temporary enrollment hold	4	5	6	7	8	9	10

Prior distribution: Beta (0.5,0.5)

Criteria for 40+ or more evaluable participants will be calculated such that the sub-study will be put on temporary hold if the posterior probability that the true event rate exceeds 20% is greater than or equal to 0.80.

Evaluable participants are defined as those having an identified event or those without such an event who have been followed for at least 35 days from first dose.

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

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

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

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

Table 8. Minimum Number of Participants with Identified Treatment-Related Events That Would Prompt Temporary Enrollment Hold (GBS/GB-like AEs, Peripheral Neuropathy/IR Neurologic AEs)

Number of Evaluable Participants	**20-39**	**40-64**	**65-90**	**-**	**-**	**-**	**-**	**-**	**-**
Minimum number of participants with Grade 3-4 treatment-related GBS/GB-like events that would lead to a temporary enrollment hold*	2	3	4	-	-	-	-	-	-
Number of Evaluable Participants	**6-11**	**12-19**	**20-27**	**28-35**	**36-43**	**44-52**	**53-60**	**61-69**	**70-78**
Minimum number of participants with Grade 4 treatment-related sensory neuropathy /IR neurologic AE (excluding ICANS) or Grade 3-4 treatment-related motor neuropathy events that would lead to a temporary enrollment hold**	2	3	4	5	6	7	8	9	10

Prior distribution: Beta (0.5,0.5).

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

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

** The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, if there are 2 participants experiencing the identified AEs out of the first 4 evaluable participants, the study will be put on hold).

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

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

7.2.2. Interim Analysis for Futility

For Phase 2 part of the study, an interim analysis for futility will be conducted on the first 25 participants enrolled and treated. The primary endpoint of ORR will be evaluated at this analysis using a futility boundary based on the predictive probability. More specifically, a combination may stop for futility if the predictive probability of observing ≥38 objective responses in 50 patients at the primary analysis based on the data observed at the interim analysis is <0.05.

The posterior beta-binomial predictive distribution for the number of responders in the second stage of the study is as follows:

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

where IA.r and IA.n denote the number of responses and number of participants at the interim analysis, r_2 and n_2 denote the number of responses and number of participants from the second stage of the study ($n_2 = 25$), and B denotes the Beta function.

The futility boundary based on the posterior predictive distribution can be obtained using the exact method to calculate the probability of observing ≥38 objective responses in 50 participants at the primary analysis, ie,

$$P(IA.r + r_2 \geq 38|IA.r, IA.n) = \sum_{r_2=38-IA.r}^{n_2} \pi(r_2|IA.r, IA.n)$$

With 25 participants at the interim analysis, if there are ≤16 (64%) objective responses observed, further accrual may be stopped for the combination. Otherwise, the study will proceed as planned to the primary analysis as described in Section 6.1.2.

The exact futility boundary will be updated prior to the time of the analysis based on the actual number of participants enrolled and treated in this sub-study.

8. REFERENCES

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9. APPENDICES

9.1. Appendix 1: BLRM Design CCI

This section provides the details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model CCI

Statistical Model

The statistical model for dose-DLT data CCI .

The monotherapy RP2D of elranatamab is 76 mg, which was determined in Study C1071001. In this sub-study, the initial dose level of elranatamab will be 4 mg with a priming dose of 4 mg for the first dose. The dose level of nirogacestat will remain at 100 mg BID.

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Description of the Meta-Analytic-Predictive Approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies. Let r_{ds} and n_{ds} be the number of participants with a DLT, and the total number of participants, respectively, at dose d in historical trial s ($s = 1, \ldots, \langle S \rangle$). The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

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[redacted]

The historical trials are partitioned into $\langle G \rangle$ exchangeability groups, with the exchangeability group membership of historical trial s being represented by $g(s)$. The new trial is assigned to exchangeability group $g(*)$. The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1, \ldots, \langle G \rangle$. Covariance matrix ψ_g is defined by the standard deviations (t_{g1}, t_{g2}), and correlation r (a common value for r is used across all groups). The parameters t_{g1} and t_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets (t_{g1}, t_{g2}) it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

CCI

[redacted]

The MAP prior for single-agent model parameters in the new trial, $(log(\alpha^*), log(\beta^*))$, is the predictive distribution

$$(log(\alpha^*), log(\beta^*)) \,|(r_{ds}, n_{ds} : s = 1, \ldots, \langle S \rangle)$$

Since the predictive distribution is not available analytically, the Markov chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using Just Another Gibbs Sampler (JAGS) version 4.3.0.

CCI

[redacted]

Table 9. Historical Dose Limiting Toxicity Data CCI

CCI	Number of Participants	Number of Participants with DLTs
	6	0
	4	0
	4	0
	4	0
	6	0
	6	0

Abbreviations: CCI ; DLT=dose limiting toxicity; CCI

CCI Priors for t_{1p} and t_{2p} are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

The prior distributions for the model used for deriving the MAP priors are specified in Table 10.

Table 10. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior CCI

Parameter	Prior distribution
μ_{1p}	N (mean = 0, sd =2)
μ_{2p}	N (mean = 0, sd=1)
CCI	
r_p	Uniform (-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Single Agent Nirogacestat

Dose-DLT data for nirogacestat as presented in Table 11 of the first-in-patient, dose-finding Phase 1 study (Messersmith et al 2015)[7] are used to derive the prior of the single agent logistic parameters for nirogacestat.

Table 11. Historical Dose Limiting Toxicity Data on Nirogacestat

Nirogacestat Dose Level (mg; BID)	Number of Participants	Number of Participants with DLTs
20	3	0
40	3	0
80	3	0
100	6	1
130	3	0
150	6	1
220	6	1
330	2	2

Abbreviations: BID=twice daily; DLT=dose limiting toxicity; mg=milligrams.

CCI [redacted] Priors for t_{1n} and t_{2n} are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

CCI [redacted]

The prior distributions for the model used for deriving the MAP priors are specified in Table 12.

Table 12. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior CCI [redacted]

Parameter	Prior distribution
μ_{1n}	N (mean = 0, sd = 2)
μ_{2n}	N (mean = 0, sd=1)
CCI [redacted]	
r_n	Uniform (-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Prior Distribution for the Interaction Parameter

Based on pharmacometrics assessment the drug-drug interaction between elranatamab and nirogacestat is expected to be low, although uncertainty remains. CCI [redacted] The prior for η_{12} is specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses:

CCI [redacted]

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 13. Table 14 illustrates the resulting prior distribution of DLT rate derived from the priors given in Table 13. Based on the available information, the starting dose elranatamab = 4 mg satisfies the EWOC criterion.

Table 13. Prior Distribution for the Model Parameters in Nirogacestat BID model

Parameter	Mean	Standard deviations	Correlation
Elranatamab single agent parameters: CCI [redacted]			
$(\log(\alpha_1), \log(\beta_1))$	CCI [redacted]		
Nirogacestat single agent parameters: CCI [redacted]			
$(\log(\alpha_2), \log(\beta_2))$	CCI [redacted]		
Interaction parameter: Normal prior			
η_{12}	CCI [redacted]		

η12: Two-way interaction between elranatamab and nirogacestat.

Abbreviations: CCI [redacted].

Table 14. Summary of Prior Distribution of Dose Limiting Toxicity Rates for [redacted]

[redacted]	Prior Probabilities that DLT Rate is Within the Interval			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
	0.656	0.249	0.095	0.169	0.156	0.035	0.122	0.698
	0.589	0.269	0.141	0.198	0.185	0.037	0.136	0.812
	0.475	0.284	0.241	0.255	0.232	0.033	0.169	0.913
	0.428	0.269	0.303	0.288	0.256	0.029	0.192	0.945
	0.362	0.209	0.429	0.364	0.308	0.016	0.260	0.988

Abbreviations: DLT=dose limiting toxicity; [redacted];
SD=standard deviation.

Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next cohort of participants is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future participants, EWOC criteria and maximum amount of escalation allows. In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 15 shows some hypothetical dose escalation data scenarios for this sub-study and the corresponding recommendations for the next dose. [redacted]

Table 15. Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose

Scenarios	[redacted]	Pr(TT) at Next Dose	Pr(OD) at Next Dose
1		0.246	0.066

Table 15. Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose

Scenarios	CCI	Pr(TT) at Next Dose	Pr(OD) at Next Dose
2		0.357	0.170
3		0.348	0.186
4		0.376	0.137
5		0.445	0.205
6		0.336	0.112
7		0.161	0.178
8		0.458	0.077
9		0.493	0.184
10		0.478	0.028
11		0.402	0.231

CCI

Abbreviations: BID=twice daily; CCI ; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; CCI

Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated and in each scenario 1000 trials were simulated.

Simulation Scenarios

Several scenarios are considered for this sub-study (Table 16). Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, the true DLT probability equals to mean of prior DLT. Scenarios 2-3 represent an increase in DLT rate compared to Scenario 1.

Table 16. Dose Limiting Toxicity Rate Scenarios

Scenarios	CCI [redacted]				
1. Mean prior DLT rate	0.169	0.198	0.255	0.288	0.364
2. 30% more toxic than the mean prior DLT rate	0.220	0.257	0.331	0.374	0.473
3. Higher dose is overly toxic	0.169	0.237	0.331	0.432	0.728

* Nirogacestat dose is fixed at 100 mg BID.

Abbreviations: BID=twice daily; CCI [redacted].

Simulation Details

Simulations were performed using R version 3.6.1 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.3.0 to perform the MCMC analyses.

CCI [redacted]

For this sub-study, the starting dose was elranatamab 4 mg (QW) and nirogacestat 100 mg BID. The maximum number of participants per trial was set to 30. The trial was stopped when the following criteria were met:

- At least 6 participants have been treated at the recommended MTD $\tilde{d}$.
- The dose $\tilde{d}$ satisfies one of the following conditions:
  - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
  - A minimum of 18 participants have been treated in the trial.

The following metrics were assessed in the simulations:

- Percentage of participants receiving dose combination(s) in the target toxicity interval;
- Percentage of participants receiving an overdose;

- Percentage of participants receiving an under dose;
- Probability that recommended MTD at the end of the trial is in the target toxicity interval;
- Probability that recommended MTD is an overdose;
- Probability that recommended MTD is an under dose;
- Percentage of trials stopped without MTD declaration;
- Average sample size.

Simulation Results

Operating characteristics for this sub-study are presented in Table 17. The percentage of trials with a correctly identified MTD ranges from 48.0% to 89.6%. The average sample size is approximately 14 to 18 participants.

Table 17. Operating Characteristics

Scenarios	Participant Allocation (%)			Prob of Declare MTD (%)			Prob of Stop with no MTD Found (%)	Average Sample Size
	UD	TT	OD	UD	TT	OD		
1. Mean prior DLT rate	24.1	75.9	0	4.3	89.6	0	6.1	18
2. 30% more toxic than the mean prior DLT rate	0	73.7	26.3	0	48.0	29.7	22.3	14
3. Higher dose is overly toxic	0	70.4	29.6	0	52.6	31.5	15.9	15

Abbreviations: MTD=maximum tolerated dose: OD=overdose; TT=target toxicity; UD=under dose.

9.2. Appendix 2: BLRM Design CCI

CCI

[redacted]

Table 188. Prior Distribution for the Model Parameters CCI

Parameter	Mean	Standard deviations	Correlation
Elranatamab single agent parameters: CCI			
$(\log(\alpha_1), \log(\beta_1))$	CCI		
Nirogacestat single agent parameters: CCI			
$(\log(\alpha_2), \log(\beta_2))$	CCI		
Interaction parameter: Normal prior			
η_{12}	CCI		

η12: Two-way interaction between elranatamab and nirogacestat.
Abbreviations: CCI

CCI

Table 19. Start of PA8 Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose

Scenarios	CCI	Pr(TT) at Next Dose	Pr(OD) at Next Dose
1		0.295 0.219	0.030 0.162
2		0.396	0.137
3		0.206 0.209	0.021 0.145
4		0.294	0.2497
5		0.277	0.241

CCI; mg=milligrams;
Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing.

9.3. Appendix 3: List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	anatomic Therapeutic Chemical
AUC	area under the curve
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
BCMA	B-cell maturation antigen
BLQ	below the limit of quantitation
BLRM	Bayesian logistic regression model
BMA	bone marrow aspirate
BMI	body mass index
BOR	best overall response
BP	blood pressure
CRR	complete response rate
CI	confidence interval
Cmax	maximum observed concentration
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DI	dose intensity
DLT	dose limiting toxicity
DOCR	duration of complete response
DOMRD	duration of minimal residual disease
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
EMD	extramedullary disease

Abbreviation	Term
EORTC MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients core module
EOS	end of study
EOT	end of treatment
ICANS	immune cell-associated neurotoxicity syndrome
IMWG	International Myeloma Working Group
irAE	immune-related adverse event
IRT	interactive response technology
LLN	lower limit of normal
LLOQ	lower limit of quantitation
MRD	minimal residual disease
MUGA	multigated acquisition
N/A; NA	not applicable; not assessed
NAb	neutralizing antibody
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
OTR	outside toxicity reference
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia's method)
RDI	relative dose intensity
RP2D	recommended phase 2 dose
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
sMRD	sustained minimal residual disease

Abbreviation	Term
SMQ	Standardised MedDRA Queries
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse events
T_{max}	time for C_{max}
TTR	time to response
ULN	upper limit of normal
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

Protocol C1071004
(MAGNETISMM-4)

SUB-STUDY B

PHASE 1B/2, OPEN LABEL UMBRELLA STUDY OF ELRANATAMAB (PF-06863135), A B-CELL MATURATION ANTIGEN (BCMA) CD3 BISPECIFIC ANTIBODY, IN COMBINATION WITH OTHER ANTI-CANCER TREATMENTS IN PARTICIPANTS WITH MULTIPLE MYELOMA

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 28 Jan 2022

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1. VERSION HISTORY

This SAP for study C1071004, Sub-Study B is based on the protocol amendment v6.0 (dated 02 December 2021). Sub-study B was first added under the Master Protocol Amendment 4 dated 09 Aug 2021, which was intended for FDA's review and endorsement. The sub-study B protocol amendment v5.0 was done as of 08 Nov 2021 per FDA's comments, amendment v6.0 was done as of 02 Dec 2021. It's then decided the sub-study B SAP v1.0 will be generated to align with amendment 6. No participants were enrolled prior to protocol amendment v6.0.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28 Jan 2022	Amendment 6.0		

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses for sub-study B of C1071004 umbrella study. C1071004 sub-study B is a prospective, open-label, multi-center, Phase 1b study to evaluate safety, efficacy, PK, and pharmacodynamics of elranatamab in combination with lenalidomide and dexamethasone in participants with Relapsed/refractory multiple myeloma (RRMM):

- **Dose escalation part** is to evaluate the tolerability, safety and select a recommended dose and regimen for elranatamab in combination with lenalidomide and dexamethasone (combination RP2D).

- **Dose expansion part** is to further evaluate the overall safety of the combination at RP2D.

The general methodology for summary and statistical analyses that apply to all sub-studies in the umbrella protocol are described in the Master SAP. This SAP provides statistical methodology and analyses that are specific to sub-study B.

2.1. Study Objectives, Endpoints, and Estimands

Dose Escalation Part

Type	Objectives	Endpoints	Estimands
Primary			
Safety	• To assess safety and tolerability of elranatamab in combination with lenalidomide and dexamethasone in participants with RRMM in order to select a RP2D(s) for the combination	• DLTs during DLT observation period.	• The primary estimand is DLT rate estimate based on data from DLT-evaluable participants during the DLT observation period, which is 42 days from C0D1 through C1D28.
Secondary			
Safety	• To evaluate the overall safety profile of elranatamab in combination with lenalidomide and dexamethasone	• AEs as characterized by type, frequency, severity as graded by NCI CTCAE version 5.0, timing, seriousness, and relationship to elranatamab in combination with lenalidomide and dexamethasone. The severity of CRS and ICANS will be assessed according to ASTCT criteria (Lee et al, 2019);[1] • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• N/A
Efficacy	• To evaluate anti-myeloma activity of elranatamab in combination with lenalidomide and dexamethasone	• ORR and CRR, per IMWG response criteria as determined by investigator; • Time to event endpoints: TTR, DOR, DOCR, PFS per IMWG response criteria as determined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• N/A

PK	• To evaluate the PK of elranatamab given alone and in combination with lenalidomide and dexamethasone	• Free and total PK parameters of elranatamab in serum: C_{max}, T_{max}, AUC_{last} after elranatamab administration alone as a priming dose.	• N/A
	• To evaluate the PK of lenalidomide when administered with elranatamab	• Pre- and post-dose concentrations (free and total) of elranatamab in combination with lenalidomide and dexamethasone; • Trough plasma concentrations of lenalidomide at selected cycles.	• N/A
Immunogenicity	• To evaluate immunogenicity of elranatamab in combination with lenalidomide	• Incidence and titers of ADA and NAb against elranatamab.	• N/A
Tertiary/Exploratory			
Biomarker	• To explore correlations between elranatamab exposure and efficacy, safety, and biomarker endpoints, if data allow	• Selected PK, efficacy, safety, and biomarker endpoints.	• N/A
	• To understand the relationship between elranatamab in combination with dexamethasone and lenalidomide and the biology of the participant's MM	• Measurements of biomarkers (DNA, RNA, protein, or defined cell types) resulting from analyses of peripheral blood and/or BM biospecimens.	• N/A
PRO	• To assess the impact of elranatamab on patient-reported symptoms and functioning	• EORTC QLQ-CIPN20.	• N/A

Dose Expansion Part

Type	Objectives	Endpoints	Estimands
Primary			
Safety	• To evaluate the overall safety profile of elranatamab in combination with lenalidomide and dexamethasone	• AEs as characterized by type, frequency, severity as graded by NCI CTCAE version 5.0, timing, seriousness, and relationship to elranatamab in combination with lenalidomide and dexamethasone. The severity of CRS and ICANS will be assessed according to ASTCT criteria (Lee et al, 2019).[1] • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• N/A
Secondary			
Efficacy	• To evaluate anti-myeloma activity of elranatamab in combination with lenalidomide and dexamethasone	• ORR and CRR, per IMWG response criteria as determined by investigator; • Time to event endpoints: TTR, DOR, DOCR, PFS per IMWG response criteria as determined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• N/A
PK	• To evaluate the PK of elranatamab given alone and in combination with lenalidomide and dexamethasone. • To evaluate the PK of lenalidomide when administered with elranatamab	• PK parameters (free and total elranatamab) in serum: C_{max}, T_{max}, AUC_{last} after elranatamab administration alone as a priming dose; • Pre- and post-dose concentrations of elranatamab in combination with	• N/A

		lenalidomide and dexamethasone; • Trough plasma concentrations of lenalidomide at selected cycles.	
Immunogenicity	• To evaluate immunogenicity of elranatamab in combination with lenalidomide	• Incidence and titers of ADA and NAb against elranatamab.	• N/A
Tertiary/Exploratory			
Efficacy	• To explore additional efficacy of elranatamab in combination with lenalidomide and dexamethasone.	• sMRD negativity rate and DOMRD negativity.	• N/A
PRO	• To assess the impact of elranatamab on patient-reported symptoms and functioning	• EORTC QLQ-CIPN20.	• N/A
Biomarker	• To understand the relationship between elranatamab in combination with lenalidomide and dexamethasone and the biology of the participant's MM	• Measurements of biomarkers (DNA, RNA, protein, or defined cell types) resulting from analyses of peripheral blood and/or BM biospecimens.	• N/A
	• To explore correlations between elranatamab exposure and efficacy, safety and biomarker endpoints, if data allow.	• Selected PK, efficacy, safety and biomarker endpoints.	• N/A

2.2. Study Design

This sub-study of C1071004 protocol will evaluate safety, efficacy, PK, and pharmacodynamics of elranatamab in combination with lenalidomide and dexamethasone in participants with Relapsed/refractory multiple myeloma (RRMM). The sub-study is composed of 2 parts for the Phase 1b portion:

- **Dose escalation part** is to evaluate the tolerability, safety and select a recommended dose and regimen for elranatamab in combination with lenalidomide and dexamethasone (combination RP2D).

- **Dose expansion part** is to further evaluate the overall safety at combination RP2D.

Dose Escalation Design:

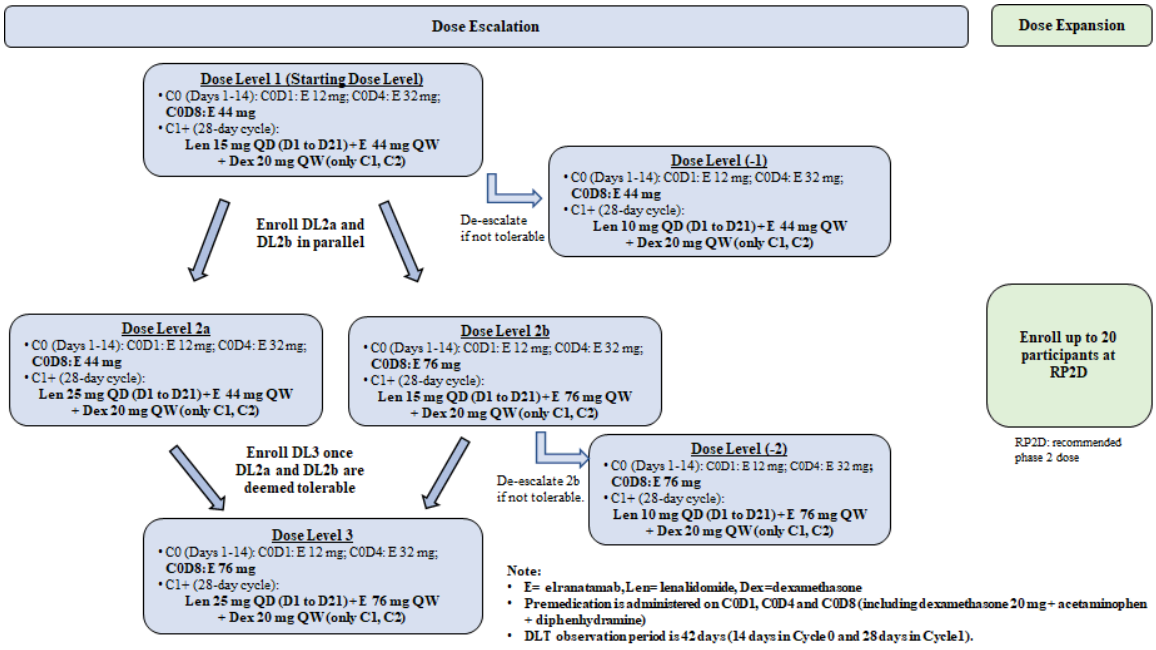
Approximately 3-6 DLT-evaluable participants will be treated at each dose level of the combination therapy. If DL1 is tolerated, two cohorts (DL2a and DL2b) will be initiated in parallel and arm allocation for participants follows an alternative allocation scheme. DL2a and DL2b must be considered tolerable before DL3 can be opened. Before moving to the next dose level, the safety data will be evaluated by a dose level review committee once evaluable participants have been followed for a minimum of 42 days after the first dose of elranatamab (14 days from the first elranatamab dose + first 28 days following the first dose of the combination of elranatamab, lenalidomide, and dexamethasone).

Dose escalation/de-escalation decisions will be guided by a BLRM approach to determine the MTD of elranatamab when administered in combination with lenalidomide and dexamethasone. However, other evidence such as safety data beyond DLT window, clinical activity, PK, and pharmacodynamics data will also be evaluated in determining the RP2D. The RP2D will be determined with agreement between the investigators and the Sponsor at the dose level review committee.

Dose Expansion Design:

The dose expansion part will begin once the combination RP2D is identified in the dose escalation part. A total of up to 20 participants (including 6 participants treated at the RP2D from the dose escalation part) will be enrolled and dosed at RP2D in the dose expansion part.

Figure 1. Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Dose Escalation

The primary endpoint of the dose escalation part is the DLTs during the DLT observation period, which is the first 42 days from Cycle 0 Day 1 through Cycle 1 Day 28 of study intervention.

3.1.2. Dose Expansion

The primary endpoints in the dose expansion part are as follows:

- AEs as characterized by type, frequency, severity, timing, seriousness, and relationship to elranatamab in combination with lenalidomide and dexamethasone;
- Laboratory abnormalities as characterized by type, frequency, severity and timing.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

For all efficacy endpoints per IMWG response criteria, BOR assessed based on reported overall responses recorded at evaluation time points from the date of first dose until the first documentation of confirmed PD, death or start of new anti-cancer therapy, whichever occurs first.

- Objective response is defined as having a BOR of confirmed sCR, CR, VGPR or PR.

3.2.1.1. Objective Response Rate

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

3.2.1.2. Complete Response Rate

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

3.2.1.3. Duration of Response

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

3.2.1.4. Duration of Complete Response

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

3.2.1.5. Progression-free Survival

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

3.2.1.6. Overall Survival

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

3.2.1.7. Time to Response

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

3.2.1.8. Minimal Residual Disease Negativity Rate

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

3.2.2. Safety Endpoints

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

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

3.2.3. Pharmacokinetic Endpoints

- Free and total PK parameters of elranatamab in serum: C_{max}, T_{max}, AUC_{last} after elranatamab administration alone as a priming dose;

- Pre- and post-dose concentrations (free and total) of elranatamab in combination with lenalidomide and dexamethasone;

- Trough serum concentrations of lenalidomide at selected cycles.

3.2.4. Immunogenicity Endpoints

- Incidence and titers of ADA and NAb against elranatamab.

3.3. Exploratory Endpoints

3.3.1. Additional Efficacy Endpoints

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

3.3.2. Translational Oncology Biomarkers Endpoints

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

- Selected PK, efficacy, safety, and biomarker endpoints

3.3.3. Patient-Reported Outcomes Endpoints

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

European Organization for Research and Treatment of Cancer - chemotherapy-induced peripheral neuropathy (EORTC QLQ-CIPN20): The EORTC QLQ-CIPN20 is a module developed by the EORTC group to assess chemotherapy-induced peripheral neuropathy.[5] It contains 20 items which can be grouped into a sensory subscale (9 items), motor subscale (8 items) and autonomic subscale (3 items).

3.4. Baseline Variables

See Section 3.4 of the master SAP for the definition of baseline variables.

3.5. Safety Endpoints

See Section 3.5 of the master SAP for the definition of the safety endpoints.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

See Section 4 of the master SAP for definitions of analysis sets.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

5.1.1.1. Phase 1b Dose Escalation

The primary objective in the Phase 1b dose escalation part of the study is to assess safety and tolerability of elranatamab in combination with lenalidomide and dexamethasone in order to select a RP2D for the combination therapy. There is no statistical hypothesis for this part. A BLRM will be utilized for dose escalation recommendation of the combination therapy.

CCI

[redacted]

Sample Size Estimation

A minimum of 3-6 DLT-evaluable participants (as defined in Section 4 in the master SAP) will be treated at each dose level of the combination therapy. The actual number of participants to be enrolled will depend on the number of dose levels evaluated and the number of participants treated at each dose level. Therefore, it cannot be determined in advance.

It is estimated that approximately up to 24 DLT evaluable participants will be enrolled and treated with elranatamab combination in the dose escalation part which will include at least 6 DLT evaluable participants treated at the elranatamab combination RP2D level.

If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants in the Phase 1b of the sub-study.

5.1.1.2. Phase 1b Dose Expansion

The primary objective in the Phase 1b dose expansion part of the study is to further evaluate the overall safety profile of elranatamab in combination with lenalidomide, and dexamethasone at RP2D. There is no statistical hypothesis for this part.

Dose expansion phase will begin once the combination RP2D is identified in the dose escalation part. A total of up to 20 participants will be enrolled and dosed at RP2D in the dose expansion part, including the 6 participants treated at the RP2D level from dose escalation part.

5.1.2. Decision Rules

5.1.2.1. Phase 1b Does Escalation

Identification of RP2D

Dose escalation/de-escalation decisions will be guided by a BLRM approach, through the posterior probability of DLT during the DLT observation period, to determine the MTD of elranatamab when administered in combination with lenalidomide and dexamethasone. BLRM takes available DLT data from all dose levels when updating posterior probability of DLT. Specifically, dose level 2a and 2b will be tested in parallel once dose level 1 is cleared. The DLT data on both dose level 2a and 2b will be used by the BLRM to recommend next dose level. However, other evidence such as safety data beyond DLT window, clinical activity, PK, and pharmacodynamics data will also be evaluated in determining the RP2D. The RP2D will be determined with agreement between the investigators and the Sponsor at the dose level review committee.

Assessment of Participant Risk

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

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

CCI

[redacted]

5.1.2.2. Phase 1b Dose Expansion

Overall safety profile of elranatamab in combination with lenalidomide and dexamethasone at RP2D will be further studied in the dose expansion part. There is no decision rule for the dose expansion part of the study. The following table lists the probability of detecting a given DLT in at least 1 participant under a possible range of true rare DLT probability. For example, the dose expansion with n=20 participants will have 64% chance to detect a rare DLT in at least 1 patient when the true DLT probability is 5%.

True DLT probability	1%	3%	5%	7%	10%
Prob of detecting DLT in >=1 patient	0.18	0.46	0.64	0.77	0.88

The final analysis will be conducted once all participants have been followed for at least 2 years from enrollment or have otherwise discontinued from the treatment.

5.2. General Methods

Unless otherwise specified, all analyses will be performed for dose escalation and expansion separately and with the cohort of RP2D in dose escalation and expansion combined.

For the dose escalation part of the study, all analyses will be performed by dose level and with all dose levels combined as well.

See Section 5.2 of the master SAP for the detail of the general statistical methods.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Phase 1b Dose Escalation

DLT rate is calculated as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants in the DLT observation period.

Analyses of DLT will be performed on DLT Evaluable Analysis Set as defined in Section 4 of the master SAP. DLT rate will be summarized and listed by dose levels.

6.1.2. Phase 1b Dose Expansion

The primary endpoints in the dose expansion part are as follows:

- AEs as characterized by type, frequency, severity, timing, seriousness, and relationship to elranatamab combination with lenalidomide and dexamethasone;
- Laboratory abnormalities as characterized by type, frequency, severity and timing.

See Section 6.6 of the master SAP for safety summaries and analyses.

6.2. Secondary Efficacy Endpoints

6.2.1. Objective Response

The observed point estimate of ORR will be calculated along with the 2-sided 95% CIs using the Clopper-Pearson method[12] (exact CI for a binomial proportion).

The frequency (number and percentage) of participants with BOR by investigator in each response category will be summarized: sCR; CR; VGPR; PR; MR; SD; PD; Not evaluable (NE).

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

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

BOR will be assessed based on reported timepoint responses by investigator recorded at evaluation time points from the date of first dose until confirmed 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 required between the disease assessments, but a different sample is required for confirmation. A confirmatory response assessment may be performed >28 days following the initial response assessment, allowing for a maximum of 1 intervening missing or not evaluable assessment.

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

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

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

Scenario	Timepoint Response at:			BOR
	Assessment 1	Assessment 2	Assessment 3	
25	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	
26	Death (due to disease under study)			
27	Death (not due to disease under study) before initiation of new anticancer therapy			NE
28	NE	No further assessment		
29	NE	NE/PD[c]	No further assessments	
30	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.

6.2.2. Complete Response Rate

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

Point estimates of CRR will be calculated along with corresponding 2-sided exact 95% CIs using the Clopper-Pearson method.[12]

6.2.3. Progression-free Survival

PFS is defined as the time from the date of first dose until the initial documentation of PD date that is subsequently confirmed per IMWG criteria as determined by investigator or death due to any cause, whichever occurs first. The rules for PD confirmation are described in Table 2.

PFS will be calculated as follows:

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

PFS will be censored as follows:

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

- For participants who start a new anticancer therapy (as defined in Section 5.2.6 in the master SAP) 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 is defined in Section 5.2.10 in the master SAP.

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

a. If there are no adequate post-baseline disease assessments prior to 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.[11]

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 [13] (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.

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

6.2.4. Duration of Response

DOR is defined, for participants with an objective response per IMWG criteria as determined by investigator, as the time from the first documentation of objective response that is subsequently confirmed, until the initial documentation of PD date that is subsequently confirmed per IMWG criteria, or death due to any cause, whichever occurs first. The rules for PD confirmation are described in Table 2.

DOR will be calculated as follows:

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

The censoring rules for DOR are as described for PFS in Section 6.2.2 in the master SAP except that participants will not be censored for no adequate post-baseline assessment, as only participants with an objective response are included in the analysis of DOR.

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

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

6.2.5. Duration of Complete Response

DOCR is defined, for participants with a confirmed CR/sCR per IMWG criteria as determined by investigator, as the time from the first documentation of CR/sCR that is subsequently confirmed, until the initial documentation of PD date that is subsequently confirmed per IMWG criteria, or death due to any cause, whichever occurs first. The rules for PD confirmation are described in Table 2.

DOCR will be calculated as follows:

$$\text{DOCR (months)} = [\text{date of event or censoring} - \text{first date of confirmed CR/sCR} + 1] / 30.4375$$

The censoring rules for DOCR are as described for DOR in Section 6.2.4.

If at least 3 participants achieve a BOR of confirmed CR/sCR and subsequently have an event, DOCR will be estimated using the same Kaplan-Meier method as described for DOR in Section 6.2.4 and displayed graphically where appropriate. Otherwise only listings will be provided.

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

6.2.6. Overall Survival

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

$$\text{OS (months)} = [\text{date of death or censoring} - \text{date of first dose} + 1] / 30.4375$$

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

OS time will be estimated using the same Kaplan-Meier method and displayed graphically as described for PFS in Section 6.2.3. Median OS and 2-sided 95% CI will be provided. The OS rate at 12, 24, and 36 months (and in subsequent 12-month increments while there are participants still at risk) will be estimated with corresponding two-sided 95% CIs.

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

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

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

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

6.2.7. Time to Response

TTR is defined, for participants with an objective response per IMWG criteria as determined by investigator, as the time from the date of first dose to the first documentation of objective response that is subsequently confirmed. For participants with EMD at baseline, MR or better cannot be confirmed until a post-baseline EMD assessment is performed and the date of confirmed response cannot be prior to the initial EMD assessment date.

TTR will be calculated in weeks as follows:

TTR (weeks) = (date of first objective response – date of first dose + 1) / 7

TTR will be summarized using simple descriptive statistics (mean, standard deviation, minimum, median, and maximum).

6.2.8. Minimal Residual Disease Negativity Rate

MRD negativity rate is defined as the proportion of participants with CR or better by investigator and negative MRD (assessed by central lab) per IMWG sequencing criteria at any time from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first. The rules for PD confirmation are described in Table 2.

MRD negativity will be defined by two thresholds, CCI .

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

- MRD negative with confirmed sCR/CR based on the Safety Analysis Set;

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

- MRD negative based on the subset of MRD evaluable patients (achieve sCR/CR and have at least one MRD assessment).

6.3. Other Secondary Endpoints

6.3.1. Pharmacokinetic/Pharmacodynamics

Pharmacokinetic parameter analyses will be based on the PK Analysis Set.

6.3.1.1. Elranatamab

PK data analyses will include descriptive summary statistics of the predose and postdose serum concentrations, and PK parameters of elranatamab by study visit and time point. Box and Whisker plots for predose elranatamab concentrations by study visit and PK parameters (C_{max} and AUC_{last}) will be generated. Values below the limit of quantitation for elranatamab and other analytes will be treated as zero in the descriptive statistics calculations. For additional details on handling missing and BLQ values, please refer to Section 5.3.1 in the master SAP.

In addition, the PK data from this study may be used to develop a population PK model. PK data from this study maybe pooled with other studies for population PK model development. 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.

6.3.1.2. Lenalidomide

PK data analyses will include descriptive summary statistics of predose serum concentrations of lenalidomide by study visit and time point. Box and Whisker plots for predose serum concentrations of lenalidomide by study visit will be generated. PK data from this study maybe pooled with other studies for population PK model development. The correlations between lenalidomide 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.

6.3.2. Immunogenicity

Immunogenicity data will be analyzed in the Immunogenicity Analysis Set.

The percentage of participants with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-baseline will be generated. Samples may also be analyzed for the presence of neutralizing antibodies (NAb), and any data will be similarly summarized. For participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit.

The potential impact of immunogenicity on PK and clinical response including pharmacodynamic markers, safety/tolerability and efficacy will be explored, if warranted by the data. This analysis may be reported separately from the CSR.

6.4. Exploratory Endpoints

6.4.1. Efficacy Analysis

6.4.1.1. Sustained MRD Negativity Rate

sMRD negativity rate will be summarized at pre-specified timepoints. Sustained xx-month MRD negativity rate is defined as the proportion of participants with negative MRD and confirmed sCR/CR with at least xx months apart without positive MRD in between, where xx=12 and 24 months and other timepoints of interest. Sustained xx-month MRD negativity rate will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method.

6.4.1.2. Duration of MRD Negativity

If data permits, DOMRD will be analyzed using Kaplan-Meier method in participants who have achieved negative MRD 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. Relapse is defined as any one or more of the following criteria:

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

The following exploratory endpoints analyses may be performed. The results may be presented separately from the main CSR.

6.4.2. Biomarker Analysis

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

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

6.4.3. Patient-Reported Outcomes

The following PRO analyses will be performed to support the CSR development. Analyses of the PRO endpoints will be based on the PRO Analysis Set.

Completion Status

The number and percentage of participants who completed the PRO at each time point will be summarized, as will the reasons for non-completion. A PRO is considered completed if at least one item was answered by the participant.

EORTC QLQ-CIPN20

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

6.5. Subset Analyses

All the subset analyses will be exploratory and descriptive; 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, analyses of ORR will only be performed if there are ≥10 participants overall within the defined subset. Deviations from these analyses will be described in the clinical study report.

The following subset analyses will be performed for ORR for the RP2D cohort based on the Safety Analysis Set:

- Baseline cytogenetics (high vs standard risk);
- Baseline extramedullary disease (yes vs no);
- Prior stem cell transplant (yes vs no);
- Disease stage (1-2 vs 3);
- Number of prior therapies (≤4, >4);
- Type of myeloma (IgG vs non-IgG vs light chain only);
- Age (<65 vs ≥65; <75 vs ≥75).

ORR in subsets will be presented in a forest plot. Other subset analyses will be performed as well if deemed clinical meaningful and feasible (sufficient sample size).

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

See Section 6.5.1 of the master SAP for baseline summaries.

6.6.2. Study Conduct and Participant Disposition

See Section 6.5.2 of the master SAP for summaries of study conduct and participant disposition.

6.6.3. Study Intervention Exposure

Exposure will be summarized based on the Safety Analysis Set.

6.6.3.1. Exposure to Elranatamab

Elranatamab is administered as a subcutaneous injection based on the dosing schedule as described in Table 5.

Table 5. Study Intervention Dose Levels and Administration

Dose Levels (DL)	Elranatamab (SC)	Lenalidomide (PO)	Dexamethasone (PO)
1 (starting dose level)	**2 step-up Priming Doses**: 12 mg C0D1 /32 mg C0D4 **Full Dose:** 44 mg at C0D8, then 44 mg QW starting on C1D1 (28-day cycle)	15 mg QD starting on C1D1 for 21 days (28-day cycle)	20 mg QW, starting on C1D1 (28-day cycle) Only for C1 and C2
2a	**2 step-up Priming Doses**: 12 mg C0D1 /32 mg C0D4 **Full Dose:** 44 mg at C0D8, then 44 mg QW starting on C1D1 (28-day cycle)	25 mg QD starting on C1D1 for 21 days (28-day cycle)	20 mg QW, starting on C1D1 (28-day cycle) Only for C1 and C2
2b	**2 step-up Priming Doses**: 12 mg C0D1 /32 mg C0D4 **Full Dose:** 76 mg at C0D8, then 76 mg QW starting on C1D1 (28-day cycle)	15 mg QD starting on C1D1 for 21 days (28-day cycle)	20 mg QW, starting on C1D1 (28-day cycle) Only for C1 and C2
3	**2 step-up Priming Doses**: 12 mg C0D1 /32 mg C0D4 **Full Dose:** 76 mg at C0D8, then 76 mg QW starting on C1D1 (28-day cycle)	25 mg QD starting on C1D1 for 21 days (28-day cycle)	20 mg QW, starting on C1D1 (28-day cycle) Only for C1 and C2
De-escalation levels			
(-1) (one dose level below DL1)	**2 step-up Priming Doses**: 12 mg C0D1 /32 mg C0D4 **Full Dose:** 44 mg at C0D8, then 44 mg QW starting on C1D1 (28-day cycle)	10 mg QD starting on C1D1 for 21 days (28-day cycle)	20 mg QW, starting on C1D1 (28-day cycle) Only for C1 and C2
(-2) (de-escalate from DL2b if DL2b is not tolerable)	**2 step-up Priming Doses**: 12 mg C0D1 /32 mg C0D4 **Full Dose:** 76 mg at C0D8, then 76 mg QW starting on C1D1 (28-day cycle)	10 mg QD starting on C1D1 for 21 days (28-day cycle)	20 mg QW, starting on C1D1 (28-day cycle) Only for C1 and C2

For dose escalation and dose expansion, a priming dose regimen will be applied within the first cycle of elranatamab treatment (C0), composed of 2 step-up priming doses (12 mg at C0D1 and 32 mg at C0D4), followed by the first full dose of elranatamab at C0D8 (44 mg or 76 mg), according to the dose-escalation design described in Figure 1. Both premedication and the priming dose regimen will mitigate the risk of CRS during C0.

A minimum of 2 days should be maintained between the 2 step-up doses (C0D1 and C0D4) and a minimum of 3 days between C0D4 and the first full dose (C0D8); a minimum of 6 days is required between doses thereafter.

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

- Treatment duration (weeks);
- Number of cycles started per participant (mean, median, min, max);
- Number and percent of participants starting a cycle (any cycle, cycle 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, >=12 cycles);
- Total cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose (%);
- Overall relative dose intensity (%);
- Number and percent of participants after 6 cycles who switched from QW to Q2W;
- Number and percent of participants, among those switching from QW to Q2W, who switched back to QW.

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

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

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

- Planned treatment duration (weeks) = 2(2 week for Cycle 0) + number of cycles started × 4 - (number of weeks in the last cycle after permanent treatment discontinuation or data cutoff for those on-treatment).
- Intended treatment duration (weeks) = (last zero/non-zero dose date – first dose date)/7 + 1 if on QW or 2 if on Q2W

  Note: If C0D4 is the last visit and dose is given at this visit, duration is 1 week.

The planned dose for a given cycle is defined as:

- Cycle 0:
  - Planned dose (mg/cycle) = Planned priming dose(s) per protocol during C0
- After Cycle 0:
  - If the participant is on QW dosing schedule for the cycle:

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

    Planned dose (mg/cycle) = Full dose × 2

  Note: Full dose=44 or 76 mg depends on DLs. For the last cycle, subtract planned doses after a participant permanently discontinues treatment or data cutoff for those on-treatment.

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

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

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

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

The RD and RDI are defined as follows:

- Cycle RD (%) = Total given dose for a given cycle (mg) /Total planned dose for a given cycle (mg) × 100;
- Overall RD (%) = Total cumulative dose (mg) /Total planned dose (mg) × 100;

- Cycle RDI (%) = Cycle DI (mg/week) /Cycle Planned DI (mg/week) × 100;
- Overall RDI (%) = Overall DI (mg/week) /Overall Planned DI (mg/week) × 100.

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

6.6.3.2. Exposure to Lenalidomide

Starting on Cycle 1, the first dosing of the two combination partners (lenalidomide and dexamethasone) will be initiated.

Escalating doses of 15 mg or 25 mg of lenalidomide PO QD will be administered on Days 1-21 of each 28-day cycle for all cycles. De-escalating dose of 10 mg is permitted, depending on the dose levels being evaluated.

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

- Treatment duration (weeks);
- Total cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose intensity (%).

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

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

Planned treatment duration, intended treatment duration, planned dose and planned DI is needed to calculate DI and RDI. The planned treatment duration 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).
- Intended treatment duration (weeks) = (last zero/non-zero dose date – first dose date)/7 + 1
- Planned dose (mg/cycle) = Full dose (mg) × 21, Full dose=15, 25 or 10 depending on DL.

  Note: 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 total cumulative dose (mg) of Lenalidomide is the sum of the actual dose levels that the participant received during the study (ie, total dose administered [mg]).

The overall planned DI is defined as:

- Overall Planned DI (mg/week) = Total planned dose (mg)/(planned treatment duration in weeks).

The overall DI and RDI of lenalidomide will be calculated for each participant during the study.

- Overall DI (mg/week) = Total cumulative dose (mg)/ Intended treatment duration (weeks);
- Overall RD (%) = [Total cumulative dose (mg) / Total planned dose (mg)] × 100;
- Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] × 100.

6.6.3.3. Exposure to Dexamethasone

Dexamethasone 20 mg will be administered three time in C0 (D1, D4, D8), and PO QW (D1, D8, D15, D22) during the first 2 cycles of the combination (C1 and C2).

The summary of treatment exposure for dexamethasone will include the following information:

- Treatment duration (weeks);
- Total cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose intensity (%).

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

- Treatment duration (weeks) = (last dose date – first dose date + 1)/7;
- Planned treatment duration (weeks) = (number of cycles started x 4) - (number of weeks in the last cycle after permanent treatment discontinuation or data cutoff for those on-treatment);
- Intended treatment duration (weeks) = (last zero/non-zero dose date – first dose date)/7 + 1.

The planned dose of dexamethasone for a given cycle is defined as:

- Cycle 0:

  Planned dose (mg/cycle) = 20 (mg) × 3.

- Cycle 1 & 2:

  Planned dose (mg/cycle) = 20 (mg) × 4.

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

The overall planned DI is defined as:

- Overall Planned DI (mg/week) = Total planned dose (mg)/(planned treatment duration in weeks).

The overall DI, RD, and the RDI will be calculated for each participant overall across all cycles as follows:

- Overall DI (mg/week) = Total cumulative dose (mg)/ Intended treatment duration (weeks);
- Overall Planned DI (mg/week) = Total planned dose (mg)/(planned treatment duration in weeks);
- Overall RD (%) = [Total cumulative dose (mg) / Total planned dose (mg)] × 100;
- Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] × 100.

6.6.3.4. Dose Reductions, Interruptions, and Delays

Dose Reduction

A dose reduction is defined as a nonzero dose that is less than the planned dose. The planned dose is the same as the prior dose except for elranatamab at C0D4 and C0D8.

For each study treatment, the number and percentage of participants with at least 1 dose reduction as well as a breakdown of dose reductions (1/2/3/ ≥4) will be summarized by dose cohort (dose escalation part) and treatment arm (dose expansion). In addition, the number and percentage of participants with at least 1 dose reduction due to an AE will also be summarized.

Dose Interruption

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

Dose Delay

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

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

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

Dose delay is not applicable to lenalidomide or dexamethasone.

6.6.4. Concomitant Medications and Nondrug Treatments

See Section 6.5.4 of the master SAP for summaries of concomitant medications and nondrug treatments.

6.6.5. Subsequent Anticancer Therapies

See Section 6.5.5 of the master SAP for summaries of subsequent anticancer therapies.

6.7. Safety Summaries and Analyses

See Section 6.6 of the master SAP for safety summaries and analyses.

7. INTERIM ANALYSES

7.1. Introduction

There are interim safety assessments planned for this sub-study.

For both dose escalation and dose expansion parts of the sub-study, an internal safety review team will review safety and tolerability data on an ongoing basis for the interim safety assessments.

7.2. Interim Analyses and Summaries

7.2.1. Interim Safety Assessments

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

- Grade 3-4 CRS;
- Grade 3-4 ICANS;
- Grade 4 treatment-related non-hematologic events (excluding CRS and ICANS);
- Grade 3-4 treatment-related GBS/GB-like AEs;
- Grade 4 treatment-related sensory neuropathy/other IR neurologic AEs (excluding ICANS);
- Grade 3-4 treatment-related motor neuropathy;
- Grade 5 events.

If the number of participants observed to have such identified events exceeds a prespecified threshold across dose levels, the sub-study will be placed on a temporary enrollment hold by the Sponsor. During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. Participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the investigator in consultation with the sponsor.

The criteria for placing the sub-study on temporary hold for safety reasons are based on Bayesian posterior probabilities. Using a non-informative Beta (0.5, 0.5) prior distribution, if the number of participants observed to have Grade 3 or 4 CRS results in a ≥0.90 posterior probability that the true Grade 3 or 4 CRS rate exceeds 20%, the sub-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. Identified Events That Would Prompt Temporary Enrollment Hold

Number of Evaluable Participants	8-11	12-14	15-18	19-22	23-26	27-30	31-34
Minimum number of participants with Grade 3-4 CRS events that would lead to a temporary enrollment hold*	4	5	6	7	8	9	10
Minimum number of participants with Grade 3-4 ICANS events that would lead to a temporary enrollment hold*	4	5	6	7	8	9	10
Minimum number of participants with Grade 4 treatment-related non-hematologic events (excluding CRS and ICANS) that would lead to a temporary enrollment hold*	4	5	6	7	8	9	10

Prior distribution: Beta (0.5,0.5)

Criteria for 35+ or more evaluable participants will be calculated such that the sub-study will be put on temporary hold if the posterior probability that the true event rate exceeds 20% is greater than or equal to 0.90.

Evaluable participants are defined as those having an identified event or those without such an event who have been followed for at least 35 days from first dose.

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

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

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

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

  Table 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	**20-39**			-	-
Minimum number of participants with Grade 3-4 treatment-related GBS/GB-like events that would lead to a temporary enrollment hold*	2			-	-
Number of Evaluable Participants	**6-11**	**12-19**	**20-27**	**28-35**	**36-43**
Minimum number of participants with Grade 4 treatment-related sensory neuropathy /IR neurologic AE (excluding ICANS) or Grade 3-4 treatment-related motor neuropathy events that would lead to a temporary enrollment hold**	2	3	4	5	6

Prior distribution: Beta (0.5,0.5).

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

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

** The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, if there are 2 participants experiencing the identified AEs out of the first 4 evaluable participants, the study will be put on hold). A minimum of 2 events are required to trigger a temporary hold.

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

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

If number of evaluable participants go beyond the one listed in the tables, number of identified events that would prompt temporary hold will be updated accordingly based on the same Bayesian criteria.

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9. APPENDICES

9.1. Appendix 1: BLRM Design [redacted]

This section provides the details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing recommendations for some hypothetical data scenarios.

Statistical Model

The statistical model for dose-DLT data [redacted].

The monotherapy RP2D of elranatamab is 76 mg, which was determined in Study C1071001. In this sub-study, the initial dose level of elranatamab will be 44 mg with two step-up priming doses of 12 mg on C0D1 and 32 mg on C0D4 for the first dose. The initial dose level of lenalidomide is 15 mg QD, and the dose level of dexamethasone will remain at 20 mg at all dose levels.

[redacted]

CCI

[redacted]

Description of the Meta-Analytic-Predictive Approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies. Let r_{ds} and n_{ds} be the number of participants with a DLT, and the total number of participants, respectively, at dose d in historical trial s $(s = 1, \ldots, \langle S \rangle)$. The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

CCI

The historical trials are partitioned into $\langle G \rangle$ exchangeability groups, with the exchangeability group membership of historical trial s being represented by $g(s)$. The new trial is assigned to exchangeability group $g(*)$. The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1, \ldots, \langle G \rangle$. Covariance matrix ψ_g is defined by the standard deviations (t_{g1}, t_{g2}), and correlation r (a common value for r is used across all groups). The parameters t_{g1} and t_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets (t_{g1}, t_{g2}) it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

CCI

The MAP prior for single-agent model parameters in the new trial, $(log(\alpha^*), log(\beta^*))$, is the predictive distribution

$$(log(\alpha^*), log(\beta^*)) \,|(r_{ds}, n_{ds} : s = 1, \ldots, \langle S \rangle)$$

Since the predictive distribution is not available analytically, the Markov chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using Just Another Gibbs Sampler (JAGS) version 4.3.0.

CCI

CCI [redacted]

Table 8. Historical Dose Limiting Toxicity Data CCI [redacted]

CCI [redacted]	Number of Participants	Number of Participants with DLTs
	6	0
	4	0
	4	0
	4	0
	6	0
	6	0

Abbreviations: CCI [redacted] DLT=dose limiting toxicity; CCI [redacted]

CCI [redacted] Priors for t_{1p} and t_{2p} are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

The prior distributions for the model used for deriving the MAP priors are specified in Table 9.

Table 9. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior CCI [redacted]

Parameter	Prior distribution
μ_{1p}	N (mean = 0, sd =2)
μ_{2p}	N (mean = 0, sd=1)
CCI [redacted]	
r_p	Uniform (-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Single Agent Lenalidomide

Dose-DLT data for lenalidomide based on literature search as presented in Table 10 are used to derive the prior of the single agent logistic parameters for lenalidomide.

Table 10. Historical Dose Limiting Toxicity Data on Lenalidomide

Study	Lenalidomide Dose Level (mg/d)	Number of Participants	Number of Participants with DLTs
Richardson et al (Richardson et al, 2002)[14]	5	3	0
	10	6	1
	25	3	0
	50	13	0
Dahut et al (Dahut et al, 2009)[15]	5	3	0
	10	3	0
	20	9	2
Miller et al (Miller et al, 2007)[16]	5	3	0
	10	5	0
	25	12	1
Zangari et al (Zangari et al, 2001)[17]	5	3	0
	10	3	0
	25	3	0
	50	6	2

Abbreviations: DLT=dose limiting toxicity; mg/d=milligrams/day.

CCI [redacted] Priors for $t_{11b}, t_{12b}, t_{13b}, t_{14b}$ and $t_{21b}, t_{22b}, t_{23b}, t_{24b}$ are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

The prior distributions for the model used for deriving the MAP priors are specified in Table 11.

Table 11. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Lenalidomide Model Parameters

Parameter	Prior distribution
μ_{1b}	N (mean = 0, sd = 2)
μ_{2b}	N (mean = 0, sd = 1)
CCI	
r_b	Uniform (-1,1)

Abbreviations: N=normally distributed; sd=standard deviation.

Single Agent Dexamethasone

As there is no historical data available for dexamethasone, a weakly informative prior distribution for the logistic model is used. As dexamethasone will be administrated at a clinically low dose level (20 mg QW), the toxicity induced by dexamethasone is expected to be very low.

Prior Distribution for the Interaction Parameter

Normal priors for the log-odds multiplier $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are used. The prior for $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses:

CCI

CCI [redacted]

Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 12. Table 13 illustrates the resulting prior distribution of DLT rate derived from the priors given in Table 12 Based on the available information, the starting dose elranatamab = 44 mg, and lenalidomide = 15 mg satisfies the EWOC criterion.

Table 12. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
Elranatamab single agent parameters: CCI [redacted]			
$(\log(\alpha_1), \log(\beta_1))$	CCI [redacted]		
Lenalidomide single agent parameters: CCI [redacted]			
$(\log(\alpha_2), \log(\beta_2))$	CCI [redacted]		
Dexamethasone single agent parameters: CCI [redacted]			
$(\log(\alpha_3), \log(\beta_3))$	CCI [redacted]		
Interaction parameter: Normal prior			
η_{12}	CCI [redacted]		
η_{13}			
η_{23}			
η_{123}			

η_{12}: Two-way interaction between elranatamab and lenalidomide;
η_{13}: Two-way interaction between elranatamab and dexamethasone;
η_{23}: Two-way interaction between lenalidomide and dexamethasone;
η_{123}: Three-way interaction among elranatamab, lenalidomide and dexamethasone.
Abbreviations: CCI [redacted].

Table 13. Summary of Prior Distribution of Dose Limiting Toxicity Rates CCI [redacted]

CCI [redacted]	Prior Probabilities that DLT Rate is Within the Interval			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
	0.671	0.246	0.083	0.154	0.118	0.036	0.118	0.495
	0.573	0.290	0.136	0.184	0.144	0.034	0.139	0.596
	0.456	0.287	0.257	0.242	0.2	0.024	0.179	0.773
	0.527	0.293	0.18	0.204	0.168	0.029	0.151	0.673
	0.463	0.275	0.261	0.241	0.204	0.021	0.176	0.778
	0.415	0.204	0.381	0.310	0.275	0.008	0.22	0.925

Dexamethasone dose fixed at 20 mg.
Abbreviations: DLT=dose limiting toxicity; Elr=Elranatamab; Len= Lenalidomide; CCI [redacted]; SD=standard deviation.

Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next cohort of participants is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future participants, EWOC criteria and maximum amount of escalation allowed. In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 14 shows possible hypothetical dose escalation data scenarios and the corresponding recommendations for the next dose(s). CCI [redacted]

Table 14. Summary of Prior Distribution of Dose Limiting Toxicity Rates for Elranatamab in Combination with Lenalidomide and Dexamethasone

Scenario	CCI	Pr(TT) at Next Dose	Pr(OD) at Next Dose
1		0.397	0.172
2		0.149	0.055
3		0.344 0.276	0.075 0.194
4		0.433 0.462	0.051 0.222
5		0.336 0.284	0.086 0.206
6		0.469 0.443	0.181 0. 209
7		0.477 0.461	0.214 0.216
8		0.586 0.540	0.142 0.207
9		0.585	0.134
10		0.312	0.115

* Dexamethasone dose is fixed at 20 mg QW.

Abbreviations: CCI ; CCI ; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; CCI .

9.2. Appendix 2: List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	anatomic Therapeutic Chemical
AUC	area under the curve
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
BCMA	B-cell maturation antigen
BLQ	below the limit of quantitation
BLRM	Bayesian logistic regression model
BM	Bone marrow
BMA	bone marrow aspirate
BMI	body mass index
BOR	best overall response
BP	blood pressure
C#D#	cycle # day # (e.g., C1D1 = cycle 1 day 1)
CRR	complete response rate
CI	confidence interval
Cmax	maximum observed concentration
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DI	dose intensity
DLT	dose limiting toxicity
DL#	Dose Level # (eg, DL1 =Dose Level 1)
DNA	deoxyribonucleic acid
DOCR	duration of complete response
DOMRD	duration of minimal residual disease
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
EMD	extramedullary disease

Abbreviation	Term
EORTC QLQ-CIPN20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire of chemotherapy-induced peripheral neuropathy module
EOS	end of study
EOT	end of treatment
EWOC	escalation with overdose control
GB	Guillain Barré
GBS	Guillain Barré Syndrome
ICANS	immune cell-associated neurotoxicity syndrome
IMWG	International Myeloma Working Group
IR	immune-related
IRT	interactive response technology
LLN	lower limit of normal
LLOQ	lower limit of quantitation
MAP	meta analytic predictive
MR	minimal response
MRD	minimal residual disease
MTD	maximum tolerated dose
N/A; NA	not applicable; not assessed
NAb	neutralizing antibody
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	oral(ly)
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QD	once daily
Q2W	every 2 weeks
QW	every 1 week
RD	Relative dose
RDI	relative dose intensity
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
RRMM	relapsed/refractory multiple myeloma
SAP	statistical analysis plan
SC	subcutaneous(ly)
sCR	stringent complete response

Abbreviation	Term
SD	stable disease
sMRD	sustained minimal residual disease
TBILI	total bilirubin
T_{max}	time for C_{max}
TTR	time to response
VGPR	very good partial response