



MAGNETISMM-8

A PHASE 1B/2, OPEN-LABEL STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF ELRANATAMAB (PF-06863135) IN CHINESE PARTICIPANTS WITH MULTIPLE MYELOMA WHO ARE REFRACTORY TO AT LEAST ONE PROTEASOME INHIBITOR, ONE IMMUNOMODULATORY DRUG AND ONE ANTI-CD38 ANTIBODY (TRIPLE-CLASS REFRACTORY MM)

Study Intervention Number: PF-06863135

Study Intervention Name: Elranatamab

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Protocol Number: C1071008

Phase: 1b/2

Brief Title: A Phase 1b/2 Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Elranatamab (PF-06863135) in Chinese Participants With Multiple Myeloma Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb (Triple-Class Refractory MM)

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Document History

| Document | Version Date |
|-------------------|---------------|
| Amendment 4 | 17 Apr 2023 |
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| Amendment 1 | 25 June 2021 |
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This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ ECs and any protocol administrative clarification letter(s).

Protocol Amendment Summary of Changes Table

Amendment 4 (17 Apr 2023)

Overall Rationale for the Amendment:

| Description of Change | Brief Rationale | Section # and Name |
|--|---|---|
| Substantial Modification(s) | | |
| Contraception check updated from 90 days to 5 months post last dose of study intervention for WOCBP and removed for male participants. | IB updates describes a longer elranatamab terminal half-life. This is reflected in longer contraception requirements for female participants. There are no longer any contraception requirements for male participants. | Section 1.3, SoA; Section 4.2.3 Choice of Contraception/Barrier Requirements; Section 5.3.1 Contraception; Section 10.4.1, Section 10.4.2, and Section 10.4.4, contraceptive and barrier guidance. |
| Non-Substantial Modification(s) | | |
| Updated key studies and referenced the IB for details on other studies in the program | Reflects updates to studies included in the recent IB | Section 2.2 Background. |
| Updated first in human studies and update other clinical studies with recent clinical data. References to the | Reflects changes in the IB | Section 2.3.1 Risk assessment. |

| Description of Change | Brief Rationale | Section # and Name |
|--|---|---|
| IB when applicable | | |
| Added “Sensitivity analysis will be performed to evaluate the impact of COVID if deemed necessary.” | Clarify the possible sensitivity analysis due to the impact of COVID-19 if necessary. | Section 9.3.1 General considerations. |
| Update to be consistent with latest template mandatory language. | Template update. | Sections 10.1.3, 10.1.4, 10.1.6, 10.1.7, 10.1.9 appendices. |

Editorial and formatting changes and clarifications were made throughout the document.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: MAGNETISMM-8, A Phase 1b/2 Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Elranatamab (PF-06863135) in Chinese Participants With Multiple Myeloma Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb (Triple-Class Refractory MM)

Rationale

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

The study will include 2 parts. Phase 1b part is dose confirmation/safety lead-in to establish the safety of elranatamab, 76 mg (C1D8) SC QW with a 2 step-up priming dose regimen of 12 mg (C1D1) and 32 mg (C1D4) SC, in order to confirm the RP2D in Chinese participants. After the RP2D is confirmed to be tolerable, the Phase 2 part will be initiated to evaluate the efficacy in Chinese participants. Participants who started from the RP2D in the Phase 1b part will contribute to the efficacy evaluation together with other participants in Phase 2.

Objectives, Endpoints, and Estimands

| Objectives | Endpoints |
|---|--|
| Primary: | Primary: |
| Phase 1b: <ul style="list-style-type: none"> To establish the safety profile of elranatamab in order to confirm the RP2D in Chinese participants Phase 2: <ul style="list-style-type: none"> To determine the efficacy of elranatamab in Chinese participants with RRMM | Phase 1b: <ul style="list-style-type: none"> DLTs observed in Cycle 1 (4 weeks) Phase 2: <ul style="list-style-type: none"> ORR by BICR per IMWG |
| Secondary: | Secondary: |
| <ul style="list-style-type: none"> To further evaluate the efficacy of elranatamab in Chinese participants with RRMM | <ul style="list-style-type: none"> DOR by BICR and investigator per IMWG CRR by BICR and investigator per IMWG ORR by investigator per IMWG DOCR by BICR and investigator per IMWG PFS by BICR and investigator per IMWG OS TTR by BICR and investigator per IMWG MRD negativity rate (central lab) per IMWG |
| <ul style="list-style-type: none"> To determine the safety and tolerability of elranatamab | <ul style="list-style-type: none"> AEs and laboratory abnormalities by type, frequency, severity (as graded by NCI CTCAE v5.0), timing, seriousness, and relationship to study therapy Severity of CRS and ICANS assessed according to ASTCT criteria¹ |

| Objectives | Endpoints |
|--|---|
| <ul style="list-style-type: none"> To evaluate the PK of elranatamab | <ul style="list-style-type: none"> PK parameters of elranatamab: C_{max}, T_{max}, and AUC_{last} Pre- and post-dose concentrations of elranatamab |
| <ul style="list-style-type: none"> To evaluate the immunogenicity of elranatamab | <ul style="list-style-type: none"> ADAs and NAbs against elranatamab |
| <ul style="list-style-type: none"> To assess the impact of elranatamab on patient-reported symptoms and functioning | <ul style="list-style-type: none"> EORTC QLQ-C30 and MY20 EORTC QLQ CIPN20 EQ-5D |
| Exploratory: | Exploratory: |
| <ul style="list-style-type: none"> To explore correlations between elranatamab exposure and efficacy, safety and PD/biomarker endpoints | <ul style="list-style-type: none"> Selected PK, efficacy, safety and PD/biomarker endpoints |
| <ul style="list-style-type: none"> To explore the relationship between elranatamab and the biology of the participant's MM | <ul style="list-style-type: none"> Measurements of biomarkers (DNA, RNA, plasma sBCMA level, protein or defined cell types) resulting from analyses of peripheral blood, and/or BM biospecimens |

Estimands

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

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention in Phase 1b part and either experience DLT(s) during the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who receive less than the minimum requirement of the planned doses of study intervention for reason other than treatment-related toxicity are not evaluable for DLTs. The minimum required exposure for DLT evaluability is 4 out of 5 planned doses of elranatamab during the DLT observation period.
- Variable: Occurrence of DLTs. DLTs are defined in Section 4.3.1.
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants.

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

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

- Variable: Objective response defined as confirmed sCR, CR, VGPR and PR according to the IMWG criteria based on BICR assessment, from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first.
- Intercurrent event(s): All data collected after an intercurrent event of subsequent anticancer therapy will be excluded except if required to confirm PD. All response assessments regardless of gaps in disease assessments will be considered. Data will be collected regardless of discontinuation from treatment. Participants who do not have a post-baseline disease assessment due to early confirmed PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience confirmed PD or stop disease assessments for any reason prior to achieving an objective response will be counted as nonresponders in the assessment of objective response.
- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an objective response and 2-sided 90% CI for ORR.

Overall Design

Study C1071008 is a Phase 1b/2, open-label study to evaluate the safety, PK, PD and the efficacy of elranatamab (PF-06863135) in Chinese participants with MM who are refractory to at least 1 PI, 1 IMiD and 1 Anti-CD38 mAb (Triple-Class Refractory MM).

The Study will include 2 parts. Phase 1b part is dose confirmation/safety lead-in to establish the safety profile in order to confirm the RP2D in Chinese participants. After the RP2D is confirmed to be tolerable, the Phase 2 part will be initiated to evaluate the efficacy in Chinese participants. Participants who started from the RP2D in Phase 1b part will contribute to the efficacy evaluation together with other participants in Phase 2. The primary objective for Phase 2 is to determine efficacy of elranatamab with respect to ORR as assessed by BICR based on IMWG criteria.

Number of Participants

A target sample size of approximate 36 participants will be enrolled and treated with study intervention, including a target of 6 participants in Phase 1b and a target of 30 participants in Phase 2.

Note: "Enrolled" means a participant's, agreement to participate in a clinical study following completion of the informed consent process. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population and Specific Inclusion/Exclusion Criteria

Chinese participants with MM who are refractory to at least 1 PI, 1 IMiD and 1 Anti-CD38 mAb (Triple-Class Refractory MM).

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Participants age ≥ 18 years.
2. Prior diagnosis of MM as defined according to IMWG criteria.²
3. Measurable disease based on IMWG criteria as defined by at least 1 of the following:
 - a. Serum M-protein ≥ 0.5 g/dL by SPEP
 - b. Urinary M-protein excretion ≥ 200 mg/24 hours by UPEP
 - c. Serum immunoglobulin FLC ≥ 10 mg/dL (≥ 100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (< 0.26 or > 1.65)
4. Refractory to at least 1 IMiD.
5. Refractory to at least 1 PI.
6. Refractory to at least 1 anti-CD38 antibody.
7. Relapsed or refractory to last anti-MM regimen.
8. ECOG performance status ≤ 2 .
9. LVEF $\geq 40\%$ as determined by a MUGA scan or ECHO.
10. Adequate hepatic function characterized by the following:
 - a. Total bilirubin $\leq 2 \times \text{ULN}$ ($\leq 3 \times \text{ULN}$ if documented Gilbert's syndrome);
 - b. AST $\leq 2.5 \times \text{ULN}$; and
 - c. ALT $\leq 2.5 \times \text{ULN}$
11. Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min (according to the Cockcroft Gault formula, by 24-hour urine collection for creatinine clearance, or according to local institutional standard method).

12. Adequate BM function characterized by the following:

- a. ANC $\geq 1.0 \times 10^9/L$ (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing);
- b. Platelets $\geq 25 \times 10^9/L$ (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and
- c. Hemoglobin ≥ 8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing).

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

- 13. Smoldering MM defined according to IMWG criteria.
- 14. Active plasma cell leukemia.
- 15. Amyloidosis.
- 16. POEMS syndrome.
- 17. Stem cell transplant within 12 weeks prior to enrollment or active GVHD.
- 18. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:
 - a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting), symptomatic pericardial effusion;
 - b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia, runs of ventricular tachycardia);
 - c. Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);
 - d. Prolonged QT syndrome (or triplicate average QTcF >470 msec at screening).
- 19. Any active, uncontrolled bacterial, fungal, or viral infection, eg, HBV, HCV, SARS-CoV2, HIV, etc. Active infections must be resolved at least 14 days prior to enrollment.

20. Ongoing Grade ≥ 2 peripheral sensory or motor neuropathy. History of GBS or GBS variants, or history of any Grade ≥ 3 peripheral motor polyneuropathy.
21. Previous treatment with an anti-BCMA directed therapy (eg, BCMA-directed ADC, BCMA-directed CAR T-cell therapy or bispecific antibody, either approved or investigational).

Intervention Groups and Duration

Participants will receive SC administration of elranatamab QW. The initial dose of elranatamab for both Phase 1b and Phase 2 will be 12 mg (C1D1) and 32 mg (C1D4) and will serve as the 2 step-up priming regimen. The dose of elranatamab should be increased to 76 mg on C1D8 as long as the participant meets the retreatment criteria listed in Section 6.5.1. If a participant does not meet these criteria on C1D8, initiation of dosing with 76 mg should be deferred until the criteria are met.

Six triple-class refractory MM participants will be enrolled to assess the DLT rate of elranatamab in Chinese participants as a safety lead-in prior to the initiation of Phase 2. The DLT observation period will be Cycle 1 (4 weeks). If the DLT rate is less than 1/3 (ie, 0 or 1 participant out of 6), Phase 2 part will be initiated at the confirmed monotherapy RP2D after the DLT observation period is concluded for all enrolled participants in the Phase 1b portion. If the DLT rate at the monotherapy RP2D meets or exceeds 1/3, the enrollment will stop for further evaluation of the available data by the sponsor and investigators, and following decision will be reflected in a protocol amendment.

If a participant has received QW elranatamab for at least 6 cycles and achieved an IMWG response category of PR or better with responses persisting for at least 2 months, the dose interval will be changed from QW to Q2W (eg, beginning C7D1) as lower dosing intensity might be adequate to maintain the response given the reduced disease burden in these participants. 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).

Each participant will receive study intervention until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

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

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

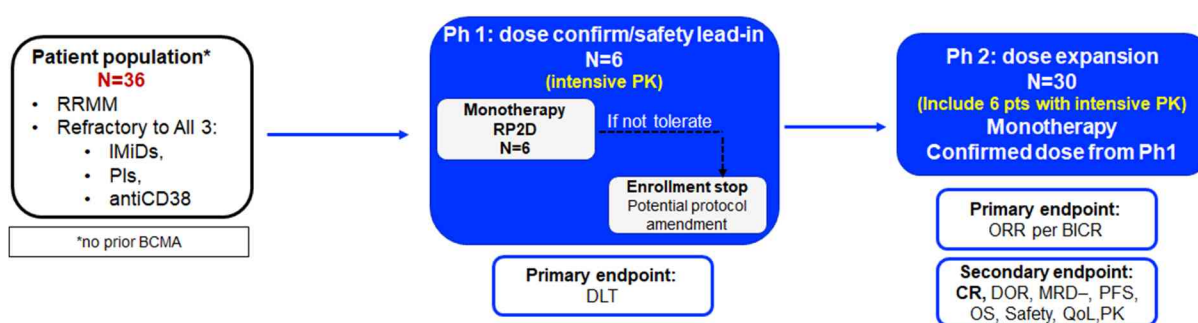
The Phase 2 part will test the null hypothesis (H_0) that the ORR by BICR as defined by IMWG is $\leq 30\%$ versus the alternative hypothesis (H_a) that the ORR by BICR as defined by IMWG is $> 30\%$ using a single-stage design based on the exact binomial distribution. The null hypothesis ORR is based on the results of the DREAMM-2 study³ and the STORM study,⁴ which were conducted in similar multiple myeloma populations with respect to prior treatments. A total of at least 36 participants will contribute to the hypothesis testing, which includes the participants enrolled and treated in Phase 2 and those participants who start from the confirmed RP2D in Phase 1b. The sample size will provide 80% power to reject the null hypothesis at a 1-sided significance level of 0.05 assuming the true ORR is $\geq 51\%$.

Based on the design, at the analysis, an observed ORR $\geq 44.4\%$ (ie, 16 responders out of the 36 patients) will be needed to reject the null hypothesis, and the cohort has demonstrated that the true ORR exceeds 30%. At the time of the analysis, the testing rule will depend on the exact number of participants enrolled and treated. The Clopper-Pearson 90% CI will also be provided for the ORR.

The analysis will be conducted once all participants have been followed for response for at least 6 months or have otherwise discontinued response assessments within the first 6 months of treatment.

All other analyses will be descriptive. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages. The time-to-event variable will be summarized using Kaplan-Meier methods and displayed graphically if applicable. The median, percentile and probabilities at particular time points will be estimated.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the [STUDY ASSESSMENTS AND PROCEDURES](#) section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. SCHEDULE OF ACTIVITIES A (Phase 1b and Phase 2)

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|---|----------------------|---|-----------------|---|----------------|----------------|--------------------------------|---|---------------|--|
| Visit Window | Day -28 to Day -1 | Day 1 Cycles 2 and later ± 3D | Day 4 -1/+3D | Day 8 Cycle 1 -1/+3D Cycles 2 and later ± 3D | Day 15 ± 3D | Day 22 ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | Day 4 visit is Cycle 1 only |
| Informed consent | X | | | | | | | | | See Section 10.1.3 |
| Eligibility criteria | X | | | | | | | | | See Section 5.1 and Section 5.2 |
| Register with IRT | X | | | | | | | | | See Section 6.3.1 |
| Demography/medical history | X | | | | | | | | | See Section 8.2.1 |
| Disease characteristics/ treatment history | X | | | | | | | | | See Section 8.1.5 |
| PROs | X | X | | | Cycle 1-3 | | X | X | | During the treatment period, PROs are administered at Days 1 and 15 for Cycles 1-3 only, then at Day 1 for every cycle from Cycle 4 to Cycle 12, then every 3 cycles beginning with Cycle 15. See Section 8.1.4 |
| Clinical Procedures/Assessments – Note: During the treatment period, all assessments must done within 72 hours prior to dosing | | | | | | | | | | |
| Physical exam | X | X | | | | | X | X | | See Section 8.2.2 |
| Neurologic exam | X | X | Cycle 1 | Cycles 1-3 | Cycles 1-6 | Cycles 1-3 | X | X | | See Section 8.2.2 |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|---|----------------------|---|---------|--|---------|---------|--------------------------------|---|---------------|---|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | Day 4 visit is Cycle 1 only |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| ICE score | | Cycle 1 | | | | | | | | See Section 8.2.2 |
| Height/weight | X | | | | | | | | | See Section 8.2.2 |
| Vital signs (temperature, HR, BP and O ₂ saturation) | X | X | Cycle 1 | Cycle 1 | Cycle 1 | Cycle 1 | X | X | | Pre-dose vital signs collected on C1D1, C1D4, C1D8, C1D15 and C1D22 should be reported on the CRF. Monitored at least every 4 hours (± 15 minutes) during the first 48 hours after first dose of study intervention (C1D1) and during first 24 hours after second dose (C1D4). See Section 8.2.3 |
| ECOG PS | X | | | | | | | | | See Section 8.2.8 |
| Triplicate 12-Lead ECG | X | Cycles 1, 2, 4 | | Cycle 1 | | | X | | | When PK sample collection coincides with ECG, perform every ECG prior to pre-dose PK sample collection and prior to elranatamab administration (and premedication). ECG assessments should be skipped if CRS symptoms are ongoing. Additional ECGs should be performed as clinically indicated. See Section 8.2.4 |
| ECHO/MUGA | X | | | | | | | | | See Section 8.2.5 |
| Elranatamab (PF-06863135) administration | | X | Cycle 1 | X | X | X | | | | Two step-up priming doses of 12 mg on C1D1 then 32 mg on C1D4, followed by 76 mg starting on C1D8 QW. |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|------------------|----------------------|---|--------|--|--------|--------|--------------------------------|---|---------------|---|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | <i>Day 4 visit is Cycle 1 only</i> |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| | | | | | | | | | | <p>Minimum of 2 days should be maintained between the C1D1 and C1D4 doses, minimum of 3 days between C1D4 dose and the first full dose (C1D8); a minimum of 6 days should be maintained between doses thereafter.</p> <p>If participant has received QW dosing for at least 6 cycles and has achieved a PR or better persisting for ≥2 months, the dose interval will be changed from QW to Q2W (eg, beginning C7D1). 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. See Section 6.1</p> <p>The windows for the different administration schedules are ± 3 days for the QW schedule and -3 /+7 days for Q2W. See Section 6 (including Section 6.5 dose modifications)</p> |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|--|----------------------|---|---------|--|--------|--------|--------------------------------|---|---------------|---|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | <i>Day 4 visit is Cycle 1 only</i> |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| Premedication for CRS | | Cycle 1 | Cycle 1 | Cycle 1 | | | | | | Must be administered 60 minutes (± 15 minutes) prior to elranatamab dose. See Section 6.8.1 |
| Hospitalization | | Cycle 1 | Cycle 1 | | | | | | | Hospitalization required for at least 2 days (~48 hours) for C1D1 and 1 day (~24 hours) for C1D4. Hospitalization from C1D1 to C1D5 may be considered. See Section 6.1. |
| AE monitoring | Assess Continuously | | | | | | | | | See Section 8.3 |
| Concomitant therapy | Assess Continuously | | | | | | | | | See Section 6.8 |
| Subsequent anti-cancer therapies/date of progression | | | | | | | Assess continuously | | | See Section 7.1 |
| Survival status | | | | | | | | X | X | See Section 7.1 May be collected by telephone. |
| Disease response assessment (per IMWG criteria) | | Cycles 2, 3, 4, etc | | | | | X | | | To be conducted on a 28-day (±1 wk) interval whether dose given or not (ie, the 28-day [±1wk] interval between assessments should be maintained regardless of dose delays/interruptions). For participants who discontinue study intervention without PD: perform at EOT visit, then at least Q4W (±1 wk) until PD, withdrawal of consent, initiation of subsequent anticancer therapy, participant lost to follow up. |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|--|----------------------|---|--------|--|--------|--------|--------------------------------|---|---------------|---|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | <i>Day 4 visit is Cycle 1 only</i> |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| | | | | | | | | | | death or defined end of study. See Section 8.1 for complete details (including requirements for repeat testing for confirmation of PD). |
| SPEP, SIFE, serum FLC | X | X | | | | | X* | X* | X* | Screening and C1D1 (if not done within 72 hours prior to dosing). Then, to be conducted on a 28-day (±1 wk) interval whether dose given or not (ie, the 28-day [±1wk] interval between assessments should be maintained regardless of dose delays/interruptions). *For participants who discontinue study intervention without PD: perform at EOT visit, then at least Q4W (±1 wk) until PD, withdrawal of consent/assent, initiation of subsequent anti-cancer therapy, participant lost to follow up-, death or defined end of study. See Section 8.1.1 for complete details (including requirements for repeat testing for confirmation of PD). |
| UPEP, UIFE (24-hour urine collection required) | X | X | | | | | X* | X* | X* | Screening and C1D1 (if not done within 72 hours prior to dosing). Then, to be conducted on a 28-day (±1 |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|--------------------------------|----------------------|--|--------|--|--------|--------|--------------------------------|---|---------------|--|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | <i>Day 4 visit is Cycle 1 only</i> |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| | | | | | | | | | | <p>wk) interval whether dose given or not (ie, the 28-day [±1wk] interval between assessments should be maintained regardless of dose delays/interruptions).</p> <p>*For participants who discontinue study intervention without PD: perform at EOT visit, then Q4W (±1 wk) until PD, withdrawal of consent, initiation of subsequent anti-cancer therapy, participant lost to follow-up, death or defined end of study. For participants without measurable disease in the urine at baseline, UPEP/UIFE is required (minimum) at suspected VGPR or CR/sCR, or at suspected PD. See Section 8.1.1 for complete details (including requirements for repeat testing for confirmation of PD).</p> |
| Imaging (PET/CT, CT or MRI) | X | Time points for disease assessments described in notes | | | | | | | | At screening, at suspected CR/sCR (if not performed within the prior 6 weeks), at suspected PD from EMD, and annually if not done within past 12 months. In addition, for participants with EMD at screening, every 12 wks (± 1 |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|------------------|----------------------|---|--|--|--------|--------|--------------------------------|---|---------------|---|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | <i>Day 4 visit is Cycle 1 only</i> |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| | | | | | | | | | | wk) and also at suspected MR, PR or VGPR. Once all EMD has resolved/disappeared, imaging can be conducted every 24 weeks (or earlier if clinically indicated) and at suspected PD. For participants with only skin involvement, skin lesions should be measured with a ruler every 4 wks (± 1 wk). Perform until PD, WOC, initiation of subsequent anticancer therapy, participant lost to FU, death, or defined EOS. See Section 8.1.3 |
| BMA/BMB | X | | Time points for disease assessments described in notes | | | | | | | At screening, suspected CR and then after 6 months, 12 months, and yearly (± 1 month) after achieving CR (provided CR is maintained clinically) until WOC, initiation of subsequent anticancer therapy, participant lost to FU, death, or defined EOS. Optional (investigator discretion) at suspected PD. If all criteria for CR are met except percent plasma cells in BM, then additional BMA should be performed every 3 months until CR is achieved, |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|---|----------------------|---|---------|--|--------|---------|--------------------------------|---|---------------|--|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | <i>Day 4 visit is Cycle 1 only</i> |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| | | | | | | | | | | as long as other CR criteria are maintained. BMB can be used in place of BMA; however, the same method for quantifying plasma cells should be used throughout the study where feasible. BMA is required for central lab MRD analysis. BMB can be used in place of BMA to assess sCR. See Section 8.1.2 |
| BMA for cytogenetics (FISH/karyotyping) | X | | | | | | | | | See Section 8.1.2 |
| Contraception check | X | X | | | | | X | X | | Only required for WOCBP through 5 months post last dose of study intervention. See Section 5.3.1 |
| Pregnancy test (β-hCG) | X | X | | | | | X | X | | Only required in WOCBP. Also to be done whenever 1 menstrual cycle is missed during the active treatment period and up to 90 days post last dose of study intervention (or when potential pregnancy is otherwise suspected). See Section 8.2.7 and Appendix 2 Table 9 |
| Hematology/chemistry | X | X | Cycle 1 | Cycle 1 | | Cycle 1 | X | X | | See Section 8.2.6 and Appendix 2 Table 9. For Cycle 1 Day 4, hematology only. |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|--|----------------------|---|---|--|--------|--------|--------------------------------|---|---------------|---|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | Day 4 visit is Cycle 1 only |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| Serum quantitative immunoglobulins (IgG, IgM, IgA, IgD, IgE)* | X | X | | | | | X | X | | *IgD or IgE, if they are available at the site, only if the heavy chain component of the disease is known to be IgE or IgD. See Section 8.2.6 and Appendix 2 Table 9 . |
| PT/INR | X | | | | | | | | | See Section 8.2.6 and Appendix 2 Table 9 . |
| Blood β-2 microglobulin | X | X | | | | | X | | | Additional samples may be taken per local practice. |
| Virus test (HBV/HCV/HIV/SARS-CoV2) | X | | | | | | | | | Active HBV, HCV, SARS-CoV2, HIV infection should be excluded from study. |
| CMV testing (quantitative PCR) | | X* | | | | | | | | *Every 1 to 3 months depending on risk factors. Section 8.2.6, Appendix 2 Table 9 and Appendix 12 . |
| Cytokine Assessment | | X (See Notes) | | | | | | | | If CRS is suspected and/or site require cytokine information for participant management, an ad-hoc cytokine sample will be collected and all samples will be analyzed per local site practice. See Section 8.7.4 and Appendix 2 Table 9 |
| Genetics and Biomarker Assessments (Central Laboratory) | | | | | | | | | | |
| BMA for MRD | X | | Samples to be collected each time there is a BMA assessment | | | | | | | See Section 8.7.1 |
| BMA for molecular profiling | X | | Samples to be collected each time there is a BMA assessment | | | | | | | See Section 8.7.2 |
| BMB for BCMA levels and/or immune cell biomarkers | X | | Samples to be collected each time there is a BMB assessment | | | | | | | Collection of this sample is optional; however, if a participant has a BMB |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|---|----------------------|---|---------|--|----------|---------|--------------------------------|---|---------------|--|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | Day 4 visit is Cycle 1 only |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| | | | | | | | | | | collected for disease assessment, collection of this sample for biomarker analysis is encouraged. See Section 8.7.3 |
| Blood sample for sBCMA levels | X | Cycles 1,2, 3, 7, 10, 13, etc. | Cycle 1 | Cycle 1 | Cycles 1 | | X | | | Pre-dose, 6 and 24 h post-dose on C1D1. Pre-dose and 24 h post-dose on C1D4. Pre-dose, 6 h post-dose on C1D8. Collect pre-dose only at C1D15, C2D1, C3D1, then Day 1 of every third cycle starting Cycle 7 (ie, C7D1, C10D1, C13D1, etc). Additional sample to be collected at EOT and time of PD. See Section 8.5.1 |
| Blood sample for circulating proteins and metabolite analysis | | Cycle 1 | Cycle 1 | Cycle 1 | Cycle 1 | Cycle 1 | | | | Collect pre-dose and 24 h post-dose on C1D1; Collect pre-dose and 24 h post-dose on C1D4. Collect pre-dose at all other time. If CRS is suspected, additional blood samples should also be collected for cytokine analysis if not already scheduled. See Section 8.7.5 |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|--|----------------------|---|-----------------|---|----------------|----------------|--------------------------------|---|---------------|--|
| Visit Window | Day -28 to Day -1 | Day 1 Cycles 2 and later ± 3D | Day 4 -1/+3D | Day 8 Cycle 1 -1/+3D Cycles 2 and later ± 3D | Day 15 ± 3D | Day 22 ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | Day 4 visit is Cycle 1 only |
| Blood sample for TCR sequencing | X | Cycles 1, 2, 3 | | | Cycle 1 | | | | | Collect pre-dose. See Section 8.7.6 |
| Blood or saliva sample for germline comparator | | Cycle 1 | | | | | | | | Collect pre-dose. See Section 8.7.7 |
| Pharmacokinetics and Immunogenicity Assessments | | | | | | | | | | |
| Blood sample for PK | | Cycles 1-4, 7, 10, etc. | Cycle 1 | Cycle 1 | Cycle 1 | Cycle 1 | X | | | Pre-dose, 6, and 24 h post-dose on C1D1; Pre-dose and 24 h post-dose on C1D4. Pre-dose, 6 h post-dose on C1D8; pre-dose only on C1D15, C1D22, C2D1, C3D1, then every 3 rd cycle starting Cycle 4 (ie, C4D1, C7D1, C10D1, etc). If the C1D4 dose (32 mg) cannot be administered within the protocol-defined window, the planned C1D4 pre-dose PK/PD sample should be collected at any time within the C1D4 visit window, If CRS is suspected, additional PK samples should be collected if not already scheduled. See Section 8.4 |
| Blood sample for ADAs and NABs | | Cycles 1-4, 7, 10, etc | | | | | X | | | Pre-dose on C1D1, C2D1, and C3D1 and every 3 rd cycle starting C4 (ie, C4D1, C7D1, C10D1, etc). If AE possibly related to ADA occurs, additional samples for ADA |

| Visit Identifier | Screening | Treatment Period (Each 28 Day Cycle) | | | | | EOT Visit | FU Visit | LTFU | Notes/Protocol Section |
|------------------|----------------------|---|--------|--|--------|--------|--------------------------------|---|---------------|--|
| | | Day 1 | Day 4 | Day 8 | Day 15 | Day 22 | | | | <i>Day 4 visit is Cycle 1 only</i> |
| Visit Window | Day -28 to Day -1 | Cycles 2 and later ± 3D | -1/+3D | Cycle 1 -1/+3D Cycles 2 and later ± 3D | ± 3D | ± 3D | ≤14D post- final dose | 28 to 35 days post- final dose | Q12W ± 14D | |
| | | | | | | | | | | and PK should be collected if not scheduled. See Section 8.8 |

Note: Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within 28 days prior to study intervention administration.

1.3.2. SCHEDULE OF ACTIVITIES B (Intensive PK/PD/Biomarker for all Phase 1b Participants and 6 Participants from Phase 2)*

PK, PD, and Biomarker Flowchart

| Visit Identifier | Up to 7 days prior to C1D1 | Treatment Period (Each 28 Day Cycle) | | | | | | | | | | | | | EOT |
|--|----------------------------|---|---------|--------|--------|-----------------|-----------------|------------|---------|------------|------------|------------|------------|--|-----|
| | | Cycle 1 | | | | | | | | | | Cycle 2 | Cycle 3 | Cycle 4 (Every 3 rd cycle) | |
| Study Day | | D1 | | D2 | D3 | D4 ⁴ | D5 ⁴ | D8 | | D15 | D22 | D1 | D1 | D1 | |
| Hours Pre/after dosing | | 0 | 6 | 24 | 48 | 0 | 24 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | |
| Collection of time window | | -1 to 0 hr | ±0.5 hr | ±3 hrs | ±3 hrs | -1 to 0 hr | ±3 hrs | -1 to 0 hr | ±0.5 hr | -1 to 0 hr | -1 to 0 hr | -1 to 0 hr | -1 to 0 hr | -1 to 0 hr | |
| Visit window | | 0 | 0 | 0 | 0 | 0 | 0 | -1/+3D | -1/+3D | ± 3D | ± 3D | ± 3D | ±3 D | ±3 D | |
| PK blood sampling for elranatamab ¹ | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cytokine evaluation in serum ² | X | X | X | X | X | X | X | X | X | X | X | X | X | 9 months (±14 days) after C1D1 | |
| Soluble BCMA ³ | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

*For schedules not listed in this flowchart, please follow [SoA A](#).

- Blood sample for elranatamab blood level:** Approximately 5 mL sample of whole blood (to provide approximately 2 mL of serum) will be collected at each time point for PK analysis of elranatamab. From Cycle 4, pre-dose PK samples will be collected only on every 3rd cycle (Cycle 4, Cycle 7, Cycle 10, etc). An additional PK sample should also be taken if CRS is suspected, and a PK sample is not already scheduled to be taken (eg, Cycle 4 onwards). All 0 hour samples will be collected prior to study intervention administration on days whereby study intervention is to be administered.
- Cytokine evaluation in serum:** See Cytokine Assessments Section [8.7.4](#) and [Appendix 2 Table 9](#) for Routine and Ad hoc Central Lab Cytokine Analysis. All samples will be analyzed centrally. All 0 hour samples will be collected prior to study intervention administration on days whereby study intervention is to be administered.
- Soluble BCMA:** A whole blood sample to provide plasma will be collected at each time point for analysis of soluble BCMA. All 0 hour samples will be collected prior to study intervention administration on days whereby study intervention is to be administered. From Cycle 4, pre-dose soluble BCMA samples will be collected only on every 3rd cycle (Cycle 4, Cycle 7, Cycle 10, etc). An additional soluble BCMA/other factor sample should also be taken if CRS is suspected, and a sample is not already scheduled to be taken (eg, Cycle 4 onwards).

| Visit Identifier | Up to 7 days prior to C1D1 | Treatment Period (Each 28 Day Cycle) | EOT |
|------------------|----------------------------|--------------------------------------|-----|
|------------------|----------------------------|--------------------------------------|-----|

4. **D4 and D5:** If the C1D4 dose (32 mg) cannot be administered within the protocol-defined window, the planned C1D4 pre-dose PK/PD sample should be collected at any time within the C1D4 visit window, the planned C1D5 24h post dose PK/PD sample shall not be collected but defer to the actual C1D4 dose for collection

2. INTRODUCTION

Elranatamab (PF-06863135), a novel BsAb that targets both BCMA on MM cells and CD3 on T-cells, is currently being developed for the treatment of RRMM.

2.1. Study Rationale

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

The study will include 2 parts. Phase 1b part is dose confirmation/safety lead-in to establish the safety of elranatamab, 76 mg (C1D8) SC QW with a 2 step-up priming dose regimen of 12 mg (C1D1) and 32 mg (C1D4) SC, in order to confirm the RP2D in Chinese participants. After the RP2D is confirmed to be tolerable, the Phase 2 part will be initiated to evaluate the efficacy in Chinese participants. Participants who started from the RP2D in Phase 1b part will contribute to the efficacy evaluation together with other participants in Phase 2.

2.2. Background

2.2.1. Multiple Myeloma

MM is a hematological B-cell malignancy characterized by dysregulated proliferation of BM plasma cells. Globally, there are approximately 160,000 new cases and 106,000 deaths per year attributed to MM.⁵ The American Cancer Society estimates that for the US in 2020, approximately 32,270 new MM cases will be diagnosed and approximately 12,830 MM-related deaths will occur.⁶ The incidence of MM in China increased significantly from 2006 to 2016. It was estimated that there were 16,500 new cases and 10,300 deaths of MM in China in 2016. The age-standardized incidence rates and mortality rates per 100,000 population were 1.03 (95% UI, 0.88-1.17) and 0.67 (95% UI, 0.59-0.77) in 2016.⁷

Despite recent advances in treatment, MM remains an incurable disease and almost all patients, even those who initially respond to treatment, are expected to relapse. Even for patients who receive ASCT, the median time to relapse is only 17.2 months.⁸ Similarly, for patients who are treated with novel PI-based or IMiD-based combination regimens as frontline treatment, the median time to relapse is 16.4 months.⁹

Moreover, MM patients typically cycle through many lines of treatment, having become relapsed/refractory to various therapeutic approaches. Trials that have treated patients with BCMA-directed therapy in the RRMM population have included heavily pretreated patients; for example, 57% of patients studied by Trudel et al had received ≥ 5 lines of therapy¹⁰ and other trials have included populations receiving a median of 6 (range 3-18) prior therapies¹¹ and a median of 5 (range 3 to 18) prior therapies.¹²

Outcomes in the RRMM population are quite poor; for example, patients with RRMM who respond poorly to PI-based or IMiD-based regimens show a median OS of only 1.5 years.¹³ Newer and more effective therapies have substantially increased patient benefit; however, in this real-world setting (N=3449), the most recent 4-year survival is only 75%.¹⁴ Results from 2 trials in patient populations similar to the current protocol are summarized in [Table 1](#). The

lack of effective and durable therapeutic options highlights the unmet medical need in the RRMM patient population.

Table 1. Efficacy Results from Trials in Similar Patient Population

| Therapy | Prior therapy (eligibility) | Median number of prior therapies | ORR | DOR (months) | Reference |
|---------------------------|-----------------------------|----------------------------------|---|------------------------------------|-----------------------------------|
| Belantamab mafodotin | IMiD, PI, anti-CD38 | 7 | 31% ^a 97.5% CI (20.8, 42.6) | 6.3 ^a IQR (3.7, 7.7) | (Lonial et al, 2020) ³ |
| | | | 34% ^b 97.5% CI (23.9, 46.0) | 6.9 ^b IQR (4.8, 7.9) | |
| Selinexor + Dexamethasone | IMiD, PI, anti-CD38 | 7 | 26% 95% CI (19, 35) | 4.4 95% CI (3.7, 10.8) | (Chari et al, 2019) ⁴ |

a. Data from 2.5 mg/kg Q3W (the approved dosing regimen for belantamab mafodotin) cohort

b. Data from 3.4 mg/kg Q3W cohort

NOTE: For both studies, ORR and DOR were assessed by an independent review committee.

In China, there is no significant difference in disease biology, disease management and clinical practice between China and US/EU. China clinical practice is consistent with global treatment guidance. In China, NMPA-approved treatments for MM include bortezomib, ixazomib, thalidomide, lenalidomide, melphalan, daratumumab and classic chemotherapy. In addition, China generic pomalidomide was just approved in China in 2020. However, classic/conventional regimens across different treatment lines are used for most patients due to currently limited treatment options for RRMM participants. The outcomes of conventional treatment regimens used for first-line, second-line treatments and beyond in RRMM patients are still quite poor. Use of Ixazomib combinations in Chinese RRMM patients is associated with a median PFS of 6.7 months.¹⁵ MM remains a fatal disease in the majority of cases. Improved treatments through the development of new therapeutic strategies with this evolving armamentarium and new drugs are still needed.

Reported SCT rate was 14.4% in a large real-world study of 940 Chinese NDMM patients.¹⁶ The possible reasons for the low SCT rates in China include fears for transplant, financial concerns (many fees for SCT, including melphalan, are not covered by health insurance), limited drug accessibility (melphalan just commercially entered China in 2019), and shortage of qualified medical service (only large reference centers or specialized centers have the ability to perform SCT).¹⁷

In addition, severe side effects, such as peripheral neuropathy and myelotoxicity of currently available drugs remain of concern. For example, the proteasome inhibitor bortezomib has become one of the backbone agents in the frontline treatment for MM; however, the non-oral administration and concerns in side effects including peripheral neuropathy hampered its long-term use in the real-world setting, with a median duration of treatment of only 6 months for bortezomib-based frontline therapy in China.¹⁷

Overall, there are high unmet medical needs for patients with MM in China.

2.2.2. BCMA and CD3

BCMA is a transmembrane glycoprotein belonging to the TNFr SF 17 superfamily. BCMA is normally expressed exclusively in lymphocytes of the B-cell lineage, including plasmablasts and differentiated plasma cells, where it is involved in the regulation of B-cell maturation. BCMA is widely expressed on malignant plasma cells collected from patients with MM whereas BCMA is detected in a very small proportion of normal BM mononuclear cells from healthy volunteers.¹⁸ Cleavage of cell surface BCMA by γ -secretase releases sBCMA¹⁹ which can act as a decoy for BCMA-directed antibodies. Inhibition of γ -secretase can reduce levels of sBCMA and increase activity of BCMA-directed therapies.²⁰ sBCMA levels in serum are elevated in patients with MM and correlate with the proportion of MM cells in the BM microenvironment. sBCMA levels are independent of renal function, which permits its use as a biomarker in patients with renal insufficiency, and BCMA is detectable in the serum of patients with non-secretory disease.²¹ Moreover, patients in 2 studies with high baseline levels of sBCMA appeared to have poorer clinical outcomes.^{18,21}

T-cells are potent immune cells capable of mediating adaptive immunity through the expression of antigen receptor complexes (TCR), which comprise an antigen-specific alpha-beta heterodimer and a transmembrane CD3 protein and mediate receptor signaling and T-cell activation.²² TCRs recognize specific protein fragments (ie, peptides) presented by MHC proteins on APCs, virally infected cells, and tumor cells. Triggering of CD3 signaling in a CD8+ T-cell synapsed with another cell presenting a target antigen can cause the T-cell to release perforin and granzyme B, resulting in cancer cell lysis and death. Cancer cells can avoid T-cell recognition and destruction by down-modulating peptide/MHC presentation. One way to remove dependence on peptide/MHC presentation is through direct bridging of a cell-surface antigen on a target cell with the extracellular CD3 on T-cells, leading to T-cell signaling equivalent to that generated by MHC/TCR-based engagement.

2.2.3. Elranatamab (PF-06863135)

Elranatamab is a heterodimeric humanized full-length bispecific IgG2 kappa mAb against BCMA and CD3. Targeted T-cell-mediated cytotoxicity follows the binding of 1 epitope of elranatamab to CD3-expressing T-cells and a second epitope to BCMA-expressing MM cells.

2.2.3.1. Nonclinical Studies of Elranatamab

In vitro, elranatamab has been shown to induce cytokine release by human T-cells and to redirect patient T-cells to lyse tumor cells from MM patients in a concentration-dependent manner. Elranatamab also showed robust anti-tumor activity in vivo following a single dose in 3 different orthotopic human MM models established in immunodeficient mice engrafted with human T-cells, and greater potency was correlated with higher BCMA expression levels. In another orthotopic tumor model with low BCMA expression levels, a second dosing of elranatamab was found to delay tumor progression. As part of a secondary pharmacology assessment, elranatamab induced cytokine release in human whole blood, which was expected due to the presence of BCMA-expressing target cells, confirming the mechanism of action. Finally, two 1-month GLP toxicology studies in cynomolgus monkeys showed mechanism-based effects, including increased T-cell activation, increased cytokines

and microscopic findings in the secondary lymphoid tissues. Decreases in circulating lymphocytes and serum globulins were also noted.

2.2.3.2. Clinical Overview

As of January 2023, elranatamab is being evaluated for the treatment of adult patients with RRMM or NDMM in 11 on-going studies. For detailed information on these studies, refer to the [IB](#).

2.2.3.2.1. First-in-Human Study of Elranatamab (C1071001)

The safety, efficacy and PK of elranatamab as a single agent are currently being evaluated in an ongoing Phase 1 study (C1071001). Part 1 dose escalation includes monotherapy (IV and SC) and Part 1.1 includes 2 priming cohorts (SC only). Part 1.1 introduced a priming strategy to mitigate CRS which involves a single lower priming dose (600 µg/kg) followed by maintenance dosing starting 1 week later at the RP2D (1000 µg/kg) on either a QW or Q2W schedule. For detailed information on the safety and efficacy data in this study, refer to the [IB](#).

Based on safety, efficacy, PK, and pharmacodynamics data from Study C1071001, the recommended Phase 2 dosing regimen has been determined as 76 mg (fixed dose equivalent of 1000 µg/kg) QW SC starting from C1D8.

2.2.3.2.2. Clinical Study C1071003

2.2.3.2.2.1. Overview of Study C1071003

Study C1071003 is an ongoing, open-label, multicenter, non-randomized Phase 2 study to evaluate the efficacy and safety of elranatamab monotherapy in patients with MM who are refractory to at least one PI, one IMiD and one anti-CD38 antibody. The study enrolled 2 independent and parallel cohorts: one with participants who are naïve to BCMA-directed therapies (Cohort A) and one with participants who have received previous treatment with BCMA-directed therapies (CAR-Ts and/or ADC) (Cohort B).

Details on the safety, efficacy, clinical pharmacology and immunogenicity of elranatamab are provided in the [IB](#).

Based on the totality of the safety, efficacy, PK, and PD from Studies C1071001 and C1071003, the recommended elranatamab dosing regimen is 2 step-up priming doses of 12 mg and 32 mg on C1D1 and C1D4 followed by a full dose of 76 mg QW SC starting from C1D8.

2.2.3.2.3. Other Elranatamab Studies

The efficacy and safety of elranatamab is being evaluated as monotherapy in an ongoing Phase 3 study (C1071007) in participants with NDMM after transplant and as monotherapy and in a combination regimen in an ongoing Phase 3 study in RRMM participants who have received at least 1 prior line of therapy (C1071005). Other Phase 1/2 studies are investigating

elranatamab as monotherapy and in combination therapy with other immunotherapy or standard of care agents.

Updates to these studies will be incorporated in the study C1071008 protocol and the Investigator's Brochure when available.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of elranatamab may be found in the Investigator's Brochure, which is the SRSD for this study.

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2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|--|
| Study Intervention: Elranatamab | | |
| CRS | <p>A known toxicity of therapeutics that function by activation of immune effector cells.</p> <p>Circulating cytokines are elevated after IV or SC administration of elranatamab.</p> <p>For further information refer to the IB.</p> | <p>Participants will be hospitalized for at least 2 days after the C1D1 dose and 1 Day for the C1D4 dose for safety surveillance. Hospitalization from C1D1 to C1D5 may be considered. (see Section 6.1.1).</p> <p>The priming regimen is expected to mitigate rate, duration, and severity of CRS (see Section 4.3).</p> <p>Guidance for monitoring, grading, and management of CRS per ASTCT criteria and guidelines is included in Appendix 11.</p> <p>Dose modification/discontinuation in the setting of Grade ≥ 2 AEs (including CRS) is described in Section 6.5.2.</p> <p>This study will include only participants who are likely to tolerate potential events of CRS by excluding participants who are particularly susceptible to complications of CRS, including those with impaired cardiac function or clinically significant CV disease (see Section 5.1 and Section 5.2).</p> <p>Premedication (see Section 6.8.1)</p> <p>Additional management for Grade ≥ 3 CRS is described in Section 9.4.1.</p> |
| ICANS | <p>A known toxicity of therapeutics that function by activation of immune effector cells.</p> <p>Data from ongoing studies suggest ICANS is infrequent. For further information refer to the IB.</p> | <p>Participants will be hospitalized for at least 2 days after the C1D1 dose and 1 Day for the C1D4 dose for safety surveillance. Hospitalization from C1D1 to C1D5 may be considered.(see Section 6.1.1).</p> <p>The priming regimen is expected to mitigate the rate, duration, and severity of ICANS (see Section 4.3).</p> <p>Regular neurologic examination will be performed by the investigator or designee (Section 8.2.2).</p> <p>Guidance for monitoring, grading, and management of ICANS per ASTCT criteria and guidelines is included in Appendix 11.</p> <p>Dose modification/discontinuation in the setting of Grade ≥ 2 AEs (including ICANS) is described in Section 6.5.2.</p> <p>Additional management for Grade ≥ 3 ICANS is described in Section 9.4.1.</p> |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|--|---|---|
| Study Intervention: Elranatamab | | |
| Peripheral neuropathy including GBS | <p>A common complication of multiple myeloma and its treatment.</p> <p>Grade 3 peripheral neuropathy has been observed with elranatamab.</p> <p>For further information refer to the IB.</p> | <p>This study excludes participants who may be particularly susceptible to new or worsening peripheral neuropathy, including those with POEMS syndrome, history of GBS or GBS variants, ongoing Grade ≥ 2 peripheral neuropathy (see Section 5.2).</p> <p>Regular neurologic examinations will be performed by the investigator (or designee) to monitor for emerging signs and symptoms of new or worsening peripheral neuropathy (see Section 8.3.11).</p> <p>The administration of drugs known to cause peripheral neuropathy should be carefully considered, and if possible, avoided by the investigator (Section 6.8).</p> <p>Participants should be closely monitored for signs and symptoms of neuropathy following infections or following the administration of any vaccine (Section 8.3.11).</p> <p>Dose modification/discontinuation for peripheral neuropathy is described in Section 6.5.2.</p> <p>Work-up recommendations for new or worsening peripheral neuropathy (Grade ≥ 2) is described in Section 8.3.11.</p> <p>Additional management for peripheral neuropathy is described in Section 9.4.1.</p> |
| Infections | <p>Infections are common in patients with RRMM due to underlying immunosuppression. As elranatamab causes plasma cell depletion, and likely contributes to worsening hypogammaglobulinemia and neutropenia, elranatamab treatment increases the risk of infections.</p> <p>For further information refer to the IB.</p> | <p>See Section 6.8.4 and Appendix 12 for infection prophylaxis.</p> <p>Monitor participants, especially those with neutropenia, for signs of infection. See Section 6.5 for dose modifications for elranatamab.</p> |

2.3.2. Benefit Assessment

The burden of MM increased in China during the past decade (2006-2016), and the mortality of MM increased from 2006 to 2014, but remained stable since 2014, regardless of the continuous increasing incidence. Improving diagnosis and treatment techniques had a positive effect on the mortality of MM, however, there are still many challenges for the management of RRMM in China. The classic/conventional regimens across different treatment lines are used for most patients due to limited treatment options for RRMM treatment in China. The outcomes of conventional treatment regimens used in RRMM patients are still quite poor. In addition, treatment-related issues, including drug availability, duration of induction and maintenance treatment, rate of transplant and economic burdens, are major concerns. Especially for patients who have been heavily treated, few viable options remain with limited accessible novel agents (see Section 2.2.1). Based on preliminary data from the ongoing Phase 1 study (C1071001), elranatamab has the potential to provide clinical benefit to participants with RRMM. In addition, elranatamab monotherapy represents a treatment option free of the AEs associated with steroid based SOC therapies. Moreover, data from Study C1071001 indicate that SC administration of elranatamab is associated with a lower rate of Grade 2 CRS relative to IV administration despite higher exposure in the SC cohorts. The SC route also represents a significant convenience benefit to participants relative to the IV administration of SOC and other experimental therapies. Lastly, ocular toxicity, a common and potentially severe AE with belantamab mafodotin-blmf, a BCMA-directed ADC,²⁴ has not been observed with elranatamab.

2.3.3. Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risk to study participants, the potential risks identified in association with elranatamab are justified by the anticipated benefits that may be afforded to participants with RRMM.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

| Objectives | Endpoints |
|---|--|
| Primary: | Primary: |
| Phase 1b: <ul style="list-style-type: none"> To establish the safety profile of elranatamab in order to confirm the RP2D in Chinese participants Phase 2: <ul style="list-style-type: none"> To determine the efficacy of elranatamab in Chinese participants with RRMM | Phase 1b: <ul style="list-style-type: none"> DLTs observed in Cycle 1 (4 weeks) Phase 2: <ul style="list-style-type: none"> ORR by BICR per IMWG |
| Secondary: | Secondary: |
| <ul style="list-style-type: none"> To further evaluate the efficacy of elranatamab in Chinese participants with RRMM | <ul style="list-style-type: none"> DOR by BICR and investigator per IMWG CRR by BICR and investigator per IMWG ORR by investigator per IMWG DOCR by BICR and investigator per IMWG PFS by BICR and investigator per IMWG OS TTR by BICR and investigator per IMWG MRD negativity rate (central lab) per IMWG |
| <ul style="list-style-type: none"> To determine the safety and tolerability of elranatamab | <ul style="list-style-type: none"> AEs and laboratory abnormalities by type, frequency, severity (as graded by NCI CTCAE v5.0), timing, seriousness, and relationship to study therapy Severity of CRS and ICANS assessed according to ASTCT criteria¹ |
| <ul style="list-style-type: none"> To evaluate the PK of elranatamab | <ul style="list-style-type: none"> PK parameters of elranatamab: C_{max}, T_{max}, and AUC_{last} Pre- and post-dose concentrations of elranatamab |
| <ul style="list-style-type: none"> To evaluate the immunogenicity of elranatamab | <ul style="list-style-type: none"> ADAs and NABs against elranatamab |
| <ul style="list-style-type: none"> To assess the impact of elranatamab on patient-reported symptoms and functioning | <ul style="list-style-type: none"> EORTC QLQ-C30 and MY20 EORTC QLQ CIPN20 EQ-5D |
| Exploratory: | Exploratory: |
| <ul style="list-style-type: none"> To explore correlations between elranatamab exposure and efficacy, safety and PD/biomarker endpoints | <ul style="list-style-type: none"> Selected PK, efficacy, safety and PD/biomarker endpoints |
| <ul style="list-style-type: none"> To explore the relationship between elranatamab and the biology of the participant's MM | <ul style="list-style-type: none"> Measurements of biomarkers (DNA, RNA, plasma sBCMA level, protein or defined cell types) resulting from analyses of peripheral blood, and/or BM biospecimens |

Estimands

This section defines the estimands associated with the primary endpoint of the study.

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

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention in Phase 1b part and either experience DLT(s) during the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who receive less than the minimum requirement of the planned doses of study intervention for reason other than treatment-related toxicity are not evaluable for DLTs. The minimum required exposure for DLT evaluability is 4 out of 5 planned doses of elranatamab during the DLT observation period.
- Variable: Occurrence of DLTs. DLTs are defined in Section 4.3.1.
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants.

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

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention.
- Variable: objective response defined as confirmed sCR, CR, VGPR and PR according to the IMWG criteria based on BICR assessment, from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first.
- Intercurrent event(s): All data collected after an intercurrent event of subsequent anticancer therapy will be excluded except if required to confirm PD. All response assessments regardless of gaps in disease assessments will be considered. Data will be collected regardless of discontinuation from treatment. Participants who do not have a post-baseline disease assessment due to early confirmed PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience confirmed PD or stop disease assessments for any reason prior to achieving an objective response will be counted as nonresponders in the assessment of objective response.
- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an objective response and 2-sided 90% CI for ORR.

4. STUDY DESIGN

4.1. Overall Design

Study C1071008 is a Phase 1b/2, open-label study to evaluate the safety, PK, PD and the efficacy of elranatamab in Chinese participants with MM who are refractory to at least 1 PI, 1 IMiD and 1 anti-CD38 mAb (triple-class refractory MM).

Study C1071008 will investigate elranatamab monotherapy in participants with MM who are triple-class refractory. It will include 2 parts. Phase 1b part is the dose confirmation/safety lead-in phase to establish the safety profile in order to confirm the RP2D in Chinese participants. After the RP2D is confirmed to be tolerable, the participants who started from the RP2D in Phase 1b part will contribute to the efficacy evaluation together with other participants in Phase 2.

The objective of Phase 1b part is to establish the safety profile in order to confirm the monotherapy RP2D (76 mg SC QW with 12 mg (C1D1) and 32 mg (C1D4) as step-up priming doses SC) from global available data in Chinese participants before initiation of Phase 2 part of the study using a primary endpoint of DLT. Six triple class refractory participants with MM who had progression after at least 1 regimen in each category (triple-class refractory) will be enrolled and treated at the RP2D to assess the DLT rate of elranatamab. The DLT observation period will be Cycle 1 (4 weeks). If the DLT rate is less than 1/3 (0 or 1 participant out of 6), Phase 2 part will be initiated after the DLT observation period is concluded for all enrolled participants in Phase 1b portion. If the DLT rate at the monotherapy RP2D meets or exceeds 1/3, the enrollment will stop until further evaluation of sponsor and investigators, and the following decision will be reflected in a protocol amendment.

The Phase 2 part is a single stage design to evaluate the efficacy and safety in Chinese participants. The primary endpoint in Phase 2 part is ORR by BICR, as defined by IMWG. BICR will review data from site sourced components of response assessment (eg, hemoglobin, calcium, creatinine, serum protein electrophoresis, urine protein electrophoresis, serum free light chain and ratio, select bone marrow pathology report data, imaging report summaries) and provide assessment of best response, date of response onset, and date of progression (if applicable), while remaining blinded to investigator-assessed responses.

Additionally, all participants from Phase 1b (6 in total) and approximately 6 participants from Phase 2 will undergo intensive PK sampling to obtain the PK profile of elranatamab at timepoints specified in Section 1.3.2 SoA B (Additional PK, Immunogenicity and Biomarker Flowchart). Sparse PK sampling will also be collected in all participants in the Phase 2 part (Section 1.3.1 SoA A).

4.2. Scientific Rationale for Study Design

4.2.1. Exclusion of Prior BCMA-directed therapy

Numerous BCMA-directed therapies are currently under investigation^{3, 12, 25} and it is likely that some potential participants will have previously received at least 1 of these therapies.

Considering there is no BCMA-directed therapy approved by NMPA, this study will exclude participants who have been previously exposed to BCMA-directed therapy studies.

4.2.2. Biomarkers

The objectives of biomarker sample collections and exploratory analyses will be to evaluate candidate predictive biomarkers that may be useful in identifying patients who may benefit from treatment with elranatamab and to further evaluate mechanisms of action and/or resistance to elranatamab. Results from these exploratory analyses will provide additional insights further informing our understanding of the benefit-risk profile and biologic effects of the elranatamab.

Biomarker analyses will be performed on BMA samples that are collected at screening and those that are collected for disease assessment while on-treatment. MRD will be assessed using NGS at a central laboratory. The patient-specific pre-treatment sample analysis detects the patient-specific lymphocyte antigen receptor DNA sequences that are a direct measure of the malignant B/plasma or T-cell clone. On-treatment BMA samples are used to monitor the identified clones and determine MRD positivity or negativity with a threshold of 10^{-5} . The IMWG updated MM response categories define MRD-negative responses in the BM (assessed by next-generation flow cytometry or NGS) as an independent factor predicting prognosis during MM treatment.²⁶ RNA and DNA sequencing analysis of baseline and on-treatment BMA samples will provide information about gene mutations and/or gene signatures that may correlate with response and resistance. A blood or saliva sample will be used as a germline comparator to assist in the identification of somatic mutations. Additional blood samples will be collected at various time points for exploratory biomarker assessments as described in Section 8.7.

4.2.3. Choice of Contraception/Barrier Requirements

Studies to evaluate the development toxicity of elranatamab have not been conducted. Therefore, the use of a highly effective method of contraception is required for WOCBP. There are no contraception requirements for males (see [Appendix 4](#)). The duration of the contraception required for WOCBP after the last dose of the study intervention is 5 months.

4.3. Justification for Dose

The RP2D of elranatamab in the ongoing Study C1071001 is 76 mg QW administered as a SC injection with a priming dose of 44 mg for the first dose.

In Part 1 (dose-escalation) of the first-in-human Study C1071001, body-weight based doses ranging from 0.1 µg/kg to 50 µg/kg QW IV infusion and 80 µg/kg to 1000 µg/kg QW SC were evaluated in participants with RRMM, the majority of whom were triple-class refractory, to estimate the MTD and select the RP2D. A total of 2 participants in the IV cohorts had TEAEs that were considered DLTs, while no DLTs were observed in the SC cohorts including the highest tested dose of 1000 µg/kg. Therefore, the MTD was not reached in Study C1071001. Despite achieving similar or higher exposure levels (C_{max} and AUC_{τ}) at SC doses ≥ 130 µg/kg relative to the highest IV dose level of 50 µg/kg, SC dosing appeared in

general to be associated with a lower rate of Grade 2 CRS, the most common TEAE. Therefore, elranatamab will be dosed via SC route in this study.

Population PK analysis based on concentration-time data from all IV and SC cohorts in the dose escalation part of Study C1071001 indicated that body weight is not a clinically relevant covariate on elranatamab exposure. Therefore, a fixed dose will be used for further development including in study C1071008.

Evidence of clinical efficacy was observed in the Phase 1 study (C1071001), particularly at doses ≥ 215 $\mu\text{g/kg}$ SC with acceptable safety profile across all dose levels in the dose escalation cohort. The ORR at the highest tested dose of 1000 $\mu\text{g/kg}$ SC was 83.3% (5 of 6 participants). The ORR observed at the 1000 $\mu\text{g/kg}$ dose cohort despite the relatively high baseline sBCMA levels in this cohort coupled with the acceptable and manageable safety profile and preliminary population PK analysis of limited body weight impact on elranatamab clearance supported the selection of fixed dose equivalent of 1000 $\mu\text{g/kg}$ dose level, 76 mg, as the RP2D with a fixed dose equivalent of 600 $\mu\text{g/kg}$ dose level, 44 mg, as a priming dose to be administered on Cycle 1 Day 1.

As indicated in [IB](#), CRS began within the first 3 days of dosing in all participants with CRS. Therefore, to maximize the potential for clinical activity while improving the safety margin of elranatamab, a fixed dose equivalent of 1000 $\mu\text{g/kg}$ dose level, 76 mg, was selected as the RP2D with 2 step-up priming dose regimen implemented during the first week of treatment (12 mg on C1D1, 32 mg on C1D4). The rationale for the 2 step-up priming doses is described as follows. In the SC cohorts from Study C1071001, CRS events occurred mainly after the first dose with only 2 out of 50 participants experiencing CRS after the second dose, and no CRS events observed after the third or later doses. The rates of Grade 1 and 2 CRS events in participants receiving dose levels ≥ 600 $\mu\text{g/kg}$ (which is the body weight dosing equivalent of 44 mg) are 62.5% and 37.5%, respectively, according to ASTCT grading. The maximum severity of CRS was consistently observed after the first dose, including participants in the priming cohorts who received a higher dose 7 days after the priming dose, indicating that CRS is associated mostly with the initial exposure (ie, the first dose). A logistic regression analysis that included data from both IV ($n=23$) and SC cohorts ($n=43$) from Study C1071001 showed an association between elranatamab C_{max} within 24 hours post first dose ($C_{\text{max-24h}}$) and probability of CRS of All Grades and Grade ≥ 2 (according to ASTCT criteria ¹).

To mitigate CRS, the current study will evaluate a regimen that includes premedications as well as 2 step-up priming doses of 12 mg on C1D1 and 32 mg on C1D4 before the first full elranatamab dose on C1D8. The logistic regression analysis indicates that, after a starting dose of 12 mg on C1D1, the predicted probabilities of All Grades and Grade ≥ 2 CRS are 55% (95% CI: 29% to 78%) and 14% (95% CI: 5% to 31%), respectively. Furthermore, increases in the levels of several cytokines (including IL-6, IL-2, IL-10, and IL-2RA) were observed at the predicted $C_{\text{max-24h}}$ of 12 mg dose. This suggests that the 12 mg dose is expected to stimulate the immune system such that CRS events with the second step-up dose of 32 mg, if any, would be less frequent and of lower grade. Given the predicted immune

stimulation at 12 mg and the CRS profile observed in Study C1071001 where CRS events were associated mainly with the first dose and occasionally with the second dose, additional CRS events on C1D8 (first full dose and the third dosing instance) are considered unlikely.

Priming dose approaches are commonly applied for T cell engager bispecific medications to initially sensitize the immune system at lower doses therefore reducing the rate and grade of CRS.

The dose of elranatamab should be increased to 76 mg on C1D8 as long as the participant meets the criteria listed in Section 6.5.1. If a participant does not meet these criteria on C1D8, initiation of dosing with 76 mg should be deferred until these criteria are met.

If a participant has received QW dosing for at least 6 cycles and has achieved IMWG response of a PR or better with responses persisting for at least 2 months, the dose interval will be changed from QW to Q2W (eg, beginning C7D1) as a lower dose intensity might be adequate to maintain the response given the reduced disease burden in these participants. 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.

4.3.1. Dose Limiting Toxicity (DLT) Definition

Monitoring of DLTs will occur in Phase 1b. The purpose of Phase 1b is to establish the safety and tolerability of elranatamab in order to confirm the RP2D in Chinese participants before Phase 2 initiation, the DLT observation period will be up to the end of Cycle 1 in each participant. Severity of AEs will be graded according to NCI CTCAE v5.0. The severity of CRS and ICANS will be assessed according to the modified grading described by ASTCT (See Section 10.11).

A participant is classified as DLT-evaluable if he/she meets either criteria. If a participant does not meet these criteria, he/she may be replaced.

- Experiences a DLT during the DLT observation period (irrespective of whether the participant received the minimum requirement of the planned doses and scheduled safety assessments during the DLT observation period).
- In the absence of a DLT, receives the minimum requirement of the planned doses of each investigational product and has received scheduled safety assessments during the DLT observation period.

The minimum required exposure for DLT evaluability is 4 out of 5 planned doses of elranatamab during the DLT observation period. Participants without DLTs who do not receive the minimum required exposure for reasons other than treatment-related toxicity are not evaluable for DLT assessment and may be replaced.

For the purpose of RP2D determination, additional late toxicities in the context of all safety data available will also be considered. Safety information from any participants that do not meet DLT-evaluable criteria could still be considered for overall Phase 1b decisions.

As described in Table 2, any of the following AEs observed within the DLT observation period and considered related to elranatamab will be classified as DLTs. Participants with dose reductions or missed dose(s) due to treatment-related toxicity not listed in Table 2 during the DLT observation period will be discussed between the investigator and sponsor and may be classified as DLTs. Participants experiencing a DLT may resume dosing only if adequate recovery is achieved within the allowed time window and if permitted for the specific toxicity (Section 6.5.1).

Table 2. Hematological and Non-hematological Dose-limiting Toxicities

| |
|--|
| Hematological |
| <ul style="list-style-type: none"> Grade 4 neutropenia lasting >5 days. |
| <ul style="list-style-type: none"> Febrile neutropenia (defined as an ANC <1000/mm³ with a single temperature of >38.3°C [101°F], or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour). If fever is determined to be a symptom of CRS confirmed by clinical course and cytokine levels, and resolves in a manner consistent with CRS, this would no longer be considered a DLT, and the participant may resume treatment. |
| <ul style="list-style-type: none"> Grade ≥3 neutropenia with infection. |
| <ul style="list-style-type: none"> Grade 4 thrombocytopenia: <ul style="list-style-type: none"> For participants with baseline platelets ≥50,000/mm³, any platelet count <25,000/mm³ is a DLT For participants with baseline platelets ≥25,000/mm³ and <50,000/mm³, any platelet count < 10,000/mm³ is a DLT, while platelet counts < 25,000 and ≥10,000 are a DLT only if associated with Grade ≥2 bleeding. |
| <ul style="list-style-type: none"> Grade 3 thrombocytopenia with Grade ≥2 bleeding. |
| Non-hematological |
| <ul style="list-style-type: none"> Grade ≥4 AEs. |
| <ul style="list-style-type: none"> Grade 3 CRS, except those CRS events that have <ul style="list-style-type: none"> i) not been maximally treated (ie, lack of administration of standard of care treatment per the institution's, Investigator's, or treating physician's guidelines for the management of CRS) or ii) improved to ≤ Grade 1 within 48 hours. |
| <ul style="list-style-type: none"> Grade 3 AEs, with the exception of: <ul style="list-style-type: none"> AEs attributed to a CRS event (ie, Grade 3 transaminitis) Grade 3 nausea, vomiting and diarrhea that improve to Grade ≤ 2 within 72 hours after maximal medical management has been initiated Grade 3 fatigue lasting < 1 week Grade 3 AEs that recover to baseline or Grade 1 within 5 days |

Table 2. Hematological and Non-hematological Dose-limiting Toxicities

| |
|--|
| <ul style="list-style-type: none"> Confirmed DILI meeting Hy's law criteria (See Section 10.6). |
| <ul style="list-style-type: none"> Grade 3-4 laboratory abnormalities with the exception of: <ul style="list-style-type: none"> Grade 3-4 laboratory abnormalities that are not associated with clinical sequelae and improve to Grade ≤ 2 with appropriate management or supplementation within 72 hours of their onset. |
| <ul style="list-style-type: none"> Grade 2 clinically important or persistent AEs (eg, AEs responsible for significant dose delay) may also be considered a DLT following review by the investigators and the Sponsor. |
| <ul style="list-style-type: none"> Other clinically important or persistent AEs (eg, AEs responsible for significant dose delay or dose reduction) may also be considered a DLT following review by the investigators and the sponsor. DLTs need to represent a clinically significant shift from baseline. |
| <ul style="list-style-type: none"> Grade 3 ISR^a |

a. Allergic reaction, or anaphylaxis will not be considered as a DLT.

4.4. End of Study Definition

This study will be completed when all participants have been followed for OS for at least 2 years from the date of first dose.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

- Participants age ≥18 years.
 - A female participant is eligible to participate if she is not pregnant or breastfeeding. Refer to [Appendix 4](#) for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

- Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Prior diagnosis of MM as defined according to IMWG criteria.²
4. Measurable disease based on IMWG criteria as defined by at least 1 of the following:
 - a. Serum M-protein ≥ 0.5 g/dL by SPEP
 - b. Urinary M-protein excretion ≥ 200 mg/24 hours by UPEP
 - c. Serum immunoglobulin FLC ≥ 10 mg/dL (≥ 100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (< 0.26 or > 1.65)
5. Refractory to at least 1 IMiD (as defined in *Note* below).
6. Refractory to at least 1 PI (as defined in *Note* below).
7. Refractory to at least 1 anti-CD38 antibody (as defined in *Note* below).
8. Relapsed or refractory to last anti-MM regimen.

Note: Refractory is defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response.

9. ECOG performance status ≤ 2 .
10. LVEF $\geq 40\%$ as determined by a MUGA scan or ECHO.
11. Adequate hepatic function characterized by the following:
 - a. Total bilirubin $\leq 2 \times \text{ULN}$ ($\leq 3 \times \text{ULN}$ if documented Gilbert's syndrome);
 - b. AST $\leq 2.5 \times \text{ULN}$; and
 - c. ALT $\leq 2.5 \times \text{ULN}$
12. Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min (according to the Cockcroft Gault formula, by 24-hour urine collection for creatinine clearance, or according to local institutional standard method).
13. Adequate BM function characterized by the following:
 - a. ANC $\geq 1.0 \times 10^9/\text{L}$ (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing);
 - b. Platelets $\geq 25 \times 10^9/\text{L}$ (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and

- c. Hemoglobin ≥ 8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing).

14. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤ 1 .

Informed Consent:

- 15. Capable of giving signed informed consent as described in [Appendix 1](#), which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Smoldering MM defined according to IMWG criteria.
2. Active plasma cell leukemia.
3. Amyloidosis.
4. POEMS syndrome.
5. Stem cell transplant within 12 weeks prior to enrollment or active GVHD.
6. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:
 - a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting), symptomatic pericardial effusion;
 - b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia, runs of ventricular tachycardia);
 - c. Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);
 - d. Prolonged QT syndrome (or triplicate average QTcF >470 msec at screening).
7. Ongoing Grade ≥ 2 peripheral sensory or motor neuropathy. History of GBS or GBS variants, or history of any Grade ≥ 3 peripheral motor polyneuropathy.

8. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
9. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

10. Previous treatment with an anti-BCMA directed therapy (eg, BCMA-directed ADC , BCMA-directed CAR T-cell therapy or bispecific antibody, either approved or investigational).

Prior/Concurrent Clinical Study Experience:

11. Previous administration with an investigational product (eg, drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

12. Any active, uncontrolled bacterial, fungal, or viral infection, eg, HBV, HCV, SARS-CoV-2, HIV, etc. Known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatment, active hepatitis B (defined as positive HBs antigen and positive hepatitis B viral DNA test above the lower limit of detection of the assay), or active hepatitis C (defined as a positive hepatitis C antibody result and quantitative (HCV) RNA results greater than the lower limits of detection of the assay). Active infections must be resolved at least 14 days prior to enrollment.

Other Exclusions:

13. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
14. Known or suspected hypersensitivity to the study intervention or any of its excipients.
15. Live attenuated vaccine within 4 weeks of the first dose of study intervention.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception from the permitted list of

contraception methods (see [Appendix 4](#) Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Section 1.3.1 SoA A (including long term follow-up visit/contacts covering the required contraception period [through 5 months post last dose of study intervention for WOCBP [[Appendix 4](#)]], the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant. If a participant is confirmed to be pregnant, treatment should be discontinued.

Contraception check is only required for WOCBP.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) or individuals who consent but are unable to enroll due to study enrollment hold may be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to elranatamab (PF-06863135).

6.1. Study Intervention(s) Administered

| | |
|--------------------------------|---|
| Intervention Name | Elranatamab (PF-06863135) |
| Cohort(s) | All enrolled |
| Type | Biologic |
| Unit Dose Strength(s) | 40 mg/mL in a 6 mL Type I clear glass vial (nominal volume of 1.9 mL) |
| Dosage Level(s) | 76 mg QW; 12 mg, 32 mg priming doses (44 mg and 32 mg may be used for management of toxicity.) |
| Route of Administration | SC |
| Use | Experimental |
| IMP or NIMP | IMP |
| Sourcing | Provided centrally by the sponsor. |
| Packaging and Labeling | Study intervention will be provided in a carton containing 1 vial. Each vial and carton will be open labeled as required per China's requirement. |

6.1.1. Administration

Qualified and trained investigator site personnel will administer elranatamab to participants by SC injection. Ideally, each injection may be up to 2 mL in volume; however, if the maximum volume allowed per institution's policy is lower than 2 mL, the number of injections may be increased to accommodate this difference in volume and ensure the correct dose is delivered.

Elranatamab should be administered to the abdomen, with preference given to the lower quadrants when possible. Refer to [Appendix 9](#) for details on administration of multiple injections to the abdomen. Study staff should refer to the IP Manual for specific instructions on the handling, preparation, and administration of study intervention.

Participants will receive elranatamab as a SC injection administered QW on Days 1, 8, 15 and 22 of each 28-day cycle. Elranatamab is also administered on C1D4. A minimum of 2 days should be maintained between the 2 step-up priming doses (C1D1 and C1D4), a minimum of 3 days between C1D4 dose and the first full dose (C1D8); a minimum of 6 days should be maintained between doses thereafter. If a participant has received QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval will be changed from QW to Q2W (eg, beginning C7D1) (see Section 6.5.3). 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).

Dose modifications may occur according to the guidelines described in Section 6.5.

The first doses of study intervention for both Phase 1b and Phase 2 will be 12 mg (C1D1) and 32 mg (C1D4), which will serve as priming doses and will be administered on an inpatient basis. Participants are required to be hospitalized and monitored for CRS/ICANS for at least 2 days (~48 hours) beginning on Cycle 1 Day 1, and for 1 day (~24 hours) for C1D4, for both Phase 1b and Phase 2. Hospitalization up to 5 days from C1D1 to C1D5 inclusive may be considered.

The dose of elranatamab should be increased to 32 mg on C1D4 and to 76 mg on C1D8 for both Phase 1b and Phase 2 as long as the participant meets the redosing criteria listed in Section 6.5.1. If a participant does not meet these criteria on C1D4 and C1D8, dosing should be deferred until the criteria are met.

For both the priming doses and first full dose (76 mg), premedication for CRS is required (see Section 6.8.1)

Each participant will receive study intervention until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.
3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.
4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
5. Study interventions should be stored in their original containers.

6. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
7. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Vials are single-use.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of biotherapy agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation of participants to study intervention will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed at the study visits summarized in the [SoA A](#).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

A record of the number of study intervention dispensed to and administered to each participant must be maintained.

6.5. Dose Modification

Criteria for dose modification due to toxicity and efficacy are presented in the following sections.

The recommended dose modification guidelines for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection can be found in [Appendix 8](#).

6.5.1. Retreatment criteria

During a cycle: Re-treatment following interruption for treatment-related toxicity and for peripheral neuropathy (any causality) within a cycle should follow the dose modification and guidance section below (Section [6.5.2](#)).

Participants must receive both elranatamab priming doses before receiving the planned full dose (76 mg). If the C1D4 dose (32 mg) cannot be administered within the protocol-defined window, elranatamab treatment may resume at the planned C1D4 dose (32 mg) upon meeting the re-treatment criteria. Upon re-treatment, if the C1D4 dose (32 mg) was tolerable, the elranatamab dose should be increased to the planned full dose (76 mg) approximately 4 days later, after which QW dosing with the planned full dose (76 mg) should continue (until Q2W is permitted, Section [6.1.1](#)).

Dose reductions, as outlined in Section [6.5.2](#) ([Table 3](#)), are only applicable after the first full planned dose (76 mg) is administered.

At the start of a cycle: Re-treatment at the start of any new cycle should not occur until all of the following parameters have been met:

- $ANC \geq 1.0 \times 10^9/L$;

- Platelets count $\geq 25 \times 10^9/L$;
- Recovery of treatment-related nonhematologic toxicities to baseline or Grade ≤ 1 severity;
- For any dosing day (at start of a cycle or during a cycle [Section 6.5.2]), No ongoing CRS or ICANS of any grade;
- Recovery of treatment-emergent peripheral neuropathy to Grade ≤ 1 severity.

6.5.2. Dose Modifications for Elranatamab-Related Toxicity and for Peripheral Neuropathy

The recommended dose modifications for elranatamab-related toxicities and peripheral neuropathy are presented in Table 3. All dose modifications should be based on the worst preceding toxicity and must be recorded on the CRF.

Table 3. Dose Modifications for Elranatamab-Related Toxicity and for Peripheral Sensory or Motor Neuropathy^a

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|----------------------------------|--|---|--|
| Elranatamab-related Non-hematologic (excluding peripheral Sensory or Motor neuropathy – see below) ^a | Continue at the same dose level. | Continue at the same dose level. Alternatively, per investigator discretion, withhold dose until toxicity is Grade ≤ 1 , then resume at the same dose level. | Withhold dose until toxicity is Grade ≤ 1 , or has returned to baseline, then restart with the dose reduced by 1 level. ^{b,f} | Permanently discontinue. ^{b,f} |
| Elranatamab-related Hematologic ^{a,c,d} | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤ 2 or has returned to baseline, then resume treatment at the same dose level. ^d If toxicity reoccurs, dosing should be reduced by 1 dose level. If toxicity reoccurs despite dose reduction, dosing may be reduced by 1 more dose level. If toxicity reoccurs after a maximum of 2 dose reductions, participant will be permanently | Withhold dose until toxicity is Grade ≤ 2 or returns to baseline, then reduce by 1 dose level. ^d If toxicity reoccurs despite dose reduction, dosing should be reduced by 1 more dose level. If toxicity reoccurs after a maximum of 2 dose reductions, participant will be permanently discontinued from treatment. |

Table 3. Dose Modifications for Elranatamab-Related Toxicity and for Peripheral Sensory or Motor Neuropathy^a

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|--|---|--------------------------------------|--------------------------------------|
| | | | discontinued from treatment. | |
| Peripheral Sensory or Motor neuropathy (all causality) ^a See Section 8.3.11 for recommended work-up | Continue at the same dose level Continue to monitor the participant for signs of worsening neuropathy | Withhold dose until resolution to Grade ≤ 1 , then resume at a reduced dose level. Continue to monitor the participant for signs of worsening neuropathy. ^e If Grade ≥ 2 neuropathy reoccurs, permanently discontinue elranatamab. | Permanently discontinue elranatamab. | Permanently discontinue elranatamab. |

- a. Dose reduction and discontinuation guidance is not applicable following the first and second doses (priming doses C1D1 and C1D4). If after the C1D4 priming dose, a participant experiences a treatment-related adverse event that leads to dose interruption (ie, dose held on Cycle 1 Day 8), elranatamab treatment may restart at the same dose (32 mg) upon meeting the retreatment criteria (Section 6.5.1). If the 32 mg was tolerable, the elranatamab dose should be increased to full dose (76 mg). In case of ongoing CRS or ICANS of any grade on any dosing day, dosing will be held until CRS or ICANS resolution. A long-term interruption during priming period within the first cycle may increase the risk of developing CRS upon treatment resumption (eg, a longer than 2 weeks of interruption within the first cycle between the 32 mg priming dose and the first full dose [76 mg]). Resuming treatment with a 32 mg dose before administering the first full (76 mg) dose may be considered after consultation with the sponsor.
- b. Grade 3 or 4 nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification or permanent discontinuation.
- c. Excludes lymphopenia which is expected based on the elranatamab mechanism of action.
- d. For thrombocytopenia: dosing can continue if platelets $\geq 25 \times 10^9/L$. For Grade 4 (first occurrence), resume at same dose level when platelets $\geq 25 \times 10^9/L$; for Grade 4 (second occurrence), resumption at a reduced dose level is recommended when platelets $\geq 25 \times 10^9/L$.
- e. Consider additional diagnostic work-up (see Section 8.3.11).
- f. Excludes laboratory abnormalities that are not considered clinically relevant.
- Note:** Cycles will not be extended to allow make-up for missed doses.

Doses may be held as needed until toxicity resolution. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

Missed doses will not be made up and cycles will not be extended to allow for missed doses. A minimum of 2 days should be maintained between the 2 step-up doses (C1D1 and C1D4), a minimum of 3 days between C1D4 dose and the first full dose (C1D8); a minimum of 6 days is required between doses thereafter.

C1D1 will be based on Day 1 of elranatamab dosing. After C1D1, for each cycle, if elranatamab cannot be administered on the planned day (within the window prespecified in the SoA), it should be skipped until the next planned dose (ie, if Day 15 cannot be administered within ± 3 days of planned dose, the dose should be skipped until Day 22).

If re-treatment criteria are not met within 4 weeks of treatment interruption/delay, study intervention should be permanently discontinued, unless the benefit/risk assessment per the investigator suggests otherwise, in agreement with the sponsor. In the event of a treatment interruption/delay lasting > 4 weeks for reasons other than treatment-related toxicity (eg, elective surgery), treatment resumption will be decided in agreement with the sponsor.

Permitted dose reductions are outlined in Table 4.

Table 4. Dose Levels for Elranatamab

| Dose | Remarks |
|-------|---|
| 76 mg | Dose to be administered starting Cycle 1 Day 8 (refer to Section 6.1.1 and 4.2). |
| 44 mg | This dose level may also be used for management of elranatamab-related toxicity. |
| 32 mg | Second step-up priming dose to be administered on C1D4. This dose level may be used for management of elranatamab-related toxicity. |
| 12 mg | First step-up priming dose to be administered on C1D1 only. |

Dose reductions of elranatamab below 32 mg are not allowed (12 mg is only to be used for C1D1); participants requiring reductions below 32 mg will be permanently discontinued from the treatment. Once a dose has been reduced for a given participant, all subsequent doses should be administered at that dose level unless: 1) further dose reduction is required, or 2) dose re-escalation is agreed by the investigator and the sponsor, which will only be permitted in Phase 2.

The study will be subject to potential amendment if RP2D (76mg SC QW with 12/32 mg SC as step-up priming dose) safety is not confirmed in Chinese participants in Phase 1b as determined by the study sponsor and investigators.

6.5.3. Dose Modification Based on Durable Overall Response

If a participant has received elranatamab QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval should be changed from QW to Q2W (eg, beginning C7D1). 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).

6.6. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to study participants beyond the end of the study.

Availability of study treatment following closure of the study through expanded access/compassionate/continued use mechanism if the investigator and participant desire to continue treatment and if there is documented continued benefit from study treatment for the participant would be at the discretion of the sponsor and subject to study treatment availability and compliance with local laws and regulations.

6.7. Treatment of Overdose

For this study, if a participant receives a dose $\geq 10\%$ higher than the planned dose of elranatamab, it will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs, including signs of CRS, and laboratory abnormalities for at least 28 calendar days after the overdose.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 28 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

6.8.1. Premedication Required for Cytokine Release Syndrome Prophylaxis

For both the priming doses and first full dose (76 mg), administer these medications 60 minutes (± 15 minutes) prior to elranatamab dose:

- acetaminophen 650 mg (or paracetamol 500 mg)*
- diphenhydramine 25 mg (or equivalent), oral or IV*
- dexamethasone 20 mg (or equivalent), oral or IV

* Different but comparable doses due to local strength variations and medication administrations per local label are permissible.

Similar premedications for doses at other time points may be given at the discretion of the investigator.

See [Appendix 11](#) for management of CRS and ICANS^{1,27,28}.

6.8.2. Permitted Concomitant Medications/Therapies

All concomitant treatments, including drug and nondrug interventions and blood products, will be recorded on the CRF at timepoints as specified in the [SoA A](#).

Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the investigator. The concurrent use of herbal medicinal products or herbal supplements should be avoided.

Hormonal contraceptives that meet the contraception requirements of this study are allowed to be used in participants who are WOCBP (see [Appendix 4: Contraceptive and Barrier Guidance](#)). For participants who receive oral contraceptives that are metabolized by CYP enzymes cytokines released during elranatamab treatment may cause drug-drug interaction with hormonal oral contraceptives at both PK and PD levels, and may accentuate the side effects associated with oral contraceptives.

See [Appendix 11](#) for management of CRS and ICANS.^{1,27,28}

Elranatamab has been demonstrated to transiently increase cytokine levels (eg, IL-6) in vivo in monkeys and humans (also demonstrated via in vitro assays) which is expected with CD3-targeted BsAbs.

Cytokines have been shown to result in modest and temporary inhibition of major CYP enzymes (eg, CYP3A4 and CYP2C9). Therefore, treatment with elranatamab can result in modest and temporal increase in the exposure of concomitant medications that are substrates for these enzymes. Caution should be used upon concomitant use of sensitive substrates of CYP enzymes with narrow therapeutic index (eg, CYP3A4: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus; CYP2C9: phenytoin, warfarin) especially during the initial treatment cycle. If the use of warfarin is clinically necessary, caution and additional INR monitoring is recommended during the initial treatment cycle.

The administration of drugs known to cause peripheral neuropathy should be carefully considered, and if possible, avoided by the investigator.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and study intervention required to minimize the risk of impaired wound healing and bleeding has not been determined. Postoperatively, the decision to reinstitute study intervention should be based on a clinical assessment of satisfactory wound healing and other aspects of surgical recovery.

Palliative radiotherapy during study therapy is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates in the medical record that the need for palliative radiotherapy is not

indicative of PD. The appropriate interval of time between radiotherapy and study intervention has not been determined.

All COVID-19 vaccines are permitted and should be recorded as concomitant medications (standard AE collection and reporting processes should be followed). The timing of COVID-19 vaccine administration relative to study intervention is at the discretion of the investigator although, if possible, it is best to avoid the DLT observation period and to avoid vaccine administration within 48 hours before or after the first and second doses of study intervention.

Participants with MM are at increased risk of severe disease and complications from COVID-19 infection^{29,30}. Participants should be regularly educated on the continuing risk and symptoms of COVID-19 infection, best practices to reduce the risk of infection including mask usage, and the importance of regular testing including at home.

Participants are to be tested for COVID-19 upon exposure to COVID-19 and at signs or symptoms of COVID-19 infection (eg. new or worsening fever, cough, sore throat, shortness of breath or fatigue). Frequent reflex testing is encouraged. A positive COVID-19 test result should be immediately reported to the study investigator and documented as an AE.

Participants who develop COVID-19 infection while on study should be managed in accordance with their treating healthcare provider's standard of care and local and/or regional guidelines, considering all treatments available to study participants, including PAXLOVIDTM and monoclonal antibody treatments. In accordance with standard of care practice, it is expected that initiation of treatment will start as soon as possible and ideally within 24 hours following a positive COVID-19 test. Where feasible, the sponsor will supply PAXLOVIDTM that may be used for treatment of COVID-19 in accordance with prescribing information³¹.

Investigators should ensure that eligible participants are educated on the correct administration of PAXLOVIDTM and to ensure that access to PAXLOVIDTM or other approved treatments for COVID-19 is available to all participants.

6.8.3. Prophylaxis for Infections

The administration of antibacterial and/or antiviral agents for infection prophylaxis in participants at increased risk of infection should be done in accordance with NCCN, ESMO, IMWG guidelines and/or local institutional guidelines. Monitor immunoglobulin levels for the occurrence of hypogammaglobulinemia and consider administering intravenous immunoglobulin for IgG level < 400 mg/dL. Refer to Section [10.12 Appendix 12](#) for all anti-infectious prophylaxis and monitoring.

6.8.4. Prohibited During the Study

No additional anticancer therapy (including anticancer Chinese herbal medicine) will be permitted while participants are receiving study intervention.

Chronic systemic corticosteroid use for palliative or supportive purposes is not permitted; however, steroid replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily is acceptable. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Note: Results from the planned interim analyses (Section 9.4) may be used for sponsor decisions regarding termination of the study or for specific cohorts and/or investigator decisions regarding discontinuation of individual participants from study intervention or from the study.

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Participant refused further treatment (Participants will have the option of refusing further treatment but will continue in the follow-up period of the study for safety/efficacy assessments), See Section 8.1 and Section 8.2;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- AEs requiring discontinuation (as described in Section 6.5.2, Dose Modification for Toxicity), or any AE that in the judgement of the investigator compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest;
- Confirmed disease progression (PD as defined by IMWG) (see Appendix 10);
- Lack of efficacy (eg, increase of disease burden not qualifying as PD according to IMWG criteria).
- Pregnancy;
- Participant begins breastfeeding;
- Significant protocol violation that, in the opinion of the investigator and/or sponsor, renders the participant unsuitable for further study intervention administration; Participant is noncompliant with study procedures or study intervention that in the judgment of the investigator or sponsor renders the participant unsuitable for further study participation;
- Lost to follow-up;
- Death;

- Completed;
- Study terminated by sponsor.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, disease assessments, subsequent anticancer therapies, and survival. See below and the [SoA A](#) or data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed. Survival status can be obtained by any means including telephone, during a visit, chart review, or contact with someone who is knowledgeable of the participant's survival status (eg, relative, friend, referring healthcare provider).

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, post-treatment study follow-up, and/or future collection of additional information.

Follow-Up Visit:

At least 28 calendar days, and no more than 35 calendar days after discontinuation of study intervention, participants will return to undergo safety assessments, review of concomitant treatments, contraception check, and PROs (see [SoA A](#) for all activities).

Participants continuing to experience AEs at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected (see also Section 8.3.1 for AE reporting period). If the unresolved AE is considered by the investigator as possibly related to or associated with ADA formation, the participant will be asked to return for drug concentration and ADA blood sampling at up to 3 month intervals, until the last follow-up of the AE.

Long Term Follow-Up:

Participants will be followed for at least 2 years from enrollment, continuing per End of Study Definition (see Section 4.4)

Follow-up will be conducted every 3 months from the last dose of study drug to confirm survival status and collect information including new anti-cancer therapies, AEs and contraception check (see [SoA A](#), active AE reporting period as defined in Section 8.3.1, and contraception check period in Section 5.3.1); the follow-up may be conducted by telephone. Date of disease progression recorded in the source notes will be collected. Public records may be used to find current contact information and/or to document date of death if permitted by local law.

NOTE: for participants who discontinue study intervention without disease progression, disease response assessments should continue at least Q4W (± 1 wk) until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, participant lost to follow up, death or defined end of study.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Completed;
- Study terminated by sponsor;

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data (apart from the collection of publicly available information as described in Section 7.2.1) should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the [SoA](#). Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the [SoA](#), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the [SoA A](#).

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the

investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

All disease responses will be assessed according to IMWG response criteria ([Appendix 10](#)) and entered on the CRF. All response categories (except stable disease) require 2 consecutive assessments (confirmation).

Disease assessments are to be conducted per [SoA A](#): 28 day (± 1 wk) interval whether dose given or not (ie, the 28-day interval [± 1 wk] between assessments should be maintained regardless of dose delays/interruptions).

Disease assessments should continue until confirmed PD, withdrawal of consent, start of new anticancer therapy, lost to follow-up, death, or defined end of study (whichever occurs first).

Efficacy data will be subjected to a BICR. An independent, external committee with expertise in myeloma will review data from site-sourced components of response assessment (eg, select laboratory assessments, select bone marrow pathology report data) and provide overall response assessments at different time points using IMWG response criteria, while remaining blinded to investigator-assessed responses as specified in the BICR Charter.

8.1.1. Laboratory Assessment for Evaluation of Disease Response

The following laboratory assessments will be performed locally for evaluation of disease response according to IMWG criteria ([Appendix 10](#)). Assessments are to be conducted at the time points specified in the [SoA A](#). Assessments will include:

- SPEP for the measurement of serum proteins, including M protein..
- SIFE for definitive identification of specific M proteins (including IgG, IgA, IgM, and kappa and lambda light chains). SIFE will be required at baseline, when SPEP shows no measurable protein, at suspected VGPR or CR/sCR and at suspected PD (clinical or biochemical).
- 24-hour UPEP for the measurement of urine M proteins. If any scheduled 24-hour UPEP is missed or is non-evaluable, a second attempt for collection of an evaluable specimen should be scheduled within 7 days of the missed assessment. For participants without measurable disease in the urine at baseline, UPEP is only required at suspected VGPR or CR/sCR, or at suspected PD (clinical or biochemical).
- 24-hour UIFE for definitive identification of specific M proteins (including IgG, IgA, IgM, and kappa and lambda light chains). UIFE will be required at baseline, when

UPEP shows no measurable protein, at suspected VGPR or CR/sCR and at suspected PD (clinical or biochemical).

- Involved and uninvolved serum FLC analysis, required only when both serum and urine M components are deemed nonmeasurable (including at suspected CR). Serum free kappa, free lambda and free kappa/lambda ratio will be collected.

Note: For participants treated with daratumumab less than 114 days prior to C1D1, daratumumab will interfere with SPEP, and SIFE. Therefore, for these participants, serum FLC assay should be completed at screening, C1D1, and along with all subsequent disease assessments. Serum M-protein (M-spike), if measurable at baseline, should also be followed at the same time points as serum FLC with the most representative marker of disease status used for IMWG assessment.

On days of elranatamab administration, all samples will be collected prior to dosing beginning at Cycle 2.

In participants with 2 M-protein bands at baseline, unless the second band is due to daratumumab or other therapeutic mAb interference, the sum of the 2 spikes should be used for monitoring of disease.

When PD (clinical or biochemical) is suspected, applicable tests (eg, SPEP, SIFE, UPEP, UIFE, serum FLC tests) should be repeated for confirmation prior to initiation of new anticancer therapy.

Note that if a participant had measurable serum or urine M-protein (M-spike) at baseline, unless the band is due to/confounded by the presence of daratumumab or other therapeutic mAb, PD cannot be defined by increases in serum FLC alone. Serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable or uninterpretable. Furthermore, careful attention should be given to new positive immunofixation results appearing in participants who have achieved a CR, when the isotype is different. This may represent oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.

8.1.2. Bone Marrow Sample Assessments for Evaluation of Disease Status

BM evaluations will be performed to follow disease status according to IMWG criteria ([Appendix 10](#)) at the time points specified in the [SoA A](#).

In addition, screening BMA samples will be evaluated locally by FISH (and karyotyping if an adequate sample is obtainable) to report chromosomal abnormalities, including but not limited to those defining high-risk MM [eg, t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q)].³² In the case of an unevaluable BMA sample, the most recent cytogenetic results available should be reported.

BMA samples will be collected and the percentage of plasma cells will be evaluated as per the [SoA A](#).

BMB/BMA samples will be collected as per [SoA A](#) to evaluate the percentage of plasma cells and in case of suspected sCR, to evaluate the presence/absence of clonal cells by immunohistochemistry, immunofluorescence, or flow cytometry analysis ([Appendix 10](#)). Either BMA or BMB can be used; however, the same method for quantifying plasma cells should be used for a participant throughout the study where feasible.

When BM plasma cell infiltration is assessed by both BMA and BMB, the highest value of plasma cell infiltration should be utilized for response evaluation.

The same BM location used for disease characterization at baseline should be employed in post-baseline BM sampling if clinically feasible.

When BMA/BMB samples are taken for response evaluation, samples for biomarker analysis will also be collected (see [Section 8.7](#)).

BMA obtained while a participant is in suspected or actual CR will be evaluated by a central lab for MRD using NGS (see [Section 8.7.1](#)).

All relevant reports must be available for source verification and for potential peer review (including BICR review).

8.1.3. Imaging Assessments (PET/CT, CT and/or MRI)

Imaging will be completed for evaluation of disease response according to IMWG criteria ([Appendix 10](#)) at the time points specified in the [SoA A](#). For participants with only skin involvement, skin lesions should be measured with a ruler at timepoints specified in the [SoA A](#).

Screening images will be used to determine evaluable target lesions for each participant. The same imaging technique should be used throughout the study (pre- and post-baseline assessments).

Bone lesions and any soft tissue plasmacytoma documented at baseline must undergo serial monitoring. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. Any plasmacytoma that has been irradiated will not be suitable for response assessment; however, it must be monitored for PD.

Measurement of lesion size will be determined by the SPD.

Imaging obtained per the participant's standard of care prior to study enrollment and signing of consent do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before start of study intervention, (2) the same technique can be used to follow identified lesions throughout the study for a given participant, and (3) appropriate documentation is available in the participant's source notes indicating that these assessments were performed as standard of care.

All participant's files and radiologic images must be available for source verification and for potential peer review (including BICR review).

8.1.4. Patient-Reported Outcomes

Whenever possible, the PROs should be completed at the beginning of the study visit prior to receiving any study intervention, prior to any other study assessment or consultation with the investigator, and prior to being informed of their current disease status. However, if it's not possible to complete the PROs at the beginning of the study visit, it is acceptable to have the participant complete the PROs before the end of the indicated study visit. The PROs will be administered at the time points specified in the [SoA A](#).

Cancer-specific global health status and quality of life, functioning, and symptoms data will be collected using the EORTC QLQ-C30 and MY20 questionnaires and general health status will be assessed using the EQ-5D health questionnaire. The EORTC QLQ CIPN20 assesses chemotherapy-induced peripheral neuropathy ³³.

EORTC QLQ-C30 is a well-known, reliable and valid self-administered questionnaire used in oncology trials.^{34,35} The QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, emotional, cognitive and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale. All the scales and single-item measures range in score from 0 to 100. Higher scores on the functional scales represent higher levels of functioning. Higher scores on the global health status/quality of life scale represent higher health status/quality of life. Higher scores on symptom scales/items represent a greater presence of symptoms.

The EORTC 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 can be grouped into a disease symptom subscale (6 items), side effects of treatment subscale (10 items), body image (1 item) and future perspective subscale (3 items).³⁶

The EQ-5D is a 6-item patient-completed questionnaire designed to assess health status in terms of a single index value or utility score. There are 2 components, a Health State Profile which has individuals rate their level of problems in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a VAS in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with lower scores representing higher levels of dysfunction. All scoring and handling of data will follow the User's Guide defined by the EuroQoL Group.

The EORTC QLQ CIPN20 is a module developed by the EORTC group to assess chemotherapy-induced peripheral neuropathy ³³. It contains 20 items which can be grouped into a sensory subscale (9 items), motor subscale (8 items) and autonomic subscale (3 items).

8.1.5. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's MM, including date of initial diagnosis, current stage (Table 5), relevant disease characteristics, and prior treatments including systemic therapy, radiation, and/or stem cell transplant will be recorded on the CRF. Best response and date of disease progression (as applicable) for each prior treatment regimen will be recorded.

Table 5. Staging Systems for Multiple Myeloma

| Stage | International Staging System (ISS) | Revised-ISS (R-ISS) |
|-------|--|--|
| I | Serum beta-2 microglobulin < 3.5 mg/L, Serum albumin ≥ 3.5 g/dL | ISS stage I and standard-risk chromosomal abnormalities by FISH ^a and Serum LDH < the upper limit of normal |
| II | Not ISS stage I or III | Not R-ISS stage I or III |
| III | Serum beta-2 microglobulin ≥ 5.5 mg/L | ISS stage III and either: <ul style="list-style-type: none"> high-risk chromosomal abnormalities by FISH^b or Serum LDH > the upper limit of normal |

a. Standard risk chromosomal abnormalities by FISH = no high-risk chromosomal abnormality.

b. High risk chromosomal abnormalities by FISH = Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)

Source: (Palumbo et al, 2015)³⁷.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the [SoA A](#). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs and demographic data collected at screening will be reported on the CRF.

8.2.1. Participant Demographics and Other Baseline Characteristics

Demographic data and medical history will be collected at screening by the investigator or qualified designee, including relevant medical and surgical history, and current illnesses.

8.2.2. Physical Examinations

Physical examinations will be performed at time points specified in the [SoA A](#). At screening, a comprehensive physical examination should be conducted including, general appearance, head, skin, neck, eyes, ears, nose, throat, mouth, lungs, heart, abdomen, lymph nodes, extremities, musculoskeletal, and a thorough neurologic examination (see below). For subsequent visits, physical examinations may be targeted as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Neurological examinations including assessment of mental state, motor function, sensory function, gait, deep tendon reflexes, cranial nerve function, station, and coordination will be performed at times specified in the [SoA A](#). All neurological examinations will be reported on the CRF.

All physical examinations, including neurological examinations, occurring on dosing days must be performed prior to elranatamab administration. Any treatment-emergent abnormal physical/neurological examination findings will be recorded as AEs.

Screening weight and height will be reported on the CRF.

Physical examination findings collected during the study (not including neurological examinations, see above) will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE ([Appendix 3](#)) must be reported according to the processes in Sections [8.3.1](#) to [8.3.3](#).

Baseline encephalopathy assessment will be performed using the ICE tool ¹ ([Appendix 11](#)) at C1D1. The ICE tool will also be used as part of assessing each suspected ICANS event.

8.2.3. Vital Signs

Vital signs (temperature, HR or pulse rate, BP and O₂ saturation) should be collected per institutional standards at time points specified in the [SoA A](#) prior to blood collection. Pre-dose vital signs collected on Day 1, Day 8, Day 15 and Day 22 of Cycle 1 should be reported on the CRF. Vital signs associated with AEs should be collected in the CRF. All other vital sign data collected during the course of the study will be considered source data only and will not be required to be reported on the CRF.

All vital sign measurements occurring on dosing days must be performed prior to elranatamab administration (and prior to premedication, as applicable). Abnormal vital sign results identified after the first dose of elranatamab constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy or require changes in elranatamab dosing.

Vital signs will be monitored at least every 4 hours (\pm 15 minutes) during the first 48 hours after first dose of study intervention (C1D1) and 24 hours after second dose of study intervention (C1D4) (see [Appendix 11](#)).

8.2.4. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the [SoA A](#) section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex duration. 15-lead or 18-lead ECGs per local practice is acceptable. For ECG machines that do not report QTcF, calculation of QTcF from QT and heart rate, for example using online tools, is acceptable. Alternative lead placement methodology using torso leads

(eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

A triplicate ECG (3 serial ECGs conducted within approximately 5 to 10 minutes total time) will be performed at all time points specified in the [SoA A](#). ECG will be performed prior to PK sample collection and elranatamab administration (and prior to premedication, as applicable). ECG assessments should be skipped if CRS symptoms are ongoing to avoid the confounding effects of CRS on ECG measurements. Additional ECGs should be performed as clinically indicated.

If mean QTcF is >500 msec, ECGs should be re-evaluated by a qualified person at the institution for confirmation. If a) the change in postdose QTcF interval remains ≥ 60 msec from the baseline and QTcF is >450 msec; or b) an absolute QTcF value is ≥ 500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

Abnormal findings reported by the ECG machine should be reviewed for accuracy by the investigator in order to decide if they are clinically significant. Any findings of clinical concern will also be reviewed by a cardiologist. New or worsened clinically significant findings in the ECG occurring after the informed consent must be recorded as an AE in the eCRF using [Appendix 7](#) as a guide. ECG tracings should be made available if requested by the sponsor.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in [Appendix 7](#).

8.2.5. Echocardiograms/Multigated Acquisition Scans

ECHO or MUGA will be performed at screening as specified in the [SoA A](#). If additional assessments are performed, the same method should be used throughout the study.

8.2.6. Clinical Safety Laboratory Assessments

See [Appendix 2](#) for the list of clinical safety laboratory tests to be performed and the [SoA A](#) for the timing and frequency. All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the [SoA A](#).

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the active AE reporting period (see Section 8.3.1) after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See [Appendix 6](#) for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

All safety laboratory tests will be performed locally.

8.2.7. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the [SoA A](#). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.8. ECOG Performance Status

ECOG PS ([Table 6](#)) will be assessed at Screening. ECOG PS should be obtained on the scheduled day, even if study intervention is temporarily discontinued.

Table 6. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

| | |
|---|---|
| 0 | Fully active, able to carry on all predisease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in [Appendix 3](#).

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 90 calendar days, except as indicated below, after the last administration of the study intervention. NOTE, as indicated in Section 8.3.1.2: If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

Only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to elranatamab.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in [Appendix 3](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 3](#).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow -up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section [7.3](#)).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in [Appendix 3](#).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental

exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
 - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by for example, inhalation, or skin contact.
 - A male family member or healthcare provider who has been exposed to the study intervention by for example, inhalation, or skin contact, then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until pregnancy completion (or until pregnancy termination).
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

CRS is a known toxicity of therapeutics that function by activation of immune effector cells. CRS is defined as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leakage causing hypoxia and end organ dysfunction. Symptoms associated with CRS vary greatly and may be difficult to distinguish from other conditions. The severity of symptoms can be mild to life threatening, thus there should be a high index of suspicion for CRS if these symptoms occur.

The severity of CRS will be assessed according to the ASTCT consensus criteria. See [Appendix 11](#).

For both the priming doses and first full dose (76 mg), premedication for CRS is required (See Section [6.8.1](#)).

ICANS is a known toxicity of therapeutics that function by activation of immune effector cells. ICANS is defined as “a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema”.¹ It has been observed following administration of some CAR T-cells and BsAbs, and can occur independently of CRS.

The severity of ICANS will be graded according to the ASTCT consensus criteria. See [Appendix 11](#).

Adverse events of special interest (AESIs) are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections [8.3.1](#) through [8.3.4](#). An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

Additional management for Grade ≥ 3 CRS and ICANS is described in Section [9.4.1](#).

8.3.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

| Safety Event | Recorded on the CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|---------------------|---|---|
| Medication errors | All (regardless of whether associated with an AE) | Only if associated with an SAE |

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.3.11. Peripheral neuropathy

Peripheral neuropathy is a common complication of MM and its treatment. Peripheral neuropathy can be caused by MM itself, either by the paraneoplastic effects of the monoclonal protein (polyneuropathy is an essential feature of POEMS syndrome) or in the form of radiculopathy from direct compression, and particularly by certain therapies, including IMiDs and proteasome inhibitors. Symptoms are usually symmetric and include paresthesias, numbness, burning sensation and muscle weakness; these are generally mild, but in rare cases can be disabling or even life-threatening. Treatment-emergent peripheral neuropathy symptoms are usually symmetric, distal and progressive³⁸. Recently, peripheral neuropathy has been described following administration of BCMA-directed bispecific T-cell engagers²⁵.

Peripheral neuropathy (including GBS) is considered an important potential risk of elranatamab.

Work-up for new or worsening Grade ≥ 2 peripheral neuropathy should include a neurology consult, imaging (eg MRI of the spine), NCV/EMGs, and lumbar puncture to assess CSF. In consultation with a neurologist, appropriate therapy for peripheral neuropathy (eg, steroids and/or IV immunoglobulin) should be considered.

Closely monitor participants for signs and symptoms of neuropathy following infections or following the administration of any vaccine.

8.4. Pharmacokinetics

All participants will have blood samples collected for PK assessments of elranatamab serum concentrations at the time points specified in the [SoA A](#). In the event of suspected CRS, unexpected or serious AE, or AE leading to discontinuation of study intervention, additional PK samples should be collected if not already scheduled. Additionally, participants enrolled into Phase 1b and approximately 6 participants from Phase 2 will undergo a relatively intensive sampling for PK as specified in [SoA B](#).

The actual date/time of sample collection should be documented in the CRF. For each time point, blood samples of approximately 5 mL, to provide approximately 2 mL of serum, will be collected for measurement of serum concentrations of elranatamab. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of PK sample collection as well as the date and time of the last dose prior to PK sample collection for each sample will be recorded in the CRF.

The actual times may change, but the number of samples will remain the same. All effort should be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the visit window specified in the [SoA](#) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the CRF. For predose PK samples, collection should occur prior to administration of elranatamab on that day. If the C1D4 dose (32 mg) can only be administered after the protocol-defined window, the planned C1D4 pre-dose PK/PD sample should be collected at any time within the C1D4 visit window.

Samples will be used to evaluate the PK of elranatamab. Each serum sample will be divided into 2 aliquots, to provide approximately 1 mL serum for each aliquot. Samples collected for analyses of elranatamab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study and/or evaluation of the bioanalytical method.

Samples collected for measurement of elranatamab concentrations will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Refer to the lab manual for detailed collection, processing and shipping procedures.

8.5. Pharmacodynamics

Pharmacodynamics samples will be at the time points specified in the [SoA](#).

As part of understanding the pharmacodynamics of elranatamab, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data may not be included in the CSR.

Some samples may be analyzed using a validated analytical method in compliance with applicable SOPs while others may be analyzed using a non-characterized assay (non-validated). The pharmacodynamics samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the pharmacodynamics sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.5.1. Blood to Assess sBCMA Levels

A whole blood sample, to provide plasma for sBCMA assessment, will be collected at the times specified in the [SoA](#) (for pre-dose samples, collection should occur prior to administration of elranatamab on that day). An additional plasma sample for sBCMA assessment should also be collected at the time of PD if a sample is not already scheduled to be taken. Collection of samples up to and including 24 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, 36 minutes for the 6-hour post-dose time point and 2 hours and 24 minutes for the 24-hour post-dose time point) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the CRF. Instructions for sample collection, processing, storage and shipment will be provided in the study manual. sBCMA levels will be measured in plasma at baseline and at various time points during study treatment, which may enable correlations between sBCMA levels and drug exposure and response.

8.6. Genetics

8.6.1. Specified Genetics

Unless prohibited by local regulations or ethics committee decision, genetic assessments will be performed utilizing BMA, blood and/or saliva samples as described in the [SoA A](#).

Please refer to relevant subsections in Section 8.7.

8.6.2. Banked Biospecimens for Genetics

No banked biospecimens will be collected according to China regulation.

8.7. Biomarkers

Unless prohibited by local regulations or ethics committee decision, the following samples for biomarker research are required and will be collected from all participants in this study as specified in the [SoA](#).

8.7.1. Bone Marrow Aspirate for Minimal Residual Disease (MRD)

A BMA sample will be taken at the time points specified in the [SoA A](#). Next-generation sequencing of the sample taken predose identifies rearranged immune receptors (eg, IgH, IgK, and IgL receptor gene sequences), as well as select translocation sequences. This unique immunoglobulin receptor repertoire defines the patient-specific malignant plasma cell clone (the index clone) and is used as a reference that is compared to subsequent samples collected after initiation of treatment. BMA samples will be used to determine the MRD negativity rate with a threshold of 10^{-5} whenever a BMA/BMB sample is taken for disease response evaluation.

At screening, if a freshly collected BMA sample is not available for identification of the dominant malignant myeloma clone, the sponsor may request an additional BMA sample from the site **as long as they were collected after last pre-trial therapy and prior to C1D1 (ie, no intervening treatment between collection and C1D1).**

If the central lab is unable to identify an index malignant myeloma clone with the on-treatment sample, the sponsor may request an additional BMA sample from the site.

8.7.2. Bone Marrow Aspirate for Molecular Profiling

A BMA sample will be collected at the times specified in the [SoA A](#), and will be used to analyze candidate DNA, RNA, or relevant signature of markers for their ability to identify those participants who are most likely to benefit from treatment with the study drug. Participants will be required to provide BMA samples whenever a sample is taken for disease response evaluation.

RNA and DNA sequencing analysis will be performed and the data will be used to examine correlations between gene mutation status and gene expression signatures with response. As samples will be collected while participants are on treatment and at EOT, this analysis may also reveal biomarkers that correlate with resistance and relapse.

8.7.3. Bone Marrow Biopsy to Assess BCMA and/or Immune Cell Protein Biomarkers

A BMB may be collected at the times specified in the [SoA A](#). BMB sample may be taken at suspected PD). This sample will be used for IHC, immunofluorescence or multiplex imaging assays to enumerate and assess the distribution of a range of markers implicated in MM (eg, BCMA, CD138, CD38, immune cell populations).

8.7.4. Cytokine Assessments

Samples will be collected for central evaluation of cytokines at the time points specified in the [SoA A](#) and [Appendix 2](#) unless prohibited by local regulation. Instructions for sample collection, processing, storage and shipment will be provided in the study manual. All samples will be analyzed centrally. If CRS is suspected and coincides with a day pharmacodynamic samples are not collected per the [SoA](#), an ad-hoc cytokine sample should be collected (see [Appendix 2: Clinical Laboratory Tests](#)). In addition, should the site require

cytokine information for participant management, the site will have the option of collecting an additional sample for local analysis.

8.7.5. Serum to Assess Circulating Proteins and Metabolite Analysis

A blood sample will be collected at time points specified in the [SoA A](#) (for predose samples, collection should occur prior to administration of elranatamab on that day). This sample will be used for circulating protein and/or metabolomics analysis. This sample may also be used for additional research based on emerging knowledge of MM biology. See Section [8.5.1](#) for post-dose collection window guidance.

8.7.6. Blood for T-cell Receptor (TCR) Sequencing

A blood sample will be collected from all participants at the time points described in the [SoA A](#) (for predose samples, collection should occur prior to administration of elranatamab on that day). This sample will be used to assess the clonality, diversity and pharmacodynamics of the peripheral blood TCR repertoire.

8.7.7. Blood or Saliva Sample for Germline Comparator

Unless prohibited by local regulations or ethics committee decision, a blood or saliva sample will be collected from all participants on Cycle 1 Day 1 before the first dose of elranatamab, and will be used for exploratory targeted and/or whole exome/genome sequencing. These samples will be used as a germline comparator to identify somatic tumor DNA mutations and will not be used to generate free-standing germline sequencing results.

Specified metabolomic research is not included in this study.

8.8. Immunogenicity Assessments

Blood samples of approximately 5 mL, to provide a minimum of 2 mL serum, will be collected for determination of ADA and NAb into appropriately labeled tubes at times specified in the [SoA A](#).

Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Participants having an unresolved AE that is possibly related to anti-elranatamab antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration blood sampling at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

Samples collected for determination of ADA and NAb may also be used internally for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

As part of understanding the immunogenicity of the investigational product, samples may be used for evaluation of the bioanalytical method and/or additional characterization of an observed immunogenicity response. These data will be used for internal exploratory purposes and will not be included in the CSR.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in an SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

The Phase 2 part will test the null hypothesis (H_0) that the ORR by BICR as defined by IMWG is $\leq 30\%$ versus the alternative hypothesis (H_a) that the ORR by BICR as defined by IMWG is $> 30\%$ using a single-stage design based on the exact binomial distribution. The null hypothesis ORR is based on the results of the DREAMM-2 study³ and the STORM study,⁴ which were conducted in similar multiple myeloma populations with respect to prior treatments.

9.1.1. Estimands

This section defines the estimand associated with the primary endpoint of the study.

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

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention in Phase 1b part and either experience DLT(s) during the DLT

observation period or complete the DLT observation period without DLT. Participants without DLTs who receive less than the minimum requirement of the planned doses of study intervention for reason other than treatment-related toxicity are not evaluable for DLTs and will be replaced. The minimum required exposure for DLT evaluability is 4 out of 5 planned doses of elranatamab during the DLT observation period.

- Variable: Occurrence of DLTs. DLTs are defined in Section 4.3.1.
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants.

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

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least 1 dose of study intervention.
- Variable: objective response defined as confirmed sCR, CR, VGPR and PR according to the IMWG criteria based on BICR assessment, from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first.
- Intercurrent event(s): All data collected after an intercurrent event of subsequent anticancer therapy will be excluded except if required to confirm PD. All response assessments regardless of gaps in disease assessments will be considered. Data will be collected regardless of discontinuation from treatment. Participants who do not have a post-baseline disease assessment due to early confirmed PD, who receive anticancer therapies other than the study intervention prior to achieving an objective response, or who die, experience confirmed PD, or stop disease assessments for any reason prior to achieving an objective response will be counted as nonresponders in the assessment of objective response.
- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an objective response and 2-sided 95% CI for ORR.

9.2. Analysis Sets

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

| Participant Analysis Set | Description |
|--------------------------|---|
| Safety Analysis Set | All participants enrolled to study intervention and who take at least 1 dose of study intervention. |

| Participant Analysis Set | Description |
|-----------------------------|--|
| DLT Evaluable Analysis Set | All participants enrolled to phase 1b part and who have experienced a DLT in the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who received less than minimum requirement of the planned doses of elranatamab for reason other than treatment-related toxicity are not evaluable for DLTs and will be replaced. The minimum required exposure for DLT evaluability is 4 out of 5 planned doses of elranatamab during the DLT observation period, provided a dose was not missed due to toxicity attributed to study drug. |
| PK Analysis Set | The PK analysis set is a subset of the safety analysis set and will include participants who have at least one concentration measurement. |
| Immunogenicity Analysis Set | The immunogenicity analysis set is a subset of the safety analysis set and will include participants who have at least one sample tested for ADA. |
| Biomarker Analysis Set | The biomarker parameter analysis set is a subset of the safety analysis set and will include participants who have at least one baseline biomarker assessment. Analysis sets will be defined separately for biomarkers based on blood, saliva, and bone marrow aspirate samples. |
| PRO Analysis Set | The PRO analysis set will include all participants in the safety analysis set who completed a baseline and at least one post-baseline PRO assessment. |

Note: "Enrolled" means a participant's, agreement to participate in a clinical study following completion of the informed consent and was assigned to treatment. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

The study will include 2 parts: a Phase 1b part to establish the safety profile to confirm the RP2D in Chinese participants and a Phase 2 part to determine the efficacy and safety of elranatamab in Chinese participants. Efficacy and safety analyses will be conducted on the

safety analysis set. Sensitivity analysis will be performed to evaluate the impact of COVID if deemed necessary.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages. The time-to-event variables will be summarized using Kaplan-Meier methods and displayed graphically if applicable. The median, percentile and probabilities at particular time points will be estimated.

Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

9.3.2. Primary Endpoint(s)

- DLT is the primary endpoint of the Phase 1b part. The occurrence of DLTs observed in this part will be used to estimate the DLT rate and confirm the RP2D in Chinese participants. DLT rate will be summarized in the DLT evaluable analysis set. Adverse events constituting DLTs will be listed.
- Objective response defined as confirmed sCR, CR, VGPR and PR according to the IMWG criteria based on BICR assessment, from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first, is the primary endpoint of the Phase 2 part.

ORR by BICR is defined as the proportion of participants with an objective response by BICR per IMWG criteria, and will be analyzed in the safety analysis set. The primary analysis of ORR will include participants who started from the RP2D (including the participants from both Phase 1b and Phase 2 parts). The point estimate of ORR by BICR will be calculated along with the 2-sided exact 90% and 95% CIs using the Clopper-Pearson method. The null hypotheses will be tested at 1-sided alpha of 0.05 using exact binomial test.

9.3.3. Secondary Endpoint(s)

All secondary efficacy endpoints will be analyzed in the safety analysis set.

9.3.3.1. Secondary Efficacy Endpoints

ORR by investigator is the proportion of participants in the analysis population with an objective response as assessed by investigator. Point estimates of ORR by investigator will be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method.

CRR is the proportion of participants in the analysis population with a CR/sCR according to the IMWG criteria. Point estimates of CRR will be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method.

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

DOR is defined, for participants with an objective response per IMWG criteria, as the time from the first documentation of objective response that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. DOR will be censored on the date of the last adequate disease assessment for participants who do not have an event (confirmed PD or death due to any cause), on the date of the last adequate disease assessment before the new anticancer therapy for participants who start a new anticancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments. DOR will be summarized using Kaplan-Meier method and displayed graphically. Median DOR by BICR and 2-sided 95% CI (based on the Brookmeyer-Crowley method) will be provided.

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

DOCR is defined, for participants with a CR/sCR per IMWG criteria, as the time from the first documentation of CR/sCR that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. DOCR will be censored on the date of the last adequate disease assessment for participants who do not have an event (confirmed PD or death due to any cause), on the date of the last adequate disease assessment before the new anticancer therapy for participants who start a new anticancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments. DOCR will be summarized using Kaplan-Meier method and displayed graphically. Median DOCR and 2-sided 95% CI will be provided.

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

PFS is defined as the time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause, whichever occurs first. PFS will be censored on the date of the last adequate disease assessment for participants who do not have an event (confirmed PD per IMWG criteria or death due to any cause), on the date of the last adequate disease assessment before the new anticancer therapy for participants who start a new anticancer therapy prior to an event, or on the date of the last adequate disease assessment before the gap for participants with an event after a gap of 2 or more missing disease assessments. Participants who do not have an adequate post-baseline disease assessment will be censored on the date of first dose 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. PFS will be summarized using Kaplan-Meier method and displayed graphically. Median PFS and 2-sided 95% CI will be provided.

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

OS is defined as the time from the date of first dose until death due to any cause. Survival status is expected to be collected irrespective of study intervention discontinuation or participant's request to discontinue study procedures. All participants who have not withdrawn consent for further participation in the study should be followed for survival until

the end of the study. OS for participants not known to have died are censored on the date of they are last known alive. OS will be summarized using Kaplan-Meier method and displayed graphically. Median OS and 2-sided 95% CI will be provided.

TTR is defined, for participants with an objective response per IMWG criteria, as the time from the date of first dose to the first documentation of objective response that is subsequently confirmed. TTR will be summarized using mean, standard deviation, minimum, median, and maximum.

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

MRD negativity rate is the proportion of participants with negative MRD (assessed by central lab) per IMWG sequencing criteria by BMA from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy. Point estimates of MRD negativity rate will be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method.

9.3.3.2. Pharmacokinetic Analyses

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

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

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

For participants with sparse PK sampling only (all rest participants from phase 2), pre-dose and post-dose trough elranatamab concentrations will be summarized descriptively by cycle.

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

9.3.3.3. Immunogenicity Analyses

For immunogenicity data, the percentage of participants with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and after first dose will be generated. Samples may also be analyzed for the presence of NAb, and any data

will be similarly summarized. For participants with positive ADA or NAb, the magnitude (titer), time of onset, 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.

9.3.3.4. Safety Analyses

All safety analyses will be performed in the safety analysis set.

9.3.3.4.1. Adverse Events

AEs (except CRS and ICANS) will be graded by the investigator according to NCI CTCAE v5.0 and coded using MedDRA. CRS and ICANS will be assessed by the investigator according to the ASTCT criteria described by Lee et al 2019¹ (See Section 10.11) and coded using MedDRA. AEs will be characterized by type, frequency, severity, timing, seriousness, and relationship to elranatamab. AEs will be presented with and without regard to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described. Additional summaries will be provided for AEs that are observed with higher frequency and for AESIs identified in Section 8.3.8, including CRS and ICANS.

9.3.3.4.2. Laboratory Test Abnormalities

Clinical laboratory data will be classified by grade according to NCI CTCAE version 5.0 and will be analyzed using summary statistics. The worst on-treatment grades during the treatment period will be summarized. Shifts in toxicity grading from baseline to highest grade during the on-treatment period will be displayed. Results for laboratory tests that are not part of NCI CTCAE will be presented as below, within, or above normal limits. Only participants with post-baseline laboratory values will be included in these analyses. Further details of analyses for all the laboratory parameters will be provided in the SAP.

9.3.3.5. Electrocardiogram Analyses

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

Safety QTcF Assessment

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

9.3.4. Exploratory Endpoint(s)

The details of exploratory endpoint (DNA, RNA, plasma sBCMA level, protein or defined cell types) analyses will be described in the SAP. The details of exploratory correlation between elranatamab exposure and efficacy, safety and PD/biomarker endpoints, if performed, will be described and reported separately in PMAPs/PMARs.

Results from exploratory analyses will be reported in the CSR where possible. However, given the exploratory nature of the objective and endpoints, the analyses may not be completed at the time of CSR preparation. If results of exploratory endpoint analyses cannot be included in the CSR, they will be disseminated as appropriate to the scientific community through presentation at scientific meetings and/or publication in peer-reviewed scientific journals.

9.3.5. Other Analyse(s)

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

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

9.4.1. Interim Safety Assessments

The sponsor will review cumulative safety data during the study conduct. In addition, the incidence of Grade 3-4 CRS, Grade 3-4 ICANS, and Grade 4 treatment related nonhematologic events (excluding CRS and ICANS), Grade 3-4 treatment-related GBS/GB-like AEs, Grade 3-4 treatment-related peripheral motor neuropathy, Grade 4 treatment-related peripheral neuropathy/immune-related (IR) neurologic events, and Grade 5 events will each be monitored by the sponsor throughout the study. If the number of participants observed to have such identified events exceeds a prespecified threshold, the study will be placed on a temporary enrollment hold for sponsor's further assessment. (See Section 10.1.9). During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. Participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the investigator in consultation with the sponsor.

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

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

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

Table 7. Minimum Number of Participants With Identified Events That Would Prompt Temporary Enrollment Hold

| Number of Evaluable Participants (Phase1b+2) | 6 | 7-9 | 10-13 | 14-18 | 19-22 | 23-26 | 27-30 | 31-35 | 36 |
|--|---|-----|-------|-------|-------|-------|-------|-------|----|
| Minimum number of participants with Grade 3-4 CRS events that would lead to a temporary enrollment hold* | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Minimum number of participants with Grade 3-4 ICANS events that would lead to a temporary enrollment hold* | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 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 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

Prior distribution: Beta (0.5,0.5)

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

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

* The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, if there are 3 participants experiencing the identified AE out of the first 6 evaluable participants, the study will be put on hold).

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

- If the number of evaluable participants observed to have 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 (Phase 1b+2) | 17-36 ^a | | | | |
|--|--------------------|-------|-------|-------|-----------------|
| 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 (Phase 1b+2) | 6-11 | 12-19 | 20-27 | 28-35 | 36 ^b |
| Minimum number of participants with Grade 4 treatment-related sensory neuropathy /IR neurologic AE (excluding ICANS) or Grade 3-4 treatment-related motor neuropathy events that would lead to a temporary enrollment hold** | 2 | 3 | 4 | 5 | 6 |

Prior distribution: Beta (0.5,0.5)

a. Criteria for 36+ or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 3% is ≥ 0.80 .

b. Criteria for 36+ or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 10% is ≥ 0.80 .

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

*The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, if there are 2 participants experiencing the identified AE out of the first 17 evaluable participants, the study will be put on hold). Before the number of evaluable participants reaches 17, if there are 2 participants experience the identified AE then the study will be put on temporary hold. In other words, as long as 2 participants with identified AE are observed the study will be put on temporary hold regardless of the number of evaluable participants at the time. 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 AE out of the first 5 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,
- 1 Grade 5 event of ICANS,
- 1 Grade 5 treatment-related peripheral neuropathy or IR neurologic event,
- Any 2 treatment-related Grade 5 events (excluding CRS and ICANS and peripheral neuropathy/IR neurologic event).

9.5. Sample Size Determination

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

The primary objective of the Phase 1b part is to establish the safety of elranatamab in order to confirm the RP2D in Chinese participants. There will be no formal hypothesis testing in this part. DLT will be evaluated. If $<1/3$ DLT observed in the first 6 evaluable participants treated from monotherapy RP2D, the study will proceed to Phase 2 part. Otherwise, a lower dose level will be evaluated. Approximately 6 participants will be enrolled and treated in Phase 1b. All the analyses will be descriptive.

In the FIP Study C1071001, as of data-cutoff date 07 September 2020, there were 15 participants who achieved an objective response among the 20 participants who were treated at dose level ≥ 215 ug/kg. The ORR was 75% with the 95% exact CI (51%-91%). Therefore, it is assumed that the true ORR with elranatamab will be $\geq 51\%$. A total of 36 participants will be contributed to the hypothesis testing, which includes the participants enrolled and treated in Phase 2 and those participants who started from the confirmed RP2D in Phase 1b. The sample size will provide 80% power to reject the null hypothesis at a 1-sided significance level of 0.05 assuming the true ORR is $\geq 51\%$.

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

The 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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or

www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs and SAPs. Clinical documents will have personally identifiable information anonymized.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not

be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow

the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the clinical monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit. The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or the sponsor's designee (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the [SoA A](#) section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

In addition to safety laboratory tests, serum beta-2 microglobulin is also required.

Table 9. Protocol Required Safety Laboratory Assessments

| Hematology | Chemistry | Other |
|---|---|---|
| <ul style="list-style-type: none"> • Hemoglobin • Platelet count • WBC count <p>Absolute*:</p> <ul style="list-style-type: none"> • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes • Plasma cell count <p>(*Reported in percent if absolute values are not available. Results will be reported as absolute values after conversion and graded according to the CTCAE v5 criteria)</p> | <ul style="list-style-type: none"> • BUN (or blood urea) • Creatinine • Glucose (non-fasting) • Calcium (total) • Sodium • Potassium • Chloride • Total CO₂ (bicarbonate)^a • AST, ALT • Total bilirubin • Alkaline phosphatase • Albumin • Total protein • Lactate dehydrogenase (LDH)^b • Uric acid^b • Serum beta-2 microglobulin^{b d} | <ul style="list-style-type: none"> • PT/INR • Pregnancy test (β-hCG)^c • IL-6, IL-10, IL-2, sIL-2R, IL-12, IL-4, IL-5, IL-13, IL-17, IL-1b, IL-8, IFNγ, and TNF-α <p>Optional Ad hoc Local Lab Cytokine Analysis^a</p> <ul style="list-style-type: none"> • IL-6, IL-10, IL-1β, TNF-α, other cytokines per local practice • Serum quantitative immunoglobulins (IgG, IgM, IgA, IgD, IgE).^e • CMV testing (by quantitative PCR), every 1 to 3 months depending on risk factors (see Appendix 12) |

- Not required if not included in the chemistry panel at the site laboratory. Investigators will follow up per standard of care of the institution (eg, blood gas analysis) if warranted by required laboratory test results.
- At baseline (minimum), and as clinically indicated.
- For female participants of childbearing potential only. Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL.
- Required for multiple myeloma staging.
- IgD or IgE, if they are available at the site, only if the heavy chain component of the disease is known to be IgE or IgD.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

| AE Definition |
|--|
| <ul style="list-style-type: none"> • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |

| Events <u>Meeting</u> the AE Definition |
|---|
| <ul style="list-style-type: none"> • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE: <ul style="list-style-type: none"> • Is associated with accompanying symptoms. • Requires additional diagnostic testing or medical/surgical intervention. • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. • Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |

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Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the [Assessment of Severity](#) section).

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

| Safety Event | Recorded on the CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|--|---|--|
| SAE | All | All |
| Nonserious AE | All | None |
| Exposure to the study intervention under study during pregnancy or breastfeeding | All AEs/SAEs associated with exposure during pregnancy or breastfeeding Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF. | All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). ** |
| Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB). | None. Exposure to a study non-participant is not collected on the CRF. | The exposure (whether or not there is an associated AE or SAE) must be reported.*** |

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Severity

The investigator will make an assessment of severity for each AE reported during the study and assign it to 1 of the following categories listed below (as defined by the NCI CTCAE system). An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

| GRADE | Clinical Description of Severity |
|-------|---|
| 1 | MILD AE |
| 2 | MODERATE AE |
| 3 | SEVERE AE |
| 4 | LIFE-THREATENING; urgent intervention indicated |
| 5 | DEATH RELATED TO AE |

The severity of CRS and ICANS will be graded according to ASTCT criteria.¹ See [Appendix 11](#).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

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A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥ 100 -fold between the estimated maternal exposure due to seminal transfer and the estimated MABEL used as conservative estimate of exposure that may result in serious manifestations of developmental toxicity.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion No. 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of $< 1\%$ per year), as described below, during the intervention period and for at least 5 months after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing and Non-Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
 - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
 - A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.

5. Vasectomized partner:

- Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

- Oral;
- Intravaginal;
- Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

- Oral;
- Injectable.

8. Sexual abstinence:

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The results of genetic analyses may be reported in CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
 - Samples for specified genetic analysis (see [Section 8.6.1](#)) will be stored for up to 15 years or other period as per local requirements beyond the completion of this study (eg, CSR finalization).
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors”. In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above $3 \times \text{ULN}$ should be monitored more frequently to determine if they are an “adaptor” or are “susceptible”.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
 - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

| ECG Findings That <u>May</u> Qualify as AEs |
|---|
| <ul style="list-style-type: none"> • Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes. |
| ECG Findings That <u>May</u> Qualify as SAEs |
| <ul style="list-style-type: none"> • QTcF prolongation >500 ms. • New ST-T changes suggestive of myocardial ischemia. • New-onset left bundle branch block (QRS >120 ms). • New-onset right bundle branch block (QRS >120 ms). • Symptomatic bradycardia. • Asystole: <ul style="list-style-type: none"> • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node; • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer; • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. • Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute). • Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)). • Type II second-degree (Mobitz II) AV block. |

- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as “alerts” or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic in China and will become effective for other public emergencies only upon written notification from Pfizer. Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Eligibility

While SARS-CoV-2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if he/she has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV-2. Participants with active infections are excluded from study participation as per Exclusion Criteria (Section 5.2). When the infection resolves, the participant may be considered for re-screening.

10.8.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow-up on the safety of study participants at scheduled visits per the [Schedule of Activities](#) or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments may be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to [Appendix 4](#) and Section 10.8.3.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.8.3. Alternative Facilities for Safety Assessments

10.8.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory: see [Appendix 2](#) for a list of safety laboratory evaluations, including pregnancy testing.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.8.3.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results. The ECG may be repeated if lead placements are reversed or incorrect.

10.8.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

The following is recommended for the administration of study intervention for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV-2 infection:

- For symptomatic participants with active SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV-2 -related symptoms should have recovered to \leq Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.

- Continue to consider potential drug-drug interactions as described in Section 6.8 for any concomitant medication administered for treatment of SARS-CoV-2 infection.

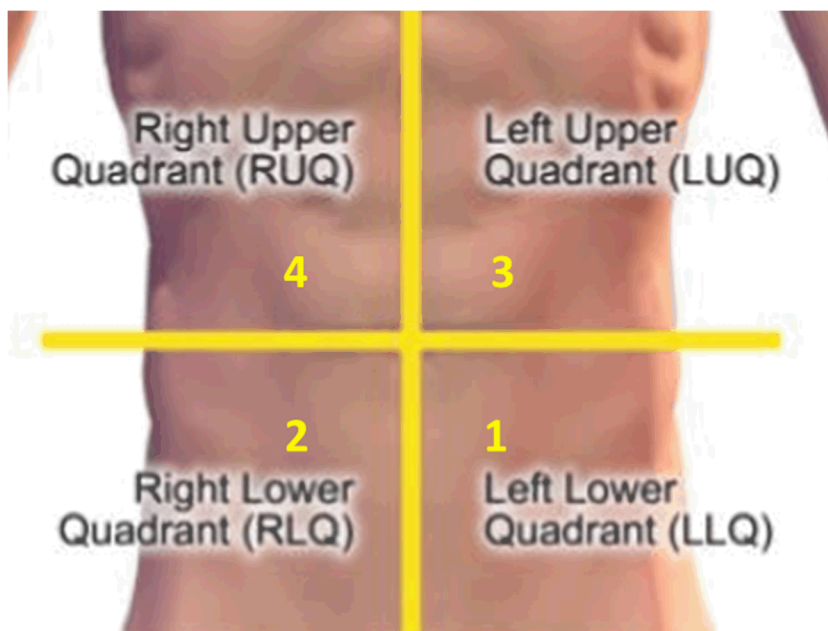
10.8.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided.

Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the medical monitor.

10.9. Appendix 9: Subcutaneous Injection Site Locations



Injection site locations include a maximum of 4 unique administration sites distributed across the 2 lower and the 2 upper abdominal quadrants (up to 1 injection location per quadrant).

Administer the required number of injections in the following order:

1. Left lower quadrant
2. Right lower quadrant
3. Left upper quadrant
4. Right upper quadrant

Injections to the abdomen are preferred. If SC injections in the abdominal location are not possible, SC injections can be administered in a distributed manner in the thighs. SC injections in the upper extremities (eg, deltoid, upper and lower arm) are not permitted.

Track the participant's injection site(s) sequentially on this diagram with a pen and mark the injection sites on the participant's abdomen according to your clinic's standard practice.

Record the location, time of each injection and any injection site reactions in the participant's source records and study CRF. Complete one CRF per injection. See Section 10.3 for AE reporting.

10.10. Appendix 10: IMWG Response Criteria for Multiple Myeloma

Participants must have measurable disease at enrollment (study entry) as defined by:

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

Whenever more than 1 parameter is used to assess response, the overall assigned level of response is determined by the lowest level of response.

All response assessments will be entered on the CRF.

All response categories require 2 consecutive assessments made any time before starting new therapy. To confirm response or PD, 2 discrete samples are required and testing cannot be based upon the splitting of a single sample.

| Response ^a | Modified IMWG Criteria |
|-----------------------------------|---|
| Stringent Complete Response (sCR) | <p>CR as defined below plus:</p> <ul style="list-style-type: none"> • Normal serum FLC ratio and absence of clonal cells in BMB/BMA by immunohistochemistry, immunofluorescence, or flow cytometry.^{b,c} • If the only measurable disease is by serum FLC levels, sCR is defined as normal serum FLC ratio of 0.26 to 1.65 plus absence of clonal cells in BMB/BMA by immunohistochemistry, immunofluorescence, or flow cytometry.^{b,c} |
| Complete Response (CR) | <ul style="list-style-type: none"> • Negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and $<5\%$ plasma cells in BMA.^{b,d} • If the only measurable disease is by serum FLC levels, CR is defined as normal serum FLC ratio of 0.26 to 1.65 plus criteria listed above.^{b,d} |
| Very Good Partial Response (VGPR) | <ul style="list-style-type: none"> • Serum and urine M-protein detectable by immunofixation but not on electrophoresis. OR • $\geq 90\%$ reduction in serum M-protein plus urine M-protein level <100 mg/24 h. • If the only measurable disease is by serum FLC levels, VGPR is defined as a $\geq 90\%$ decrease in the difference between involved and uninvolved serum FLC levels. • In addition to these criteria, if present at baseline, a $>90\%$ reduction compared with baseline in the size (SPD) of soft tissue plasmacytomas.^d |

| Response ^a | Modified IMWG Criteria |
|---|---|
| Partial Response (PR) | <ul style="list-style-type: none"> • $\geq 50\%$ reduction of serum M-protein and reduction in 24 hours urinary M-protein by $\geq 90\%$ or to < 200 mg/24 h. • If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved serum FLC levels is required in place of the M-protein criteria. • In addition to these criteria, if present at baseline, a $\geq 50\%$ reduction in the size (SPD) of soft tissue plasmacytomas is also required.^d |
| Minimal Response (MR) | <ul style="list-style-type: none"> • $\geq 25\%$ but $\leq 49\%$ reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to these, if present at baseline, a $\geq 50\%$ reduction in the size (SPD) of soft tissue plasmacytomas is also required.^d |
| No Change/Stable Disease (SD) | <ul style="list-style-type: none"> • Not meeting criteria for sCR, CR, VGPR, PR, MR or PD. |
| Progressive Disease (PD) ^{b,e,f} | <p>Any one or more of the following criteria:</p> <ul style="list-style-type: none"> • Increase of $\geq 25\%$ from lowest confirmed response value in any 1 or more of the following:^{e,f} <ul style="list-style-type: none"> • Serum M-component (the absolute increase must be ≥ 0.5 g/dL); • Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; • Urine M-protein (the absolute increase must be ≥ 200 mg/24 h). • In participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved serum FLC levels (absolute increase must be > 10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved serum FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be $\geq 10\%$) • Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD of > 1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion > 1 cm in short axis.^d • $\geq 50\%$ increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease |

a. All response categories require 2 consecutive assessments made any time before starting new therapy. Each category (except stable disease) will be considered unconfirmed until confirmatory test is performed. All categories (stable disease or better) require no known evidence of PD, new bone lesions or EM plasmacytomas if imaging studies were performed; imaging studies are not required to satisfy these response requirements except for requirement of FDG PET to confirm imaging plus MRD-negative.

b. Bone marrow assessments do not need to be confirmed. Careful attention should be given to new positive immunofixation results appearing in participants who have achieved a CR, when the isotype is different. This often represents oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.

| Response ^a | Modified IMWG Criteria |
|--|---|
| c | Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by IHC or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of $>4:1$ or $<1:2$. |
| d | Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or dedicated CT scans where applicable. Measurement of tumor size will be determined by the SPD. |
| e | PD confirmation requires 2 consecutive assessments made at any time prior to the institution of any new anticancer therapy. Participants will be considered to have PD if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for participants who had a measurable serum or urine M-spike at baseline, PD cannot be defined by increases in serum FLC alone. |
| f | For PD, serum M-component increases of ≥ 1 mg/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL. |
| Source: Adapted from Kumar et al, 2016 ²⁶ | |

10.11. Appendix 11: CRS and ICANS Grading, Mitigation, and Management

10.11.1. Cytokine Release Syndrome

Participants are required to be hospitalized and monitored for CRS/ICANS for at least 2 days (~48 hours) beginning on C1D1, and for 1 day (~24 hours) for C1D4. Hospitalization up to 5 days from C1D1 to C1D5 may be considered. (see Section 6.1.1).

For both the priming doses and first full dose (76 mg), premedication for CRS is required (see Section 6.8.1).

CRS is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation. CRS is a potentially life-threatening toxicity that has been observed following administration of immune-based therapies for cancer (antibodies and adoptive T-cell therapies). CRS is likely to be a common toxicity that can be managed through supportive care and anti-cytokine interventions.

In cases of suspected CRS, a serum sample should be provided for cytokine release assay analysis by the local lab as long as the sampling does not interfere with the medical treatment of the participant. If CRS is suspected, additional blood samples should also be collected for central cytokine analysis if not already scheduled.

Early intervention should be undertaken at the first sign of CRS; signs may include pyrexia, tachycardia, tachypnea and/or hypotension, and are temporally related to elranatamab in the absence of alternative etiologies.

CRS grading will follow ASTCT criteria (Table 10).¹ For CRS management, published treatment guidelines are recommended,^{27,28} but they may be modified as needed by the responsible investigator according to the best practices at their institute.

Table 10. ASTCT CRS Grading

| CRS parameter: | Fever ^a | With Hypotension | And/or ^b Hypoxia |
|----------------|--------------------------------|---|--|
| Grade 1 | Temp $\geq 38^{\circ}\text{C}$ | None | None |
| Grade 2 | | Not requiring vasopressors | Requiring low-flow ^c nasal cannula, low-flow ^c facemask or blow-by |
| Grade 3 | | Requiring a vasopressor with or without vasopressin | Requiring high-flow ^c nasal cannula, high-flow ^c facemask, nonrebreather mask, or Venturi mask |
| Grade 4 | | Requiring multiple vasopressors (excluding vasopressin) | Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation) |

Note: Organ toxicities associated with CRS should be graded according to CTCAE v5.0 and do not influence CRS grading.

- a Fever: Temp $\geq 38^{\circ}\text{C}$ and not attributable to any other cause. In participants who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
- b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with Temp of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.
- c Low-flow nasal cannula or facemask is defined as oxygen delivered at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula or facemask is defined as oxygen delivered at > 6 L/min. This is modified from original ASTCT criteria to differentiate between low-flow and high-flow facemask.

Source: Lee et al, 2019¹

CRS management guidelines by ASTCT Severity Grading^{27,28}

For all participants, during the first 48 hours after the first dose of study intervention, and during the first 24 hours after second dose of study intervention:

- Monitor vital signs every 4 hours, minimally, for worsening of condition. Fever, regardless of grade of CRS, is managed as described under Grade 1 CRS.

Grade 1 CRS:

Fever

- Acetaminophen/paracetamol and hypothermia blanket for the treatment of fever.
- NSAIDs such as ibuprofen can be used as second treatment option for fever if not contraindicated.
- Assess for infection using blood and urine cultures, and chest radiography.
- Empiric broad-spectrum antibiotics and filgrastim if neutropenic.
- Maintenance IV fluids for hydration.
- Symptomatic management of constitutional symptoms or organ toxicity.
- Consider tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever.

Grade 2 CRS:

- Monitor vital signs every 4 hours, minimally, for worsening of condition.

Hypotension

- IV fluid bolus of 500-1000 ml of normal saline. Consider giving a second fluid bolus if systolic BP remains <90 mmHg.
- Consider tocilizumab 8 mg/kg (maximum dose 800 mg) IV or siltuximab 11 mg/kg IV for treatment of hypotension refractory to fluid boluses; tocilizumab can be repeated after 6 hours if needed.
- If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain ECHO, and initiate other methods of hemodynamic monitoring.
- In participants at high-risk (bulky disease, older age and/or comorbidities) or if hypotension persists after 1-2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen.
- Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension.

Grade 3 CRS:

- Monitor participant (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Hypotension

- IV boluses, as needed, as recommended for Grade 2 CRS.
- Tocilizumab or siltuximab as recommended for Grade 2 CRS if not administered previously.
- Vasopressors as needed.
- Dexamethasone 10 mg IV every 6 hrs; if refractory, increase to 20 mg IV every 6 hrs.

Hypoxia

- Supplemental oxygen including high-flow oxygen delivery.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above for Grade 2 CRS.

Grade 4 CRS:

- Monitor participant (including continuous ECG monitoring) in an ICU and obtain ECHO if not done already.

Hypotension

- IV boluses, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as recommended for Grade 3 CRS.
- Methylprednisolone 1 g/day IV.

Hypoxia

- Supplemental oxygen via positive pressure/mechanical ventilation.
- Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above for Grade 2 CRS.

10.11.2. Immune effector cell-associated neurotoxicity syndrome (ICANS)

Although less commonly seen than CRS, ICANS has been observed with some T-cell directed therapies and may manifest as aphasia, delirium, encephalopathy, lethargy, difficulty concentrating, agitation, tremor, seizures, and cerebral edema.¹ If ICANS is observed in relation to elranatamab, the ASTCT criteria will be used for grading¹ and published guidelines are recommended for management.^{1,27,28} These treatment guidelines may be modified as needed by the responsible investigator according to the best practices at their institute.

Table 11. Immune Effector Cell-Associated Encephalopathy (ICE) Score

| Category | Task | Points |
|--------------------|--|--------|
| Orientation | Orientation to year, month, city, hospital | 4 |
| Naming | Ability to name 3 objects | 3 |
| Following commands | Ability to follow simple commands | 1 |
| Writing | Ability to write a standard sentence | 1 |
| Attention | Ability to count backwards from 100 by 10 | 1 |

Table 12. ASTCT ICANS Grading

| Neurotoxicity Domain | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|-----------------------|------------------|---|--|
| ICE score^a | 7-9 | 3-6 | 0-2 | 0 (unarousable and unable to perform ICE) |
| Depressed level of consciousness^b | Awakens spontaneously | Awakens to voice | Awakens only to tactile stimulus | Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma |
| Seizure | N/A | N/A | Any clinical seizure that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention | Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between |
| Motor findings^c | N/A | N/A | N/A | Deep focal motor weakness such as hemiparesis or paraparesis |
| Elevated ICP/cerebral edema | N/A | N/A | Focal/local edema on neuroimaging ^d | Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI (abducens nerve) palsy; or papilledema; or Cushing's triad |

Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a participant with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

a A participant with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a participant with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0; these symptoms do not influence ICANS grading.

d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It should be graded according to CTCAE v5.0.

Source: Lee et al, 2019¹

ICANS Management Guidelines Per ASTCT^{27,28}

ICANS Grade 1:

- Vigilant supportive care; aspiration precautions; IV hydration.
- Withhold oral intake of food, medicines, and fluids; assess swallowing.
- Convert all oral medications and/or nutrition to IV if swallowing is impaired.
- Avoid medications that cause CNS depression.
- Neurology consultation.
- If suspected, evaluate for elevated ICP with fundoscopic exam for papilledema and lumbar puncture for CSF opening pressure.
- MRI of the brain with and without contrast; CT scan of the brain can be performed if MRI is not feasible.
- Daily 30 min EEG until symptoms resolve.
- Consider anti-IL-6 therapy with tocilizumab 8 mg/kg (maximum 800 mg) IV or siltuximab 11 mg/kg IV in case of concurrent CRS.

ICANS Grade 2:

- Supportive care and neurological work-up as described for Grade 1 ICANS.
- Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 1 ICANS and if not administered previously.
- Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if refractory to anti-IL-6 therapy, or for ICANS without concurrent CRS.
- Consider transferring participant to ICU if ICANS associated with Grade ≥ 2 CRS.

ICANS Grade 3:

- Supportive care and neurological work-up as indicated for Grade 1 ICANS.
- ICU transfer is recommended.
- If EEG shows non-convulsive status epilepticus:
 - Assess airway, breathing, and circulation; check blood glucose.
 - Lorazepam 0.5 mg IV, with additional 0.5 mg IV every 5 minutes, as needed, up to a total of 2 mg to control electrographical seizures.
 - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
 - If seizures persist, transfer to ICU and treat with phenobarbital loading dose of 60 mg IV.

- Recommended maintenance therapy after resolution of non-convulsive status epilepticus are as follows:
 - lorazepam 0.5 mg IV every 8 hours for 3 doses;
 - levetiracetam 1,000 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion;
 - phenobarbital 30 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion.
- Lacosamide may also be considered for treatment of seizures should the seizures persist. Lacosamide should not be used in participants with concurrent CRS in order to avoid arrhythmias and hypotension.
- For convulsive status epilepticus:
 - Assess airway, breathing, and circulation; check blood glucose.
 - Transfer to ICU.
 - Lorazepam 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures.
 - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
 - If seizures persist, add phenobarbital at a loading dose of 15 mg/kg IV.
 - Maintenance doses after resolution of convulsive status epilepticus:
 - lorazepam 0.5 mg IV every 8 hours for 3 doses;
 - levetiracetam 1,000 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion;
 - phenobarbital 1-3 mg/kg IV every 12 hours; duration of therapy per investigator/treating physician's discretion.
 - Lacosamide may also be considered for treatment of seizures should the seizures persist. Lacosamide should not be used in participants with concurrent CRS in order to avoid arrhythmias and hypotension.
 - Continuous EEG monitoring should be performed, if seizures are refractory to treatment.
- High-dose methylprednisolone IV 1 g/day for focal/local edema.
- Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 1 ICANS and if not administered previously.
- Corticosteroids as outlined for Grade 2 ICANS if symptoms worsen despite anti-IL-6 therapy, or for ICANS without concurrent CRS; continue corticosteroids until improvement to Grade 1 ICANS and then taper.

ICANS Grade 4:

- Supportive care and neurological work-up as outlined for Grade 1 ICANS.
- ICU monitoring; consider mechanical ventilation for airway protection.
- Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 ICANS.
- High-dose corticosteroids continued until improvement to Grade 1 ICANS and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
- For convulsive status epilepticus, treat as described for Grade 3 ICANS.
- MRI of the spine should be obtained for focal motor weakness.
- To manage elevated ICP:
 - Elevate head of the participant's bed to an angle of 30 degrees.
 - Hyperventilation to achieve target partial pressure of arterial carbon dioxide (PaCO₂) of 28–30 mmHg, but maintained for no longer than 24 hours.
 - Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below):
 - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥ 320 mOsm/kg, or the osmolality gap is ≥ 40 .
 - Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50–75 ml/hour while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥ 155 mEq/l.
 - For participants with imminent herniation: initial 30 ml of 23.4% hypertonic saline; repeat after 15 min, if needed.
- If patient has Ommaya reservoir, drain CSF to target opening pressure of <20 mmHg
- Consider neurosurgery consultation for ventriculoperitoneal shunt in participants with cerebral edema, and IV anesthetics for burst-suppression pattern on EEG.
- Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension.

10.12. Appendix 12. Anti-infectious Prophylaxis and Monitoring ^{40, 41, 42, 43, 44}

Participants should receive prophylaxis below. Approved anti-infective treatments may be substituted if treatments specified below are not available.

| Prophylaxis | Therapy | Start | Stop |
|-----------------------|---|---|--|
| Anti-Bacterial | Fluoroquinolones (levofloxacin - 500 mg PO or IV daily, or equivalent) Suggested alternative for participants with allergy to quinolones: Cefpodoxime - 200 mg PO twice a day ----- | For all participants at high risk of infections (eg history of pneumonia, Grade 4 neutropenia), an initial 3-month prophylactic course of fluoroquinolones is recommended ----- After initial 3 months treatment, administer for participants with ANC <1000/ μ L | Stop after 3 months of initial prophylaxis if ANC \geq 1000/ μ L ----- After initial 3 month treatment, administer for 14 days for ANC <1000/ μ L Prophylaxis may be extended at the discretion of the investigator as clinically indicated |
| Anti-Fungal | Fluconazole - 400 mg daily (or equivalent) ----- Consider switch to posaconazole or equivalent | For participants with prolonged neutropenia (eg. ANC <500/ μ L for >7 days) ----- Prolonged ANC <500/ μ L >3 weeks | At neutropenia resolution (for example, ANC \geq 500/ μ L). Prophylaxis may be extended at the discretion of the investigator as clinically indicated. ----- Until neutropenia resolution (ANC \geq 500/ μ L) |
| Anti-viral | Acyclovir or alternative | Antiviral prophylaxis within 1 week after starting treatment is strongly recommended to prevent herpes zoster reactivation | Continue for 3 months following the end of treatment |
| CMV | CMV testing by PCR is required prior to study drug administration. On study testing should be performed on a monthly to every three-month schedule depending on risk factors and baseline CMV viral load. | For participants with CMV copy number \geq 1000/mL, or per local standard of care, initiation of antiviral treatment is recommended (other risk factors including the rise in CMV copy | Continue therapy until two consecutive measurements at least 14 days apart show viral load < 1000/mL and resolution of symptoms (if present) |

| Prophylaxis | Therapy | Start | Stop |
|---|--|---|--|
| | Valganciclovir 900 mg PO BID Alternative (ganciclovir IV foscarnet IV.) or other approved agents. | number should be considered). Treatment is required for symptomatic participants irrespective of viral load. | |
| Pneumocystis Pneumonia (PCP) | PCP prophylaxis is strongly recommended for all participants for at least 6 months Trimethoprim-sulfamethoxazole DS – 1 tablet PO daily, three times per week Alternatives: Pentamidine (or alternative), or Dapsone – 100 mg PO daily or 50 mg PO BID, or Atovaquone – 1500 mg PO daily | Day 1 of first dose of study intervention | Suggested duration: 6 months OR until CD4 count ≥ 200 cells/ μ L based on 2 consecutive measurements at least 14 days apart (whichever is longer). Prophylaxis may be extended at the discretion of the investigator as clinically indicated. |
| Hypogammaglobulinemia/ Intravenous immunoglobulin (IVIG) | Monitor immunoglobulin levels for the occurrence of hypogammaglobulinemia | Administration of immunoglobulin for IgG level < 400 mg/dL is strongly recommended | Until resolution of hypogammaglobulinemia |
| Neutropenia/G-CSF Prophylaxis^a | Prophylactic or therapeutic administration of G-CSF in participants with severe neutropenia or serious neutropenic complications consistent with the ASCO guidelines ³⁹ is strongly recommended to decrease the risk of neutropenia specifically in participants with baseline extensive BM involvement and/or low neutrophil counts. | For participants with ANC $< 1000/\mu$ L | Until resolution of neutropenia |

a. Eligibility restricts use of G-CSF within 7 days prior to C1D1.

10.13. Appendix 13: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

| Abbreviation | Term |
|---------------------|---|
| ADA | anti-drug antibody |
| ADC | antibody-drug conjugate |
| AE | adverse event |
| AESI | adverse event of special interest |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| APC | antigen-presenting cell |
| ASCT | allogeneic stem cell transplant |
| AST | aspartate aminotransferase |
| ASTCT | American Society for Transplantation and Cellular Therapy |
| AUC _τ | area under the serum concentration-time curve from time zero to time τ |
| AUC _{last} | area under the concentration-time curve from time zero to time of last measurable concentration |
| AV | atrioventricular |
| BCMA | B-cell maturation antigen |
| β -hCG | beta-human chorionic gonadotropin |
| BICR | blinded independent central review |
| BiPAP | bilevel positive airway pressure |
| BM | bone marrow |
| BMA | bone marrow aspirate |
| BMB | bone marrow biopsy |
| BMMC | bone marrow mononuclear cells |
| BOR | best overall response |
| BP | blood pressure |
| bpm | beats per minute |
| BsAb | bispecific antibody |
| BUN | blood urea nitrogen |
| C | cycle |
| C1D1 | Cycle 1 Day 1 |
| C1D4 | Cycle 1 Day 4 |
| C1D8 | Cycle 1 Day 8 |

| Abbreviation | Term |
|------------------|---|
| C1D15 | Cycle 1 Day 15 |
| C1D22 | Cycle 1 Day 22 |
| C12D1 | Cycle 12 Day 1 |
| C15D1 | Cycle 15 Day 1 |
| CAR | chimeric antigen receptor |
| CB | clinical benefit |
| CCR | cumulative complete response |
| CD38 | cluster of differentiation 38 |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatinine kinase |
| CMV | cytomegalovirus |
| C _{max} | maximum concentration |
| CNS | central nervous system |
| CO ₂ | carbon dioxide (bicarbonate) |
| CONSORT | Consolidated Standards of Reporting Trials |
| CPAP | continuous positive airway pressure |
| CR | complete response |
| CRF | case report form |
| CRO | contract research organization |
| CRR | complete response rate |
| CRS | cytokine release syndrome |
| CSF | cerebrospinal fluid |
| CSR | Clinical Study Report |
| CT | clinical trial; computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| CYP | cytochrome P450 |
| COVID-19 | coronavirus disease-19 |
| DILI | drug-induced liver injury |
| DLT | dose-limiting toxicity |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |
| DOCR | duration of complete response |
| DOR | duration of response |

| Abbreviation | Term |
|---------------------|--|
| DU | dispensable unit |
| DVT | Deep vein thrombosis |
| EC | ethics committee |
| ECC | Emergency Contact Card |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| EDP | exposure during pregnancy |
| EEG | electroencephalography |
| EMA | European Medicines Agency |
| EM | extramedullary |
| EMD | extramedullary disease |
| EMG | electromyography |
| EORTC MY20 | European Organization for Research and Treatment of Cancer Multiple Myeloma module |
| EORTC QLQ-CIPN20 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Chemotherapy-induced peripheral neuropathy |
| 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 |
| ESMO | European Society for Medical Oncology |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| FDA | Food and Drug Administration |
| FISH | fluorescence in situ hybridization |
| FLC | free light chain |
| FSH | follicle-stimulating hormone |
| FU | follow-up |
| GBS | Guillain-Barre syndrome |
| GCP | Good Clinical Practice |
| gDNA | genomic DNA |

| Abbreviation | Term |
|--------------|--|
| GGT | gamma-glutamyl transferase |
| GLP | Good Laboratory Practice |
| GVHD | graft versus host disease |
| HA | Health Authority |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HR | hazard ratio; heart rate |
| HRT | hormone replacement therapy |
| IA | interim analysis |
| IB | Investigator's Brochure |
| ICANS | immune effector cell-associated neurotoxicity syndrome |
| ICD | informed consent document |
| ICE | immune effector cell-associated encephalopathy |
| ICH | International Council for Harmonisation |
| ICP | intracranial pressure |
| ICU | intensive care unit |
| ID | identification |
| IgA | immunoglobulin A |
| IgD | immunoglobulin D |
| IgE | immunoglobulin E |
| IgG | immunoglobulin G |
| IgH | immunoglobulin H |
| IgK | immunoglobulin K |
| IgL | immunoglobulin L |
| IgM | immunoglobulin M |
| IHC | immunohistochemistry |
| IL | interleukin |
| IMiD | immunomodulatory drug |
| IMP | investigational medicinal product |
| IMWG | International Myeloma Working Group |
| IND | investigational new drug |
| INN | International Non-proprietary Name |
| INR | international normalized ratio |
| IP manual | investigational product manual |

| Abbreviation | Term |
|--------------|--|
| IPAL | Investigational Product Accountability Log |
| IR | Immune-related |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| ISS | International Staging System |
| IV | intravenous(ly) |
| IWR | interactive Web-based response |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LTFU | long term follow-up |
| LVEF | left ventricular ejection fraction |
| mAb | monoclonal antibody |
| MABEL | minimal anticipated biological effect level |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHC | major histocompatibility complex |
| MM | multiple myeloma |
| MR | minimal response |
| MRD | minimal residual disease |
| MRI | magnetic resonance imaging |
| msec | millisecond |
| MTD | maximum tolerated dose |
| MUGA | multigated acquisition |
| N/A | not applicable |
| NAb | neutralizing antibody |
| NCCN | National Comprehensive Cancer Network |
| NCI CTCAE | National Cancer Institute common terminology criteria for adverse events |
| NCT | unique ID number for a clinical trial from clinicaltrials.gov |
| NCV | Nerve conduction velocity |
| NDMM | newly diagnosed multiple myeloma |
| NGS | next generation sequencing |
| NIMP | noninvestigational medicinal product |
| NMPA | National Medical Products Administration |
| NSAID | non-steroidal anti-inflammatory drug |
| OR | objective response |
| ORR | objective response rate |

| Abbreviation | Term |
|---------------------|---|
| OS | overall survival |
| PaCO ₂ | partial pressure of arterial carbon dioxide |
| PD | pharmacodynamics; progressive disease |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PI | proteasome inhibitor |
| PK | pharmacokinetic(s) |
| POEMS | polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes |
| PMAP | population modeling analysis plan |
| PMAR | population modeling analysis report |
| PR | partial response |
| PRO | patient-reported outcome |
| PS | performance status |
| PT | preferred term; prothrombin time |
| PVC | premature ventricular contraction/complex |
| QoL | quality of life |
| QT | time from the beginning of the QRS complex to the end of the T wave |
| QTcF | corrected QT (Fridericia method) |
| QW | once every week |
| Q2W | once every 2 weeks |
| Q3W | once every 3 weeks |
| Q4W | once every 4 weeks |
| Q12W | once every 12 weeks |
| R-ISS | Revised International Staging System |
| RNA | ribonucleic acid |
| RP2D | recommended Phase 2 dose |
| RRMM | relapsed/refractory multiple myeloma |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV2 | severe acute respiratory syndrome coronavirus 2 |
| sBCMA | soluble BCMA |
| SC | subcutaneous(ly) |
| sCR | stringent complete response |
| SCT | stem cell transplant |

| Abbreviation | Term |
|---------------------|--|
| SD | stable disease |
| SIFE | serum immunofixation electrophoresis |
| SoA | schedule of activities |
| SOC | standard-of-care |
| SOP | standard operating procedure |
| SPD | sum of the products of the maximal perpendicular diameters of measured lesions |
| SPEP | serum protein electrophoresis |
| SRSD | single-reference safety document |
| SSC | Study Steering Committee |
| SUSAR | suspected unexpected serious adverse reaction |
| TBili | total bilirubin |
| TCR | T-cell receptor |
| TEAE | treatment-emergent adverse event |
| T _{max} | maximum time |
| TNF- α | tumor necrosis factor alpha |
| TNFr SF 17 | tumor necrosis factor receptor superfamily 17 |
| TTR | time to tumor response |
| UI | uncertainty interval |
| UIFE | urine immunofixation electrophoresis |
| ULN | upper limit of normal |
| UPEP | urine protein electrophoresis |
| US | United States |
| VAS | visual analogue scale |
| VGPR | very good partial response |
| WBC | white blood cell |
| wk | week |
| WOC | Withdrawal of consent |
| WOCBP | woman of childbearing potential |

10.14. Protocol Amendment History

| Document History | | |
|------------------|--------------|---|
| Document | Version Date | Summary and Rationale for changes |
| Amendment 1 | 25 June 2021 | <ol style="list-style-type: none"> As per regulatory requirements (US FDA), and to stay consistent with global phase 2 study C1071003, updates to describe peripheral neuropathy (including GBS) as an important potential risk of elranatamab, and measures to mitigate risk including (a) addition of various new safety monitoring measures, (b) modification to participant selection (exclusion) for those potentially at higher risk; (c) addition of dose modification rules for peripheral neuropathy; (d) addition of recommended work-up for peripheral neuropathy; and (e) addition of considerations regarding concomitant medications. In addition, the criteria for placing the study on temporary hold (specifically related to neuropathy or other IR neurological AEs) were fully defined. Additional information was added in Background (Section 2.2) based on Phase 1 results. To mitigate CRS and ICANS, a 2 step-up priming dose approach (which includes premedication, and administration of elranatamab on C1D1 and C1D4 before the first full dose of elranatamab) was incorporated for the first week of study intervention. Relevant updates have been made throughout the protocol amendment. An additional visit, hospitalization periods, safety assessments, sample collections, and PROs are included in the SoA and Section 6. Clarifications have been made in Section 4.3.1, Dose Limiting Toxicity (DLT) definition. For participant selection, clarification was added around DVT, window for prior |

| Document History | | |
|------------------|---------------|---|
| Document | Version Date | Summary and Rationale for changes |
| | | <p>transplant, concerns about hypersensitivity to study intervention or any of its excipients and live attenuated vaccine administration history.</p> <p>7. Clarification on blood sampling window for sBCMA assessment in Section 8.5.1.</p> <p>8. In order to capture all potential AEs with elranatamab, including late onset immune-related neurologic AEs, the safety reporting period after last dose of study intervention has been increased to 90 days.</p> <p>9. Contraception use has been extended from 28 days to 90 days after the last dose of study intervention.</p> <p>10. Clarified requirements for laboratory assessments (Section 8.1.1).</p> <p>11. Clarified requirements for exposure during pregnancy (Section 8.3.5.1).</p> <p>12. Staging systems for multiple myeloma were more explicitly defined.</p> <p>13. Given the INN name is established, PF-06863135 has been replaced with the INN name, elranatamab.</p> <p>14. Clarifications were made throughout, including the SoA.</p> |
| Amendment 2 | 16 March 2022 | <p>1. SoA, Appendix 2, Revised local laboratory collections to include serum quantitative immunoglobulins and plasma cells.</p> <p>2. SoA, Revised BMA sampling times; Clarified BMA sampling times in cases of CR by all other parameters except bone marrow plasma cells. Reduced frequency of administration of PROs after Year 1. Clarified imaging</p> |

| Document History | | |
|------------------|--------------|---|
| Document | Version Date | Summary and Rationale for changes |
| | | <p>requirements after EMD resolution/disappearance. Removed BOR assessment.</p> <p>3. SoA, Section 8.1.2, 8.7.3, Made BMB sampling optional to better align with China clinical practice.</p> <p>4. Section 6.8.3, Add a new section of clarification that permitted concomitant treatments include infection prophylaxis and use of IV immunoglobulins.</p> <p>5. SoA, Sections 6.5.1, 6.5.2, Table 3, Clarification for dose modifications, including those for priming doses. Clarifications have been made to reflect blood sampling for PK if the C1D4 dose cannot be administered within the protocol-defined window.</p> <p>6. Section 7.1, For discontinuation reasons, added lack of efficacy.</p> <p>7. Section 8.1.2, Appendix 10, Added immunofluorescence and flow cytometry for the determination of sCR to better align with China clinical practice.</p> <p>8. Section 8.2.4, Clarified that 15-lead and 18-lead ECGs machines are also applicable for local practice.</p> <p>9. Section 8.7.1, Clarified allowed sample types for MRD evaluation. Additional samples may be requested by sponsor if freshly collected samples not available to identify the dominant malignant myeloma clone, at screening and during the on-treatment period.</p> <p>10. Section 9.3.3.1, Added more detailed description for MRD analysis</p> |

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| Document | Version Date | Summary and Rationale for changes |
| | | <p>11. Section 9.4.1 and Table 7, Updated the posterior probability threshold of $\geq 90\%$ to $\geq 80\%$ for Grade 3-4 CRS/ICANS and Grade 4 treatment related non-hematologic for the interim safety assessments. Minimum number of participants with identified events that would prompt temporary enrollment hold were updated where applicable.</p> <p>12. Editorial and formatting changes and clarifications were made throughout the document.</p> |
| Amendment 3 | 31 Jan 2023 | <p>Section 1.1, Added modifier of approximately and at least to target sample size of 36.</p> <p>Section 1.3.1, SoA, Combined description of BMA and BMB/BMA collections.</p> <p>Section 1.3.1, SoA, Changed description of frequency of PRO administration from years to cycles.</p> <p>Section 1.3.1, SoA, Added imaging at VGPR for participants with EMD at screening.</p> <p>Section 1.3.1, SoA and Section 10.2, Clarified that IgD or IgE will be tested, if they are available in the site, only if the heavy chain component of the disease is known to be IgE or IgD.</p> <p>Section 1.3.1, SoA, Section 10.2 and Section 10.12, Added CMV testing.</p> <p>Section 6.8 Concomitant Therapy,</p> <ul style="list-style-type: none"> Clarified the concurrent use of herbal medicinal products or herbal supplements should be avoided. |

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| Document | Version Date | Summary and Rationale for changes |
| | | <ul style="list-style-type: none"> Added COVID-19 monitoring and treatment guidance to provide specific infection prophylaxis and treatment guidance to sites. <p>Section 8.2.3, Clarify that vital signs included pulse should be collected instead of HR.</p> <p>Section 10.9, Clarify the order of injection site, if neither left lower quadrant nor the right is available.</p> <p>Section 2.3.1 and Section 10.12 Appendix 12 Anti-infectious Prophylaxis and Monitoring, Added recommendations for infection prophylaxis to provide guidance to investigative sites.</p> <p>Sections 10.1.1, 10.1.3, 10.1.4, 10.1.6, 10.1.7, 10.1.9, 10.1.10, Update to be consistent with latest template mandatory text.</p> |

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