MAGNETISMM-3

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

Study Intervention Number:	PF-06863135
Study Intervention Name:	Elranatamab
US IND Number:	133940
EudraCT Number:	2020-004533-21
ClinicalTrials.gov NCT:	NCT04649359
Protocol Number:	C1071003
Phase:	2
Sponsor Legal Address	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Short Title: A Phase 2 Study of Elranatamab (PF-06863135) Monotherapy in Participants With MM Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	07 October 2020	N/A
Amendment 1	07 January 2021	1. Throughout: Removed inclusion of participants age <18 years and all corresponding assent language (including removing reference to "legally authorized representative" in Section 10.1.3). 2. SoA, Section 8.1.1 and Appendix 10: FLC now specified as "serum FLC" for clarity. 3. SoA, Section 1.1, Section 4.3, Section 6.1.1 and Section 6.6.3: Removed investigator's discretion with regard to the transitions between dosing intervals (QW, Q2W). 4. SoA and Section 8.2.4: Clarified timing of ECGs: removed "postdose" as there are no scheduled postdose collections, and removed the 60-minute predose window. 5. SoA: Added rows for "Disease response assessment (per IMWG criteria)" and "Assessment of BOR" 6. SoA: Added detail around timing of UPEP, UIFE and imaging. Additional detail added to align optional BMB sampling with optional BMA sampling. 7. SoA and Section 8.2.7: Added "serum test required at screening" for clarity in alignment with footnote in Table 8 of Appendix 2. 8. SoA: Removed "within 2 hour" requirement for biomarker sample collection. 9. SoA: Added sBCMA samples beyond Cycle 7 to characterize the impact of Q2W switch on sBCMA levels from Cycle 7 and on. 10. Section 4.2.1: Modified to remove mention of participants in C1071001 who have previously received BCMA-directed BsAb. 11. Sections 4.2.2: Added MRD threshold of 10^{-5}, with the potential to measure MRD frequency up to 10^{-6}. 12. Section 4.4: Modified to specify that the study will be completed when all participants have been followed for OS for at least 2 years from the date of enrollment. 13. Section 5.1 (Inclusion criterion #15): Removed "except for AEs not constituting a safety risk for the participant by investigator judgment" 14. Section 5.2 (Exclusion criteria #2, #3 and #6): Modified for clarity.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		15. Section 6.1: Corrected vial size from 2 mL to 6 mL. 16. Section 6.1.1: Corrected timing of PF-06863135 administration from Day 21 to Day 22. 17. Section 6.6.1: Updated redosing criteria for clarity. 18. Section 6.6.1 and Table 4: Removed "or is Grade 2 and is not considered by the investigator to be a safety risk to the participant" 19. Table 4 footnote b: Added "or permanent discontinuation." 20. Section 8.1: Removed "assessment of best response, date of response onset, and date of progression (if applicable)" 21. Section 8.1.1: Minor edits for clarity 22. Section 8.1.5: Added "(as applicable)" to "Best response and date of disease progression…" 23. Section 8.2.2: Removed "Any abnormal physical examination findings observed prior to administration of the first dose of PF-06863135 should be recorded in the Medical History CRF." 24. Section 8.3.1: Removed "for survival" from "During the long-term follow-up period in this study…" 25. Section 8.8.1: Added MRD threshold of 10^{-5}. 26. Section 8.8.4 – Section 8.8.7: Removed sample volumes as these will be specified in the laboratory manual. Also added "(for predose samples, collection should occur prior to administration of PF-06863135 on that day)" to clarify that predose sample collections are to occur on the same day as treatment. 27. Section 9.1.2: Added rationale for hypotheses. 28. Section 9.2: Changed power from 80% to 90% to detect ORR of 48% (previously 45%) in Cohort A and 34% (previously 31%) in Cohort B. 29. Section 9.4.5: Added section on other safety analyses.

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		30. Section 9.5 (with references to Section 9.5 added to Section 2.3.1 and Section 8.3.8): Added interim safety assessment section for Grade ≥3 CRS, Grade ≥3 ICANS, Grade ≥4 non-hematologic events (excluding CRS and ICANS) and Grade 5 hematologic events. Also added "If the efficacy boundary is crossed, enrollment to the study will continue up to the specified number of participants, and all ongoing participants will continue with scheduled visits per the Schedule of Activities" to clarify that the study will not be stopped for efficacy at IA. 31. Appendix 2 (Table 8): Added LDH to lab assessments. Appendix 10: Removed "Participants will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status."
Amendment 2	14 February 2021	1. Title (and throughout): added study name and generic name (elranatamab). 2. SoA, Section 8.2.3: clarified vital sign monitoring during first 48 hours of first dose. 3. SoA, Section 6.5.1 (with reference added to Section 2.3.1): added premedication for CRS. 4. SoA, Sections 8.8.1, 8.8.3: clarified optional BMA/BMB sample is per investigator discretion. 5. Section 5.1: clarified bone marrow function inclusion criteria (granulocyte colony stimulating factors and transfusion support). 6. Section 6.5.2: clarified COVID-19 vaccines are permitted. 7. Sections 6.6.1, 6.6.2: clarified that dosing will be held until resolution of CRS or ICANS. 8. Section 9.3: added IA and PRO analysis sets. 9. Section 9.5.2: revised criteria for temporary enrollment hold (required regulatory change). 10. Appendix 2 (Table 8): Clarified calcium (total). 11. Footer: template version added.
Amendment 3 (country-specific: Belgium, Germany, Poland, Spain) for VHP procedure (review of Amendment 1)	24 March 2021	1. Section 5: clarifications to Inclusion Criterion 1, Exclusion Criteria 4, 8, and addition of Exclusion Criterion 12 (per VHP procedure). 2. Section 6.1.1: clarified first dose hospitalization is mandatory and clarified vital sign monitoring during this period aligning with Appendix 11 (Sections 1.3, 8.2.3) (per VHP procedure).

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		3. Section 6.5.1 (with references in Sections 1.3, 2.3.1, 6.1.1, 8.3.8, Appendix 11): added premedication for CRS. 4. Section 10.1.1: specified applicable local guidances (per VHP procedure). 5. Footer: template version added.
Amendment 4 (country-specific: United Kingdom) per MHRA (review of Amendment 1)	09 April 2021	1. Section 5.2: addition of Exclusion Criterion for administration of live attenuated vaccine within 4 weeks of first dose (per MHRA). 2. Section 6.1.1, Appendix 11: added guidance for second dose 24-hour monitoring for participants deemed at risk for CRS (per MHRA); clarified first dose hospitalization is required; clarified vital sign monitoring during first dose monitoring period aligning with Appendix 11 (Sections 1.3, 8.2.3). 3. Section 6.5.1 (with references in Sections 1.3, 2.3.1, 6.1.1, 8.3.8, Appendix 11): added premedication for CRS. 4. Section 6.5.2: clarified COVID-19 vaccines are permitted. 5. Footer: template version added
Amendment 5	02 May 2021	This amendment incorporates changes previously included in Amendment 2 (which was based on Protocol Amendment 1) and country-specific Amendments 3 and 4 (which were also based on Protocol Amendment 1); therefore Protocol Amendment 5 brings all the amendments into one document. Following is a summary of additional changes: 1. As per regulatory requirements (US FDA), 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.

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		2. Additional information was added in Background (Section 2.2) based on Phase 1 results. 3. 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. 4. An additional visit, hospitalization periods, safety assessments, sample collections, and PROs are included in the SoA and Section 6. 5. For participant selection, clarification was added around DVT and window for prior transplant. 6. 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. 7. Contraception use has been extended from 28 days to 90 days after the last dose of study intervention (as required by France HA). 8. A Steering Committee, to be involved with general oversight of the study, was established. 9. Staging systems for multiple myeloma were more explicitly defined. 10. Interim analysis set populations (for both cohort A and B) were further defined. 11. Given the INN name is established, PF-06863135 has been replaced with the INN name, elranatamab. 12. Added Appendix 12: Japan Regulatory Requirements. 13. Clarifications were made throughout, including the SoA.
Amendment 6	30 May 2021	1. Revised enrollment hold rules per regulatory requirement (US FDA): the posterior probability threshold of ≥80% is used for stopping rules for safety for treatment-related Grade 3-4 GBS (including variants), and treatment-related Peripheral Neuropathy/IR Neurologic AEs (section 9.5.2 and Appendix 13). 2. Exclusion criteria for ongoing Grade ≥2 peripheral neuropathy was revised (per regulatory requirements, US FDA).

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		3. Dose modifications for peripheral neuropathy were revised (per regulatory requirements, US FDA). 4. Clarification added for dose delays/interruptions, including windows (SoA, section 6.1.1, section 6.6.2). 5. Clarified imaging schedule, including requirement that imaging be conducted every 12 weeks for participants with baseline extramedullary disease (SoA). 6. Clarification added for availability of study treatment after end of study (section 6.7). 7. Clarified requirements for laboratory assessments (section 8.1.1). 8. Removed requirement for investigator review of completed PRO responses (including EORTC QLQ CIPN20, as regular neurologic exams are performed by the investigator) (section 8.1.4, and reference in section 2.3.1). 9. Clarified requirements for exposure during pregnancy (section 8.3.5.1). 10. Clarifications were made throughout, including SoA and Appendices.
Amendment 7	11 November 2021	1. The total number of planned participants was revised from 150 to 180 participants allowing for more robust datasets. Power/sample size calculations updated to be based on normal distribution from exact method (sections 1, 4.1, 9.2, 9.5). 2. Interim analyses (IA) revised to include a more robust data set (increased N from 60 to 90 for Cohort A) and added efficacy IA for Cohort B. IAs to be based on actual number with adequate follow-up at time of IA (section 9.5). 3. The follow-up period for final analysis was revised (section 9.2). 4. Added statement that interim analyses results can be used by the sponsor for decision-making and a statement about requirements before interim analysis can be conducted in accordance with the sponsor's SOPs (sections 7, 9.5). 5. Clarification that permitted concomitant treatments include infection prophylaxis and use

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		of IV immunoglobulins; added further considerations for oral contraceptives (section 6.5.2). 6. Clarification for dose modifications, including those for priming doses (sections 6.6.1, 6.6.2, Table 4). 7. Revised local laboratory collections to include serum quantitative immunoglobulins and plasma cells (SoA, Appendix 2). 8. Revised BMA sampling times; clarified BMA sampling times in cases of CR by all other parameters except bone marrow plasma cells (SoA). 9. Made BMB sampling optional to better align with global clinical practice (SoA, section 8.1.2, 8.8.3). 10. Added immunofluorescence and flow cytometry for the determination of sCR to better align with global clinical practice (section 8.1.2, Appendix 10). 11. Clarified allowed sample types for MRD evaluation (SoA, section 8.8.1). 12. Added allowance for use of CCI [redacted] sample in the event that the index myeloma clone is not identified from screening sample (section 8.8.1) 13. Reduced frequency of administration of PROs after Year 1 (SoA). 14. Clarified imaging requirements after EMD resolution/disappearance (SoA). 15. Removed BOR assessment (SoA). 16. For discontinuation reasons, added lack of efficacy and completed (sections 7.1 and 7.2). 17. Added more detailed description for MRD analysis (section 9.4.3). 18. Clarifications were made throughout multiple sections, including section 1, 3-5, 8, SoA and Appendices.
Amendment 8	23 December 2021	1. Added confirmed before PD (Section 1.1, 6.1.1, and 9.4.2) 2. Clarified that all participants will still be enrolled for the final analysis if the interim efficacy boundary is crossed and operating characteristics for the design are in the SAP (Section 9.5.1)

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		3. Updated the posterior probability threshold of ≥90% to ≥80% for Grade 3-4 CRS/ICANS and Grade 4 treatment related nonhematologic for the interim safety assessments (Section 9.5.2 and Table 8) 4. Editorial update (Appendix 10).
Amendment 9	29 July 2022	1. Added key secondary endpoint, ORR by BICR baseline EMD status (cohort A) (Sections 1.1, 1.2, 3, 9.1.1, 9.4.3). 2. Added CMV testing (Section 1.3, Table 10). 3. Updated alternative BMA sample types (Sections 1.3, 8.8.1). 4. Updated elranatamab clinical data (C1071001 and C1071003 study results) (Section 2.2.3, 4.2.1). 5. Added infection as a potential risk of clinical significance for elranatamab and made updates to summary of data throughout (Section 2.3.1) 6. Added more detailed guidance for infection prophylaxis (Section 6.5.2, and a new appendix, Appendix 14). 7. Added guidance about COVID-19 testing and treatment (Section 6.5.2) 8. Updates to align with SAP, including Interim Analysis plans for Cohort B (Section 9) 9. Additions to Japan Regulatory Requirements (Section 10.12.1) 10. Editorial updates (Sections 4.3, 10.15, 11).
Amendment 10	22 March 2023	1. CCI [redacted] 2. Revised elranatamab contraception requirements (WOCBP: aligned with updated elranatamab PK data as described in IB; Men: aligned with calculated safety margin between seminal transfer and estimated MABEL). (Sections 1.3, 4.2.3, 5.3.1, 10.4).

Document History		
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		3. Revised elranatamab clinical study summaries, referring protocol users to the IB for the most current information (Sections 2.2.3, 2.3.1). 4. Added more detailed descriptions in Sections 1.3 and 8.1.1 for when serum FLC should be used to assess disease response and about repeat sampling for confirmation of disease progression to match descriptions in Section 10.10. 5. Added definition of 'Final Analysis Evaluable Set' to align with statistical analysis plan (Section 9.3). 6. Revised descriptions throughout Section 10.1 to improve clarity/provide additional detail (including, but not limited to, added description of study data collection, processing and storage systems [Section 10.1.4]; clarification of protection of personally identifiable information [Section 10.1.5]; description of QTLs [Section 10.1.6]; clarifications for study start and closure [Section 10.1.8]; clarification of publication policy [Section10.1.9]; clarifications about contact card [Section 10.1.10]). 7. Removed requirement to notify study team when treatment is restarted following SARS-CoV-2 infection as protocol already includes relevant guidance (Section 10.8.4). 8. General editorial revision throughout to specify "confirmed" PD in descriptions of study intervention discontinuation and disease response requirements for consistency with descriptions in Sections 6.1.1 and 8.1. 9. General editorial revisions throughout to correct grammatical errors, to maintain consistency, and/or to improve clarity. 10. Sponsor legal address added (page 1).

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: MAGNETISMM-3, A Phase 2 Study of Elranatamab (PF-06863135) Monotherapy in Participants With MM Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb.

Rationale

The purpose of the study is to evaluate whether single-agent elranatamab can provide clinical benefit in participants with RRMM who are refractory to at least one PI, one IMiD and one anti-CD38 mAb. Because it is unknown how prior treatment with BCMA-directed therapy will affect the activity of elranatamab, this study will enroll one cohort with participants who have not previously received a BCMA-directed therapy (Cohort A) and one cohort with participants who have received previous treatment with BCMA-directed therapy (Cohort B).

Objectives, Estimands, and Endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy of elranatamab in Cohort A and Cohort B	• ORR by BICR per IMWG
Key Secondary	
• To determine additional efficacy of elranatamab in Cohort A	• ORR by BICR baseline EMD status per IMWG
Secondary	
• To determine additional efficacy of elranatamab in Cohort A and Cohort B	• DOR by BICR and investigator per IMWG • CRR by BICR and investigator per IMWG • ORR by investigator per IMWG • DOCR by BICR and investigator per IMWG • PFS by BICR and investigator per IMWG • OS • TTR by BICR and investigator per IMWG • MRD negativity rate (central lab) per IMWG
• To determine the safety and tolerability of elranatamab	• AEs and laboratory abnormalities as graded by NCI CTCAE v5.0. • Severity of CRS and ICANS assessed according to ASTCT criteria (Lee et al, 2019b).
• To evaluate the PK of elranatamab	• Pre- and postdose concentrations of elranatamab
• To evaluate the immunogenicity of elranatamab	• ADAs and NAbs against elranatamab

Objectives	Endpoints
Exploratory	
• To explore the relationship between elranatamab and the biology of the participant's MM	• Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens
• To explore correlations between elranatamab exposure and efficacy, safety and biomarker endpoints, if data allow	• Selected PK, efficacy, safety and biomarker endpoints
• To assess the impact of elranatamab on patient-reported symptoms and functioning	• EORTC QLQ-C30 and MY20 • EORTC QLQ CIPN20 • EQ-5D • PGI-S and PGI-C
• To collect healthcare resource use data	• Hospitalizations, including length of stay, ICU admissions, transfusions, infections and outpatient visits

Primary Estimand: The treatment effect of elranatamab on 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: OR 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. 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 OR, or who die, experience confirmed PD or stop disease assessments for any reason prior to achieving an OR will be counted as non-responders in the assessment of OR.

- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an OR and 2-sided 95% CI for ORR.

Overall Design

Study C1071003 is an open-label, multicenter, non-randomized, Phase 2 study to evaluate the efficacy and safety of elranatamab in RRMM participants who are refractory to at least one PI, one IMiD, and one anti-CD38 mAb. To determine the effects of prior BCMA-directed therapy on the response to elranatamab monotherapy, this study will enroll

2 independent and parallel cohorts: one with participants who are naïve to BCMA-directed therapies (Cohort A), and the other with participants who have been previously exposed to BCMA-directed therapy, as defined in Section 5.1 (Cohort B). The primary objective for each independent cohort will be to determine the efficacy (ie, ORR) of elranatamab as assessed by BICR, as defined by IMWG.

Number of Participants

Approximately 180 participants will be enrolled and treated, including approximately 120 participants in Cohort A and approximately 60 participants in Cohort B.

Intervention Groups and Duration

Participants will receive SC administration of elranatamab QW. The initial doses of elranatamab 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 criteria listed in Section 6.6.1. If a participant does not meet these criteria on C1D8, initiation of dosing with 76 mg should be deferred until the criteria are met.

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) and CCI [redacted]

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:

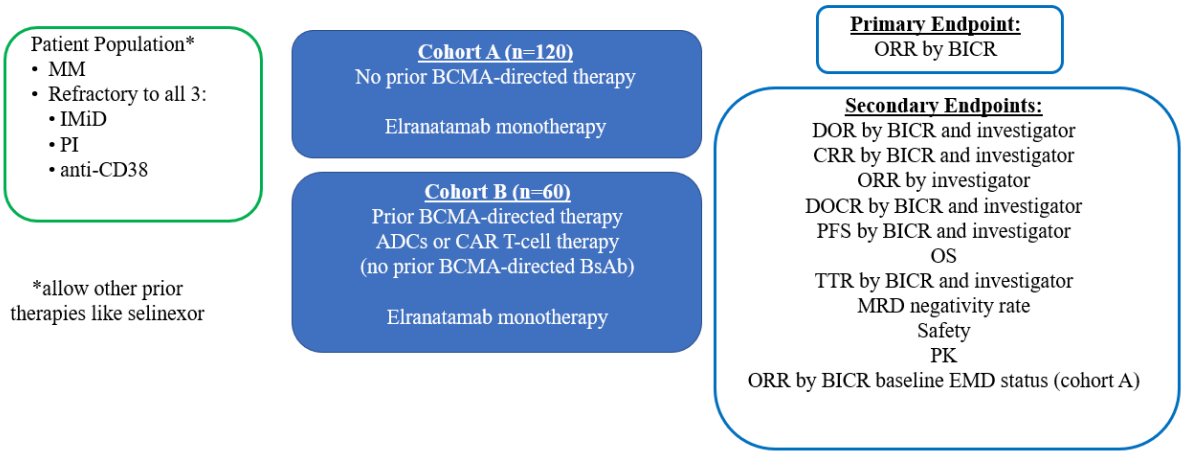
This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The E-DMC will review cumulative safety data during the study conduct as well as the interim futility and efficacy analyses.

The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

This study will also use a Steering Committee (consisting of both Sponsor representatives and at least 2 participating investigators) (see Section 9.6.2).

1.2. Schema


Patient Population*
• MM
• Refractory to all 3:
• IMiD
• PI
• anti-CD38
*allow other prior therapies like selinexor
Cohort A (n=120)
No prior BCMA-directed therapy
Elranatamab monotherapy
Cohort B (n=60)
Prior BCMA-directed therapy
ADCs or CAR T-cell therapy
(no prior BCMA-directed BsAb)
Elranatamab monotherapy
Primary Endpoint:
ORR by BICR
Secondary Endpoints:
DOR by BICR and investigator
CRR by BICR and investigator
ORR by investigator
DOCR by BICR and investigator
PFS by BICR and investigator
OS
TTR by BICR and investigator
MRD negativity rate
Safety
PK
ORR by BICR baseline EMD status (cohort A)

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.

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**	
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		No PGI-C at screening or C1D1. After Year 1, the PROs will be administered once every 3 cycles (C12D1, C15D1, etc). The PGIC will not be administered after Year 1. See Section 8.1.4
Healthcare resource use		X					X	X		See Section 8.10
Clinical Procedures/Assessments – *Note*: During the treatment period, all assessments must done within 72 hours prior to dosing (see notes for exceptions)										
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
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

Visit Identifier	Screening	Treatment Period (Each 28 Day Cycle)					EOT Visit	FU Visit	LTFU	Notes/Protocol Section *Day 4 Visit is Cycle 1 only*
		Day 1	Day 4	Day 8	Day 15	Day 22				
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**	
										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			Perform ECG prior to PK sample collection and prior to elranatamab administration (and premedication). ECG assessments should be skipped if CRS symptoms are ongoing. 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. 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. 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). CCI [redacted]

Visit Identifier	Screening	Treatment Period (Each 28 Day Cycle)					EOT Visit	FU Visit	LTFU	Notes/Protocol Section *Day 4 Visit is Cycle 1 only*
		Day 1	Day 4	Day 8	Day 15	Day 22				
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**	
										See Section 6 (including Section 6.6 dose modifications).
Premedication for CRS		Cycle 1	Cycle 1	Cycle 1						Must be administered 60 minutes (±15 minutes) prior to elranatamab dose, See Section 6.5.1.
Hospitalization		Cycle 1	Cycle 1							Hospitalization required for at least 2 days (~48 hr) for C1D1 and 1 day (~24 hr) 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 6.5
Subsequent anticancer 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	X*	X*	To be conducted on 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). Participants with measurable disease by SPEP or UPEP cannot have response assessed by serum FLC. Except for sCR, 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. Serum FLC cannot replace UPEP/UIFE in any situation where urine M component is measurable at baseline.

Visit Identifier	Screening	Treatment Period (Each 28 Day Cycle)					EOT Visit	FU Visit	LTFU	Notes/Protocol Section *Day 4 Visit is Cycle 1 only*
		Day 1	Day 4	Day 8	Day 15	Day 22				
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**	
										*For participants who discontinue study intervention without confirmed PD: perform at EOT visit, then at least Q4W (±1 wk) until confirmed PD, withdrawal of consent, initiation of subsequent anticancer therapy, participant lost to follow-up, 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 interval (±1 wk) between assessments should be maintained regardless of dose delays/interruptions). *For participants who discontinue study intervention without confirmed PD: perform at EOT visit, then at least Q4W (±1 wk) until confirmed PD, withdrawal of consent, initiation of subsequent anticancer 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 wk) interval whether dose given or not (ie, the 28-day interval (±1 wk) between

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**	
										assessments should be maintained regardless of dose delays/interruptions). *For participants who discontinue study intervention without confirmed PD: perform at EOT visit, then at least Q4W (±1 wk) until confirmed PD, withdrawal of consent, initiation of subsequent anticancer 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. If an evaluable 24-hour urine collection is missed, another attempt for collection should be made within 7 days of the missed assessment. See Section 8.1.1 for complete details (including requirements for repeat testing for confirmation of PD).

Visit Identifier	Screening	Treatment Period (Each 28 Day Cycle)					EOT Visit	FU Visit	LTFU	Notes/Protocol Section *Day 4 Visit is Cycle 1 only*
		Day 1	Day 4	Day 8	Day 15	Day 22				
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**	
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 wk), and also at suspected MR or PR. 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 confirmed PD, WOC, initiation of subsequent anticancer therapy, participant lost to FU, death, or defined EOS. See Section 8.1.3
BMA	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, as long as other CR criteria are maintained. See Section 8.1.2
BMA for cytogenetics (FISH/karyotyping)	X									See Section 8.1.2

Visit Identifier	Screening	Treatment Period (Each 28 Day Cycle)					EOT Visit	FU Visit	LTFU	Notes/Protocol Section *Day 4 Visit is Cycle 1 only*
		Day 1	Day 4	Day 8	Day 15	Day 22				
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**	
BMB/BMA	X	Time points for disease assessments described in notes								At screening and to confirm sCR. Either BMA or BMB can be used; however, the same method should be used for a participant throughout the study. Optional (investigator discretion) at suspected PD. See Section 8.1.2
Contraception check	X	X					X	X	X	Only required for WOCBP. Through 5 months post last dose of study intervention. See Section 5.3.1
Pregnancy test	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). Serum required at screening. See Section 8.2.7 and Table 8.
Hematology/chemistry	X	X	Cycle1	Cycle 1	Cycle 1	Cycle 1	X	X		See Section 8.2.6 and Table 8. For Cycle 1 Day 4, hematology only.
Serum quantitative immunoglobulins (IgG, IgM, IgA, IgD, IgE)	X	X					X	X		See Section 8.2.6 and Table 8.
CMV testing (quantitative PCR)		X*								*Every 1 to 3 months depending on risk factors See Section 8.2.6, Table 8, and Appendix 14.
PT/INR	X									See Section 8.2.6 and Table 8

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**	
Genetics and Biomarker Assessments (Central Laboratory)										
BMA for MRD	X	Samples to be collected each time there is a BMA assessment								At **screening** a freshy collected frozen BMA sample is preferred. If this sample is not available, an alternative sample collected at screening ([redacted]) can be submitted. Sample types permitted include **A)** Cell pellet/suspension, or **B)** Frozen BMMC dry cell pellet, or **C)** BMA smear slides and/or touch prep slides, or **D)** Re-cut slides from BM clot tissue block, or **E)** Re-cut scrolls from a BM clot tissue block, or **F)** gDNA isolated from BMA. A freshly collected frozen BMA sample is preferred for all **on-treatment samples**. **Alternative on-treatment samples** are **A)** Cell pellet/suspension from BMA, or **B)** frozen BMMC dry cell pellet, or **C)** gDNA isolated from BMA. See Section 8.8.1
BMA for molecular profiling	X	Samples to be collected each time there is a BMA assessment								See Section 8.8.2
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 collected for disease assessment,collection of this sample for biomarker analysis is encouraged. See Section 8.8.3

Visit Identifier	Screening	Treatment Period (Each 28 Day Cycle)					EOT Visit	FU Visit	LTFU	Notes/Protocol Section *Day 4 Visit is Cycle 1 only*
		Day 1	Day 4	Day 8	Day 15	Day 22				
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**	
Blood sample for sBCMA levels	X	Cycles 1, 2, 3, 7, 10, 13, etc.	Cycle 1	Cycle 1	Cycles 1, 2		X			Predose, 6 and 24 h postdose on C1D1. Predose and 24 h postdose on C1D4. Predose, 6 h postdose on C1D8. Collect predose only at C1D15, C2D1, C2D15, 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 8.8.4
Blood sample for circulating proteins and metabolite analysis		Cycle 1	Cycle 1	Cycle 1	Cycle 1	Cycle 1				Collect predose and 24h postdose on C1D1. Collect predose and 24 hr post dose on C1D4. Collect predose at all other times. If CRS is suspected, additional blood samples should also be collected if not already scheduled. See Section 8.8.5
Blood sample for TCR sequencing	X	Cycles 1, 2, 3			Cycle 1					Collect predose. See Section 8.8.6
Blood sample for immune cell profiling		Cycle 1, 3	Cycle 1	Cycle 1	Cycle 1	Cycle 1				Collect predose. See Section 8.8.7
Pfizer Prep D1 banked biospecimen(s)		Cycle 1								Collect predose. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. See Section 8.7.2
Saliva sample for germline comparator		Cycle 1								Collect predose. See Section 8.8.8

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**	
Pharmacokinetics and Immunogenicity Assessments										
Blood sample for PK		Cycles 1-4, 7, 10, etc	Cycle 1	Cycle 1	Cycle 1	Cycle 1	X			Predose, 6 and 24 h postdose on C1D1. Predose and 24 h postdose on C1D4. Predose, 6 h postdose on C1D8; predose only on C1D15, C1D22, C2D1, C3D1, then every 3rd cycle starting Cycle 4 (ie, C4D1, C7D1, C10D1, etc). If CRS is suspected, additional PK samples should be collected if not already scheduled. See Section 8.5
Blood sample for ADAs and NAbs		Cycles 1-4, 7, 10, etc					X			Predose on C1D1, C2D1, and C3D1 and every 3rd cycle starting C4 (ie, C4D1, C7D1, C10D1, etc). If AE possibly related to ADA occurs, additional samples for ADA and PK should be collected if not scheduled. See Section 8.9

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 whether single-agent elranatamab can provide clinical benefit in participants with RRMM who are refractory to at least one PI, one IMiD and one anti-CD38 mAb. Because it is unknown how prior treatment with BCMA-directed therapy will affect the activity of elranatamab, this study will enroll one cohort with participants who have not previously received BCMA-directed therapy (Cohort A) and one cohort with participants who have received previous treatment with BCMA-directed therapy (Cohort B).

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 (Bray et al, 2018). 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 (Siegel et al, 2020).

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 (Jimenez-Zepeda et al, 2015). 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 (Lopez et al, 2015).

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 therapy (Trudel et al, 2019) and other trials have included populations receiving a median of 6 (range 3-18) prior therapies (Mailankody et al, 2020) and a median of 5 (range 3 to 18) prior therapies (Berdeja et al, 2020b).

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 (Kumar et al, 2004). 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% (Nandakumar et al, 2019). 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, 2020b)
			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)

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.

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 (Sanchez et al, 2012b). Cleavage of cell surface BCMA by γ-secretase releases sBCMA (Laurent et al, 2015) 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 (Pont et al, 2019). 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 (Ghermezi et al, 2017b). Moreover, patients in 2 studies with high baseline levels of sBCMA appeared to have poorer clinical outcomes (Sanchez et al, 2012a; Ghermezi et al, 2017a).

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 (Smith-Garvin et al, 2009). 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 one 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 three 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 newly diagnosed MM in 11 ongoing studies. For detailed information on these studies, refer to the IB.

Enrollment in the current study (C1071003) completed in January 2022 with a total of 187 participants enrolled and treated. Study results on the safety, efficacy, clinical pharmacology and immunogenicity of elranatamab are provided in the IB.

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.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Elranatamab		
CRS	A known toxicity of therapeutics that function by activation of immune effector cells. Circulating cytokines are elevated after IV or SC administration of elranatamab. CRS signs and symptoms are expected mainly after the first and second dose and occasionally after the third dose or later of elranatamab. For further information, refer to the IB.	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). The priming regimen is expected to mitigate rate, duration, and severity of CRS (see Section 4.3). Guidance for monitoring, grading, and management of CRS per ASTCT criteria and guidelines is included in Appendix 11. Dose modification/discontinuation in the setting of Grade ≥2 AEs (including CRS) is described in Section 6.6.2. 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). Premedication (see Section 6.5.1). Additional management for Grade ≥3 CRS is described in Section 9.5.2.
ICANS	A known toxicity of therapeutics that function by activation of immune effector cells. Data from ongoing studies suggest ICANS is infrequent. For further information, refer to the IB.	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). The priming regimen is expected to mitigate the rate, duration, and severity of ICANS.(see Section 4.3). Regular neurologic examination will be performed by the investigator or designee (Section 8.2.2). Guidance for monitoring, grading, and management of ICANS per ASTCT criteria and guidelines is included in Appendix 11. Dose modification/discontinuation in the setting of Grade ≥2 AEs (including ICANS) is described in Section 6.6.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Elranatamab		
		Additional management for Grade ≥3 ICANS is described in Section 9.5.2
Peripheral neuropathy including GBS	A common complication of multiple myeloma and its treatment. Grade 3 peripheral neuropathy has been observed with elranatamab. For further information, refer to the IB.	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, and history of prior neuropathy with BCMA-directed drugs (see Section 5.2). Regular neurologic examinations will be performed by the investigator (or designee) to monitor for emerging signs and symptoms of new or worsening peripheral neuropathy. The administration of drugs known to cause peripheral neuropathy should be carefully considered, and if possible, avoided by the investigator; effective treatment and prophylaxis for infections should be prioritized. (Section 6.5). Participants should be closely monitored for signs and symptoms of neuropathy following infections or following the administration of any vaccine (Section 8.3.11). Dose modification/discontinuation for peripheral neuropathy is described in Section 6.6.2. Work-up recommendations for new or worsening peripheral neuropathy (Grade ≥2) is described in Section 8.3.11. Additional management for peripheral neuropathy is described in Section 9.5.2.
Infections	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. For further information refer to the IB.	See Section 6.5 and Appendix 14 for infection prophylaxis. Monitor participants, especially those with neutropenia, for signs of infection. See Section 6.6.2 for dose modifications for elranatamab.

2.3.2. Benefit Assessment

There are few viable treatment options for RRMM, especially for those patients who are refractory to PIs, IMiDs and anti-CD38 mAbs (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 (see IB). 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 (BLENREP (belantamab mafodotin-blmf) USPI, 2020), has not been observed with elranatamab (see IB).

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, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the efficacy of elranatamab in Cohort A and Cohort B	• ORR by BICR per IMWG
Key Secondary	
• To determine additional efficacy of elranatamab in Cohort A	• ORR by BICR baseline EMD status per IMWG
Secondary	
• To determine additional efficacy of elranatamab in Cohort A and Cohort B	• DOR by BICR and investigator per IMWG • CRR by BICR and investigator per IMWG • ORR by investigator per IMWG • DOCR by BICR and investigator per IMWG • PFS by BICR and investigator per IMWG • OS • TTR by BICR and investigator per IMWG • MRD negativity rate (central lab) per IMWG
• To determine the safety and tolerability of elranatamab	• AEs and laboratory abnormalities as graded by NCI CTCAE v5.0. • Severity of CRS and ICANS assessed according to ASTCT criteria (Lee et al, 2019).
• To evaluate the PK of elranatamab	• Pre- and postdose concentrations of elranatamab

Objectives	Endpoints
• To evaluate the immunogenicity of elranatamab	• ADAs and NAbs against elranatamab
Exploratory	
• To explore the relationship between elranatamab and the biology of the participant's MM	• Measurements of biomarkers (DNA, RNA, protein or defined cell types) resulting from analyses of peripheral blood, saliva and/or BM biospecimens
• To explore correlations between elranatamab exposure and efficacy, safety and biomarker endpoints, if data allow	• Selected PK, efficacy, safety and biomarker endpoints
• To assess the impact of elranatamab on patient-reported symptoms and functioning	• EORTC QLQ-C30 and MY20 • EORTC QLQ CIPN20 • EQ-5D • PGI-S and PGI-C
• To collect healthcare resource use data	• Hospitalizations, including length of stay, ICU admissions, transfusions, infections and outpatient visits

Estimand

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

Primary Estimand: 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: OR 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. 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 OR, or who die, experience confirmed PD, or stop disease assessments for any reason prior to achieving an OR will be counted as non-responders in the assessment of OR.

- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an OR and 2-sided 95% CI for ORR.

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

4. STUDY DESIGN

4.1. Overall Design

Study C1071003 is an open-label, multicenter, non-randomized, Phase 2 study to evaluate the efficacy and safety of elranatamab in RRMM participants who are refractory to at least one PI, one IMiD, and one anti-CD38 mAb. To determine the effects of prior BCMA-directed- therapy on the response to elranatamab monotherapy, this study will enroll 2 independent and parallel cohorts, one with participants who are naïve to BCMA-directed therapies (Cohort A; approximately 120 participants) and the other with participants who have been previously exposed to BCMA-directed therapy, as defined in Section 5.1 (Cohort B; approximately 60 participants). The primary objective for each independent cohort will be to determine the efficacy (ie, ORR) of elranatamab as assessed by BICR, as defined by IMWG.

4.2. Scientific Rationale for Study Design

4.2.1. Inclusion of Prior BCMA-directed therapy

Numerous BCMA-directed therapies are currently under investigation (Berdeja et al, 2020a; Lonial et al, 2020a; Topp et al, 2020a) and it is likely that some potential participants will have previously received one of these therapies. Because it is unknown how such prior treatment may affect the activity of elranatamab, this study will include a cohort of participants who have been previously exposed to BCMA-directed therapy. In the ongoing Phase 1 study (C1071001), disease responses of PR or better have been observed in 7 of 13 (53.8 %) participants who were previously exposed to BCMA-directed ADCs or CAR T-cell therapy (see IB).

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 (Kumar et al, 2016). 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 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 8.8.

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.2.3. Use of Contraceptives

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 (see Appendix 4). There are no contraception requirements for males.

4.3. Justification for Dose

The RP2D of elranatamab in the current study is 76 mg QW administered as a SC injection starting from C1D8. Priming doses will be used for the first week of treatment.

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 (see IB). Therefore, the MTD was not reached in Study C1071001. Despite achieving similar or higher exposure levels (C_{max} and AUCτ) 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 (see IB). 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 (see IB). Therefore, a fixed dose will be used in study C1071003.

Encouraging clinical activity was observed in the Phase 1 study (C1071001), particularly at doses ≥215 µg/kg SC with acceptable safety profile across all dose levels in the monotherapy cohorts (see IB).

To maximize the potential for clinical activity while improving the safety margin of elranatamab, a fixed dose equivalent of 1000 µg/kg dose level, 76 mg (starting on C1D8), 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 µg/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 ($C_{max-24h}$) and probability of CRS of All Grades and Grade ≥2 (according to ASTCT criteria (Lee et al, 2019b)).

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 $C_{max-24h}$ 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 6.6.1. 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.

CCI [redacted]

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 enrollment.

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:

1. Male or female participants age ≥18 years.

    - A female participant is eligible to participate if she is not pregnant or breastfeeding. Refer to Appendix 4 for all reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. 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 (Rajkumar et al, 2014).

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 one IMiD (as defined in *Note* below).

6. Refractory to at least one PI (as defined in *Note* below).

7. Refractory to at least one 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. Cohort A: Has not received prior BCMA-directed therapy.
   Cohort B: Has received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy, either approved or investigational.

10. ECOG performance status ≤2.

11. LVEF ≥40% as determined by a MUGA scan or ECHO.

12. Adequate hepatic function characterized by the following:

    a. Total bilirubin ≤2 x ULN (≤3 x ULN if documented Gilbert's syndrome);

    b. AST ≤2.5 x ULN; and

    c. ALT ≤2.5 x ULN

13. 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).

14. Adequate BM function characterized by the following:

    a. ANC ≥1.0 × 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 ≥25 × 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).

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

Informed Consent:

16. 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.
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);
    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.
8. History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B).
9. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
10. Active HBV, HCV, SARS-CoV2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.
11. 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*.

12. 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:

13. Previous treatment with an anti-BCMA bispecific antibody.

Prior/Concurrent Clinical Study Experience:

14. Previous administration with an investigational drug 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).

Other Exclusions:

15. 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.

16. Known or suspected hypersensitivity to the study intervention or any of its excipients.

17. Live attenuated vaccine must not be administered 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 is utilizing an appropriate method of contraception for the individual participant 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 SoA (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 Section 10.4]), 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). Contraception check is only required for WOCBP. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant. If a participant is confirmed to be pregnant, study intervention should be discontinued.

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 vial
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 country 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 6.6.3). CCI [redacted]

Dose modifications may occur according to the guidelines described in Section 6.6.

The first doses of study intervention 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 C1D1, and for 1 day (~24 hours) for C1D4. 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 as long as the participant meets the redosing criteria listed in Section 6.6.1. 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 6.5.1)

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

6.2. Preparation/Handling/Storage/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, or nurse practitioner) 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 the cohorts 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 treatment assignment, enrollment number, and 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.

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.

Compliance with study intervention will be documented in the source documents and CRF. Study intervention start dates, reasons for delays, dose reductions, and/or missed doses will be recorded in the CRF. Deviation(s) from the prescribed dosage regimen will be recorded in the CRF.

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

6.5. Concomitant Therapy

6.5.1. 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 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 (Neelapu et al, 2018b; Lee et al, 2019b; Neelapu, 2019a).

6.5.2. 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.

Concomitant treatment considered necessary for the participant's well-being may be given at the discretion of the investigator. The administration of antibacterial, anti-fungal, and/or antiviral agents for infection prophylaxis in participants at increased risk of infection in accordance with NCCN, IMWG, ESMO, and/or institutional guidelines is strongly encouraged (Dimopoulos et al, 2021; Kumar et al, 2020; Raje et al, 2022). Refer to Appendix 14 for all anti-infectious prophylaxis and monitoring recommendations.

Monitor immunoglobulin levels and administer intravenous immunoglobulin for IgG level <400 mg/dL. See Appendix 14.

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 vaccine administration within 48 hours before or after the first and second doses of study intervention. Individuals with MM are at increased risk of severe disease and complications from COVID-19 infection (Chari et al, 2020; Terpos et al, 2020). 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. In keeping with standard of care practice, it is recommended that participants 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 usual standard of care, local and/or regional guidelines, considering all treatments available to study participants, including PAXLOVID™ 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.Hormonal contraceptives that meet the contraception requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4). 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 (Neelapu et al, 2018a; Lee et al, 2019a; Neelapu, 2019b).

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. Effective treatment and prophylaxis for infections should be prioritized.

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 reinitiate 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.

6.5.3. Prohibited During the Study

No additional anticancer therapy 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.

6.6. 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-CoV-2 infection can be found in Appendix 8.

6.6.1. Redosing 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 6.6.2).

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 CCI [redacted]

Dose reductions, as outlined in Section 6.6.2 (Table 2), 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
- Platelet 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 6.6.2]), no ongoing CRS or ICANS (any grade)
- Recovery of treatment-emergent peripheral neuropathy to Grade ≤ 1 severity.

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

The recommended dose modifications for elranatamab-related toxicities and for peripheral neuropathy are presented in Table 2. All dose modifications should be based on the worst preceding toxicity and must be recorded on the CRF.

Table 2. 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 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 discontinued from treatment.	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.
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 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

Table 2. Dose Modifications for Elranatamab-Related Toxicity and for Peripheral Sensory or Motor Neuropathy [a]

mg) upon meeting the redosing criteria (Section 6.6.1). If the 32 mg dose was tolerable, the elranatamab dose should be increased to 76 mg. In case of ongoing CRS or ICANS of any grade on any dosing day, dosing will be held until resolution.
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 ≥25 × 109/L. For Grade 4 (first occurrence), resume at same dose level when platelets ≥25 × 109/L; for Grade 4 (second occurrence), resumption at a reduced dose level is recommended when platelets ≥25 × 109/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 CCI [redacted] 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 CCI [redacted] 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 3.

Table 3. Dose Levels for Elranatamab

Dose	Remarks
76 mg	Dose to be administered starting Cycle 1 Day 8 (refer to Section 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.

Table 3. Dose Levels for Elranatamab

Dose	Remarks
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 reescalation is agreed by the investigator and the sponsor.

6.6.3. Dose Modification Based on Durable Overall Response

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). CCI [redacted]

6.7. Intervention After the End of the Study

No study treatment will be provided to study participants after 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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Note: Results from the planned interim analyses (Section 9.5) 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.

- 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.
- AEs requiring discontinuation (as described in Section 6.6.2, 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.

- PD as defined by IMWG (see Appendix 10).
- Lack of efficacy (eg, increase of disease burden not qualifying as PD according to IMWG criteria).
- Participant becomes pregnant or begins breastfeeding.
- Significant protocol deviation 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.
- Completed.
- Death.
- Termination of the study by the 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 for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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 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, 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 confirmed disease progression, disease response assessments should continue at least Q4W (±1 wk) until confirmed 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 follow-up;
- Lost to follow-up;
- Death; and
- Study terminated by sponsor.
- Completed.

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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

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.

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 wellbeing 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 two consecutive assessments (confirmation).

Disease assessments are to be conducted per SoA: 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. Assessments will include:

- SPEP for the measurement of serum proteins, including M proteins.

- 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.
- 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 non-measurable (including at suspected CR). Serum free kappa, free lambda and free kappa/lambda ratio will be collected. Participants with measurable disease by SPEP or UPEP cannot have response assessed by serum FLC. Except for sCR, 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. Serum FLC cannot replace UPEP/UIFE in any situation where urine M component is measurable at baseline.

  ***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.

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

PD must be confirmed (unless due to EMD). 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. To confirm PD, 2 discrete samples are required, and testing cannot be based upon the splitting of a single sample.

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.

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)] (Sonneveld et al, 2016). 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.

BMB/BMA samples will be collected as per SoA 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 should be used for a participant throughout the study.

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 8.8).

BMA obtained while a participant is in suspected or actual CR will be evaluated by a central lab for MRD using NGS (see Section 8.8.1).

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. For participants with only skin involvement, skin lesions should be measured with a ruler at timepoints specified in the SoA.

Screening images will be used to determine evaluable 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

All PROs will be administered electronically. For each country, PRO translations in the official language(s) will be provided. Participants should be offered their choice of language from among the official translations for their country. 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.

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 PGI-S and PGI-C will also be collected to enable the implementation of anchor-based methods to establish meaningful change in PROs according to FDA guidance (FDA, 2014). The EORTC QLQ CIPN20 assesses chemotherapy-induced peripheral neuropathy (Postma et al, 2005).

EORTC QLQ-C30 is a well-known, reliable and valid self-administered questionnaire used in oncology trials (Aaronson et al, 1993; Osoba et al, 1997). The QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/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 (Cocks et al, 2007). 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).

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 (Rabin & de Charro, 2001). 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 PGI-S is a single-item PRO designed to assess participant's overall impression of disease severity at a given point in time. The PGI-C is a single-item PRO designed to assess the participant's overall sense of whether there has been a change in their disease since starting treatment. The PGI-S and PGI-C can be employed as anchors in responder analyses of other PRO instruments, to help interpret clinically meaningful changes in scores.

The EORTC QLQ CIPN20 is a module developed by the EORTC group to assess chemotherapy-induced peripheral neuropathy (Postma et al, 2005). 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 4), 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 4. 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: • high-risk chromosomal abnormalities by FISH[b] or • Serum LDH > the upper limit of normal

Table 4. Staging Systems for Multiple Myeloma

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).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. 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. All physical examination data (not including neurological examinations, see below) collected during the course of the study will be considered source data only and will not be required to be reported on the CRF. 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. 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.

Baseline encephalopathy assessment will be performed using the ICE tool (Lee et al, 2019b) (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, BP and O_2 saturation) should be collected per institutional standards at time points specified in the SoA prior to blood collection. Pre-dose vital signs collected on Day 1, Day 4, Day 8, Day 15 and Day 22 of Cycle 1 should be reported on the CRF. Vital signs associated with AEs may 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 should be monitored at least every 4 hours (±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 using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. 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) should not be used 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 10 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. 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.

If mean QTcF is >500 msec, ECGs should be re-evaluated by a qualified person at the institution for confirmation. If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** 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 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. 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. 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 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. 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) 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

A serum pregnancy test is required at screening; thereafter, 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. 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), at the end of treatment visit and at the follow-up visit. 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 5) will be assessed at Screening . ECOG PS should be obtained on the scheduled day, even if study intervention is being held.

Table 5. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

0	Fully active, able to carry on all pre-disease 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 and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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).

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 Electronic Data Collection Tool.

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 via the Electronic Data Collection Tool 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 (e.g., 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. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure 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 pre-procedure 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 (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a liveborn 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

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information 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 is 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 6.5.1).

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" (Lee et al, 2019b). 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.

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 via the Electronic Data Collection Tool.

Additional management for Grade ≥3 CRS and ICANS is described in Section 9.5.2.

8.3.8.1. Lack of Efficacy

Lack of efficacy 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 via the Electronic Data Collection Tool 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 via the Electronic Data Collection Tool **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 progressive (Richardson et al, 2012). Recently, peripheral neuropathy has been described following administration of BCMA-directed bispecific T-cell engagers (Topp et al, 2020b).

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. Treatment of Overdose

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

The sponsor does not recommend 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 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 plasma sample for PK analysis within 28 days from the date of the last dose of elranatamab 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.

8.5. Pharmacokinetics

All participants will have blood samples collected for PK assessments of elranatamab serum concentrations at the time points specified in the SoA. 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. 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 a minimum of 2 mL 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 (see SoA). 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. For pre-dose PK samples, collection should occur prior to administration of elranatamab on that day.

Samples will be used to evaluate the PK of elranatamab. Each serum sample will be divided into 2 aliquots, to provide a minimum of 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, or for other internal exploratory purposes.

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.

8.6. Pharmacodynamics

Biomarker samples may also be used for exploratory pharmacodynamics analyses (see Section 8.8) 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.

8.7. Genetics

8.7.1. Specified Genetics

Genetic assessments will be performed utilizing BMA, saliva, and blood samples as described in the SoA.

Please refer to relevant subsections in Section 8.8.

8.7.2. Banked Biospecimens for Genetics

A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and MM. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual.

8.8. Biomarkers

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

A BMA sample will be taken at the time points specified in the SoA. Next-generation sequencing of the sample taken pre-dose 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 and frozen BMA sample is not available for identification of the dominant malignant myeloma clone, the sponsor may request an alternative BMA sample type. The alternative BMA sample can be collected during screening or can be C[redacted]. If a participant has a clonoSEQ® MRD assay result from a previous testing that identified the index multiple myeloma clone, and the result is retrievable and useable in this study, the sponsor may give approval to use this result instead of submitting an alternative BMA sample.

Alternative BMA sample types include:

- Cell pellet/suspension from BMA, minimum 1 million cells, or
- 1 million frozen BMMC dry cells pellet collected from fresh BMA, or
- BMA smear slides and/or touch prep slides, 3-5 slides total, or
- Re-cut slides from bone marrow clot tissue block, minimum 5 slides, 8 microns thick, or
- Re-cut scrolls from a bone marrow clot tissue block, minimum 8 scrolls, 5 microns thick, or
- gDNA isolated from BMA, fresh samples preferred, minimum 1 µg.

For MRD tracking samples (i.e. collected after C1D1), if a freshly collected and frozen BMA sample is not available, an alternative sample from the list below can be submitted:

- Cell pellet/suspension from BMA, minimum 1 million cells, or
- 5-10 million frozen BMMCs dry cell pellet collected from fresh BMA, or
- gDNA isolated from BMA, fresh samples preferred, minimum 28 µg

If the central lab is unable to identify an index malignant myeloma clone with the screening (CCI [redacted]) sample, or if the central lab is unable to determine MRD status with the on-treatment sample, the sponsor may request a second BMA sample type from the site.

8.8.2. Bone Marrow Aspirate for Molecular Profiling

A BMA sample will be collected at the times specified in the SoA, 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.

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

A BMB maybe collected at the times specified in the SoA. 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, immune cell populations).

8.8.4. 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 predose 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.

8.8.5. Serum to Assess Circulating Proteins and Metabolite Analysis

A blood sample will be collected at time points specified in the SoA (for pre-dose 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 8.8.4 for post-dose collection window guidance.

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

A blood sample will be collected from all participants at the time points described in the SoA (for pre-dose 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.

8.8.7. Blood for Immune Cell Profiling

A blood sample will be collected from all participants at the time points specified in the SoA (for pre-dose samples, collection should occur prior to administration of elranatamab on that day). This sample will be used to examine the levels and distribution of blood cell populations either by RNA sequencing analysis and/or by DNA sequencing and/or by specialized epigenetic phenotyping approaches.

8.8.8. Saliva Sample for Germline Comparator

Unless prohibited by local regulations or ethics committee decision, a 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.

8.9. 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. 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.

8.10. Health Economics

Health economics/medical resource utilization will be evaluated in this study.

Healthcare resource utilization will be reported for both scheduled and unscheduled visits, covering health care resource use for disease monitoring, treatment monitoring, and management of treatment-emergent adverse events. Resource use for scheduled and unscheduled visits will be captured via the CRF. If hospital admission has occurred, additional information such as reason for admission and length of stay may be collected. These data may be supplemented with medical records. All information will be kept confidential and will be used exclusively for the study purpose. All records will be de-identified with individual's records labeled only with the assigned participant identification number.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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. Estimands and Statistical Hypotheses

9.1.1. Estimands

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

Primary Estimand: 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: OR 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.

- 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. 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 OR, or who die, experience confirmed PD, or stop disease assessments for any reason prior to achieving an OR will be counted as non-responders.

- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an OR and 2-sided 95% CI for ORR.

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

9.1.2. Statistical Hypotheses

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

In Cohort A, the study will test the null hypothesis that the ORR by BICR as defined by IMWG is ≤30% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >30%. The null hypothesis ORR for this cohort is based on the results of the DREAMM-2 study (Lonial et al, 2020b) and the STORM study (Chari et al, 2019), which were conducted in similar multiple myeloma populations with respect to prior treatments.

In Cohort B, the study will test the null hypothesis that the ORR by BICR as defined by IMWG is ≤15% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >15%. There are currently limited data available on the response rate after retreatment with a BCMA antibody drug conjugate or CAR-T therapy, but it is expected that the ORR would likely be notably lower than the BCMA naïve population. Thus, a null ORR of 15% is anticipated to be a reasonable estimate.

9.2. Sample Size Determination

The sample size for Cohort A and Cohort B was calculated to provide adequate power for testing the statistical hypotheses regarding the primary endpoint of ORR independently in the two cohorts using a two-stage design based on the exact binomial distribution. A total of 120 participants enrolled and treated in Cohort A provides approximately 98% power to reject the null hypothesis (ORR by BICR of 30%) when the alternative hypothesis that ORR by BICR of 48% is true, with a 1-sided significance level of 0.025. Similarly, a total of 60 participants enrolled and treated in Cohort B provides approximately 95% power to reject the null hypothesis (ORR by BICR of 15%) when the alternative hypothesis that ORR by BICR of 34% is true, with a 1-sided significance level of 0.025.

An IA for both (non-binding) futility and efficacy will be conducted for Cohort A and Cohort B; details are described in Section 9.5.

At the time of the SAP amendment prior to the interim analysis, enrollment had exceeded the 120 Cohort A and 60 Cohort B participants. Enrollment closed in January 2022 with 123 Cohort A and 64 Cohort B participants enrolled and treated.

At the time of the final analysis, the rule for rejecting the null hypothesis based on an exact binomial test will depend on the number of participants enrolled and treated in each cohort, respectively. At the final analysis in Cohort A, if there are ≥48 (39.0%) objective responders by BICR observed out of 123 participants enrolled and treated in the cohort, it will be concluded that the null hypothesis is rejected, and the cohort has demonstrated that the true

ORR by BICR exceeds 30%. At the final analysis in Cohort B, if there are ≥16 (25.0%) objective responders by BICR observed out of 64 participants enrolled and treated in the cohort, it will be concluded that the null hypothesis is rejected, and the cohort has demonstrated that the true ORR by BICR exceeds 15%.

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

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

9.3. Analysis Sets

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

Defined Analysis Set	Description
Safety Analysis Set	The safety analysis set in each cohort will include all enrolled participants in the respective cohort who received at least one dose of study intervention. This will be the primary analysis population for evaluating participant characteristics, treatment administration/compliance and safety endpoints.
Final Analysis Evaluable Set	The final analysis evaluable set in each cohort will include all enrolled participants in the respective cohort who received at least one dose of study intervention. This will be the primary analysis population for evaluating efficacy endpoints. This is the same as the safety analysis set thus only the “safety analysis set” terminology will be used.
Interim Analysis Evaluable Set A	The interim analysis evaluable analysis set A will include the first 90 enrolled participants who received at least one dose of study intervention in Cohort A. This will be the primary analysis population for evaluating efficacy endpoints at the interim analysis for Cohort A.
Interim Analysis Evaluable Set B	The interim analysis evaluable analysis set B will include the first 30 enrolled participants who received at least one dose of study intervention in Cohort B. This will be the primary analysis population for evaluating efficacy endpoints at the interim analysis for Cohort B.
PK Analysis Set	The PK analysis set is a subset of the safety analysis set and will include participants who have at least one postdose concentration measurement.
Immunogenicity Analysis Set	The immunogenicity analysis set is a subset of the safety analysis set and will include participants who have at least one sample tested for ADA.

Defined Analysis Set	Description
Biomarker Analysis Set	The biomarker parameter analysis set in each cohort is a subset of the safety analysis set and will include participants who have at least one baseline biomarker assessment. Analysis sets will be defined separately for biomarkers based on blood, saliva, and bone marrow aspirate samples.
PRO Analysis Set	The PRO analysis set in each cohort will include all participants in the safety analysis set who completed a baseline (last PRO assessment prior to or on the first dose of study treatment) and at least one post-baseline PRO assessment.

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

9.4. 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.

9.4.1. General Considerations

The study will enroll 2 independent and parallel cohorts: one with participants who are naïve to BCMA-directed therapies (Cohort A) and one with participants who have prior exposure to BCMA-directed therapies (Cohort B). Efficacy analyses will use the Safety Analysis Set and be reported for Cohort A and Cohort B separately. Safety analyses will also use the Safety Analysis Set and be reported for each cohort and for all cohorts combined.

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.

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.

9.4.2. Primary Endpoint

In each of Cohort A and Cohort B, BOR will be assessed based on reported overall responses recorded at evaluation time points from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy, whichever occurs first.

- **OR** will encompass confirmed sCR, CR, VGPR and PR.
- **CB** will encompass confirmed sCR, CR, VGPR, PR, and MR.

The primary endpoint of ORR by BICR is defined as the proportion of participants with an OR by BICR per IMWG criteria, and will be analyzed in the Safety Analysis Set. Point estimates of ORR by BICR in each of Cohort A and Cohort B will be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method. The null hypotheses will be tested at 1-sided alpha of 0.025 independently in the two cohorts using the exact binomial test, and the corresponding 1-sided p-value will be provided separately for Cohort A and Cohort B.

9.4.3. Secondary Endpoint(s)

Analyses of secondary efficacy endpoints will use the Safety Analysis Set.

9.4.3.1. Secondary Efficacy Endpoints

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

ORR by investigator is the proportion of participants in the analysis population with an OR 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. 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 OR per IMWG criteria, as the time from the first documentation of OR 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 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 OR per IMWG criteria, as the time from the date of first dose to the first documentation of OR 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.

9.4.3.2. Pharmacokinetic Analyses

PK data analyses will include descriptive summary statistics of the pre-dose and post-dose serum concentrations of elranatamab by study visit and time point. In addition, the PK 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.

9.4.3.3. Immunogenicity Analyses

For immunogenicity data, the percentage of patients with positive ADA will be summarized. Listings and summary tabulations of the ADA data at baseline and post-randomization will be generated. Samples may also be analyzed for the presence of NAb, and any data will be similarly summarized. For patients 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.

9.4.4. Exploratory Endpoint(s)

The details of exploratory endpoint analyses, including PROs, will be described in the SAP.

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.

9.4.5. Other Safety Analyses

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

9.4.5.1. Adverse Events

AEs (except CRS and ICANS) will be graded by the investigator according to NCI CTCAE Version 5.0 and coded using MedDRA. CRS and ICANS will be assessed by the investigator according to the grading described by Lee et al (Lee et al, 2019b) (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.

9.4.5.2. 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.

9.4.5.3. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by cohort and time.

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

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

9.4.6. 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.

9.5. Interim Analyses

Interim analyses will be performed to assess futility and/or efficacy as described in details below. Participants may be discontinued from the study intervention/study as a result of interim analysis outcome, as described in Section 7. Interim analysis results may be used for decisions regarding stopping for futility, stopping for early success, or adapting the study after the interim analysis.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in the EDMC charter. In addition, the analysis details will be documented and approved in the SAP.

9.5.1. Interim Analysis for Futility and Efficacy

An IA for both (non-binding) futility and efficacy will be conducted on ORR by BICR for Cohort A based on the first 90 participants enrolled and treated in that cohort. At the IA for Cohort A, if there are ≤31 (34.4%) objective responders by BICR observed, accrual may be stopped for further evaluation due to futility; if there are ≥38 (42.2%) objective responders by BICR observed, the efficacy boundary will be crossed; if the IA crosses neither the futility boundary nor the efficacy boundary, Cohort A will proceed as planned to the final analysis as described in Section 9.2. If the efficacy boundary is crossed, enrollment to the study will continue up to the specified number of participants for the final analysis, and all ongoing participants will continue with scheduled visits per the SoA.

An IA for (non-binding) futility and efficacy will be conducted on ORR by BICR for Cohort B based on the first 30 participants enrolled and treated in that cohort. At the IA for Cohort B, if there are ≤3 (10.0%) objective responders by BICR observed, accrual may be stopped for further evaluation due to futility; if there are ≥11 (36.7%) objective responders by BICR

observed, the efficacy boundary will be crossed; if the IA crosses neither the futility boundary nor the efficacy boundary, Cohort B will proceed as planned to the final analysis as described in Section 9.2. If the efficacy boundary is crossed, enrollment to the study will continue up to the specified number of participants for the final analysis, and all ongoing participants will continue with scheduled visits per the SoA.

Each respective interim analysis will occur no earlier than the point at which all early responders (ie, those who respond within the first 3 post-baseline assessments) among the participants to be included have had their responses confirmed. At the time of the interim analysis, the testing rule will depend on the actual number of participants included in the analysis for each cohort with sufficient follow-up.

At the time of the SAP amendment prior to the interim analysis, 94 Cohort A participants were initially dosed at least 4 months prior to the data cutoff and were to be included in the interim analysis. The updated boundaries were ≤33 (35.1%) objective responders by BICR for futility and ≥41 (43.6%) objective responders by BICR for efficacy. It was determined no interim analysis will be performed for Cohort B participants as not enough participants have adequate follow-up since Cohort B has a higher incidence of EMD at baseline compared to Cohort A. The boundaries at the final analysis for Cohort B do not change if no interim analysis is performed.

Operating characteristics (Type I and Type II error) were calculated using the exact binomial distribution and are detailed in the SAP. It can be noted that the futility stopping boundary for both cohorts at the interim and final analyses use the rho family beta-spending boundary with parameter = 3 and that the efficacy stopping boundary for both cohorts at the interim and final analyses use the rho family alpha-spending boundary with parameter = 5.

9.5.2. Interim Safety Assessments

An E-DMC will review cumulative safety data during the study conduct and may make recommendations to alter the conduct of the study (see Section 9.6). In addition, the incidence of Grade 3-4 CRS, Grade 3-4 ICANS, Grade 4 treatment-related non-hematologic events (excluding CRS and ICANS), Grade 3-4 treatment-related GBS/GBS-like AEs, 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 pre-specified threshold, the study will be placed on a temporary enrollment hold by the Sponsor until discussions can be held with the Study Steering Committee and the E-DMC. During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participant start study intervention. Pending Steering Committee and E-DMC assessment, participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the investigator in consultation with the sponsor.

In the event that any criteria for temporary enrollment hold are met, written notification documenting the reason for temporary enrollment hold (or study termination) will be

provided by the sponsor to the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study (see also Section 10.1.8).

The criteria for placing the study on temporary hold for the following safety reasons are based on Bayesian posterior probabilities. Using a non-informative Beta (0.5, 0.5) prior distribution, if the number of participants observed to have Grade 3-4 CRS results in a posterior probability that the true Grade 3-4 CRS rate exceeding 20% is ≥0.80, the study will be put on a temporary hold. Separate but similar criteria will be used for participants with Grade 3-4 ICANS and treatment-related Grade 4 non-hematologic events (excluding CRS and ICANS). Table 6 summarizes the minimum number of participants with such identified events that would meet the above criteria.

Table 6. Minimum Number of Participants With Identified Events That Would Prompt Temporary Enrollment Hold (CRS, ICANS, Non-hematologic treatment-related AEs)

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

Prior distribution: Beta (0.5,0.5)

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

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

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

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

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

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

Table 7 summarizes the minimum number of evaluable participants with such identified events that would meet the above criteria. (See also Appendix 13 for additional details.)

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

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

Prior distribution: Beta (0.5,0.5)

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

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

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

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

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

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).

9.6. Data Monitoring Committee or Other Independent Oversight Committee

9.6.1. E-DMC

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The E-DMC will review cumulative safety data during the study conduct as well as the interim futility and efficacy analyses.

The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

9.6.2. Steering Committee

This study will use an SSC. The SSC (consisting of both Sponsor representatives and at least 2 participating investigators) will evaluate, upon requirement of the Sponsor, participant cases where further discussions of participant management are required (note: any final decisions about participant management reside with the investigator). The SSC will also be involved with the general oversight of the study, although any final decisions regarding study conduct will remain with the Sponsor.

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.
- In Germany, the provisions of the Medicinal Products Act (AMG), the GCP Regulation (GCP-V) and the Guideline for Good Clinical Practice (ICH-GCP E6 (R2)) apply. Provisions of General Data Protection Regulation (DSGVO) and the Federal / State Data Protection Act (BDSG / LDSG BW) are to be complied with.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and 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 guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (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 ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators 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 his/her representative will explain the nature of the study 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 guidelines, HIPAA 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 his/her 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 his or her personal data and to withdraw consent for the processing of his or her 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 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 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.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

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 his or her actual identity and medical record identification. 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. 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 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 patient-level data or full CSRs for the purposes of "bonafide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 18 months after study completion. Patient-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.

10.1.6. 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 maintain accurate documentation (source data) that supports the information entered in the CRF.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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, remote, or onsite monitoring), are provided in the 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.

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, ICH GCP, and all applicable regulatory requirements.

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.

10.1.7. 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.

10.1.8. 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 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.

10.1.9. 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.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI 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 their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an 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 participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed locally at times defined in the SoA. 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 8. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Other
• Hemoglobin • Platelet count • WBC count Absolute*: • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes • Plasma cell count (*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)	• BUN (or blood urea) • Creatinine • Glucose (non-fasting) • Calcium (total) • Sodium • Potassium • Chloride • Total CO_2 (bicarbonate) • AST, ALT • Total bilirubin • Alkaline phosphatase • Albumin • Total protein • Lactate dehydrogenase (LDH)[a] • Uric acid[a] • Serum beta-2 microglobulin[a,c]	• PT/INR • Pregnancy test (β-hCG) [b] • See Section 10.12.1 for local regulatory requirements. • Serum quantitative immunoglobulins (IgG, IgM, IgA, IgD, IgE) • CMV testing (by quantitative PCR), every 1 to 3 months (see Appendix 14)

a. At baseline (minimum), and as clinically indicated.
b. For female participants of childbearing potential only. Serum test is required at screening; for other time points, urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC.
c. Required for multiple myeloma staging

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
• 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

• 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:
 	
  • 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.
 	
• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet

the requirements as per Section 8.3.8.1. Also, "lack of efficacy" or "failure of expected pharmacological action" does not constitute an AE or SAE.

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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization 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 Intensity section).

- 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 patient 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events via the Electronic Data Collection Tool or on the CT SAE Report Form to Pfizer Safety (see sections 8.3.1, 8.3.5 and 8.3.10 for guidance). These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Electronic Data Collection Tool and the CT SAE Report Form for reporting of SAE information are 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 via the Electronic Data Collection Tool or 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, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- 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/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 Electronic Data Collection Tool / CT SAE Report Form/AE/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/SAE.

Assessment of Intensity

The investigator will report severity for each AE and SAE reported during the study based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

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

The severity of CRS and ICANS will be graded according to ASTCT criteria (Lee et al,2019b). See Appendix 11.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/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 Electronic Data Collection Tool or 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.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- 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 Paper 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 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 (minimal anticipated biological effect level) used as conservative estimate of exposure that may result in serious manifestations of developmental toxicity.

10.4.2. Female Participant Reproductive Inclusion Criteria

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 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 <u>not</u> 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

    - 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.

    - 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 by men or women 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 or bilateral tubal ligation.

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 + barrier*;
    - Intravaginal + barrier*;
    - Transdermal + barrier*.

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

    - Oral + barrier*;
    - Injectable + barrier*.

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.

*** Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:**

- 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 scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to elranatamab or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- 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 8.7.1) will be stored for up to 15 years or other period as per local requirements beyond the completion of this study (eg, Clinical Study Report finalization).

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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 × 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 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × 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 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × 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 × ULN; or >8 × 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 × ULN **or** if the value reaches >3 × 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. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (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

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS complex >120 msec).
• New-onset right bundle branch block (QRS complex >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • 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.
- Second- or third-degree AV block requiring pacemaker placement.
- 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.

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 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 possibly an accompanying informant) 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 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

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.

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-CoV2 infection:

For symptomatic participants with active SARS-CoV2 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-CoV2 infection.

Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤Grade 1 for a minimum of 72 hours.

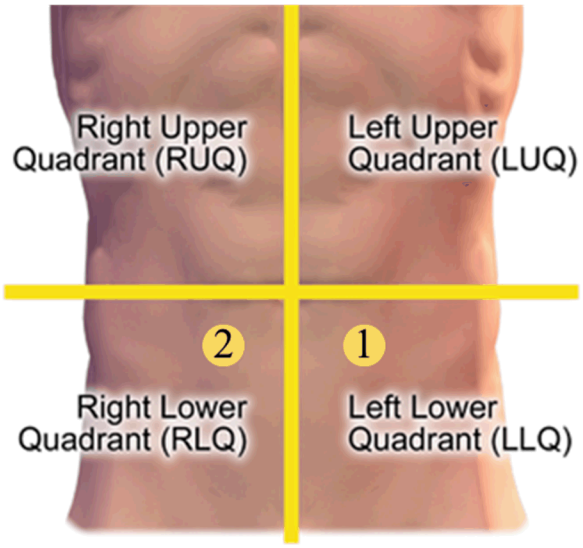
Continue to consider potential drug-drug interactions as described in Section 6.5 for any concomitant medication administered for treatment of SARS-CoV2 infection.

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 2 unique administration sites distributed across the 2 lower abdominal quadrants (up to 1 injection location per quadrant).

Administer the required number of injections in the following order:

1. Lower Left Quadrant;
2. Lower Right 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 red 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.

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 one 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)	CR as defined below plus: • 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)	• 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)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis. OR • ≥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 ≥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]
Partial Response (PR)	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h. • If the serum and urine M-protein are unmeasurable, a ≥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 ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[d]

Response[a]	Modified IMWG Criteria
Minimal Response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24h urine M-protein by 50–89%. In addition to these, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[d]
No Change/Stable Disease (SD)	• Not meeting criteria for sCR, CR, VGPR, PR, MR or PD.

Progressive Disease (PD)[b,e,f]	Any one or more of the following criteria:
	• Increase of ≥25% from lowest confirmed response value in any 1 or more of the following:[e,f]
	  • 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 ≥10%)
	• Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis.[d]
	• ≥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.

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 MRI scans, or dedicated CT scans where applicable. Measurement of tumor size will be determined by the SPD.

e PD confirmation requires two 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 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

Source: Adapted from (Kumar et al, 2016).

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 6.5.1).

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-base 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 9) (Lee et al, 2019b). For CRS management, published treatment guidelines are recommended (Neelapu et al, 2018b; Neelapu, 2019a), but they may be modified as needed by the responsible investigator according to the best practices at their institute.

Table 9. ASTCT CRS Grading

CRS parameter:	Fever[a]	With Hypotension	And/or[b] Hypoxia
Grade 1	Temp ≥38°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 ≥38°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, 2019b)

CRS management guidelines by ASTCT Severity Grading (Neelapu et al, 2018b; Neelapu, 2019a)

For all participants, during the first 48 hours after the first dose of study intervention, and during 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 (Lee et al, 2019b). If ICANS is observed in relation to elranatamab, the ASTCT criteria will be used for grading (Lee et al, 2019b) and published guidelines are recommended for management (Neelapu et al, 2018a; Lee et al, 2019a; Neelapu, 2019b). These treatment guidelines may be modified as needed by the responsible investigator according to the best practices at their institute.

Table 10. 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 11. 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	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical

Table 11. ASTCT ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
			seizures on EEG that resolve with intervention	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, 2019b)

ICANS Management Guidelines Per ASTCT (Neelapu et al, 2018b; Neelapu, 2019a)

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 min, 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 three 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 three 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 ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 hrs.
  - 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 hrs while monitoring metabolic profile and serum osmolality every 6 hrs, 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 5075 ml/hour while monitoring electrolytes every 4 hrs, 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: Country Specific Requirements

10.12.1. Japan Regulatory Requirements

On 05-Mar-2021 a protocol administrative letter was distributed that incorporated the following country-specific regulatory requirements to the C1071003 protocol; Amendment 2 (14 February 2021).

1. Female Participant Reproductive Inclusion Criteria: Female participants who are currently breastfeeding and intend to interrupt breastfeeding during the study are also excluded.

2. HBV Monitoring During the Study Treatment

For Section 8.2.6. Clinical Safety Laboratory Assessments, the following additional laboratory monitoring based on precautionary measures should be followed.

For participants with positive HBsAb and positive HBcAb but with negative HBV DNA test at screening, HB viral load should be monitored for re-activation every 12 weeks. If HBV relapse is observed, the event should be collected to the AE section of the CRF, but the data will not be required to be reported on the CRF. Participants with HBsAb positive who have been vaccinated with HBV are exempted from the testing of HB viral load.

A participant who is tested viral load positive for HBV at any time during the study will interrupt administration of PF-06863135, and should consider starting nucleoside antagonist immediately in parallel with consultation with hepatologist in accordance with the Japan Society of Hepatology (JSH) Guidelines for the management of Hepatitis B Virus infection.

3. Supplemental of Appendix 5 Genetics

Given the genetic testing in this study is for exploratory purposes only and following Pfizer process, it’s to clarify that there is no expectation to disclose these genetic testing results to the study participants, at any time.

It’s to clarify that a participant's participation in a clinical study shall not be conditional on his or her informed consent for the use of biospecimens that is not related to a clinical endpoint, the study intervention or disease being investigated in the trial, or the inclusion/exclusion criteria for the study.

4. SRSDs for tocilizumab

The sponsor lists the study intervention in the following table as safety information for the study intervention must be reported to the Japan regulatory authorities and investigator(s)/IRB/EC of the investigator site(s) in Japan in accordance with the Japanese regulatory requirements. The investigator in Japan provides the sponsor with the safety information necessary for safety reporting to the Japan regulatory authorities.

Intervention Name	Tocilizumab
Type	Biologics
Dose Formulation	Solution for injection
Unit Dose Strength(s)	8 mg/kg (maximum 800 mg)
Dosage Level(s)	Refer to Section 10.11
Route of Administration	IV
IMP or NIMP/AxMP	NIMP/AxMP*
Sourcing	Provided centrally by the sponsor. Refer to IP manual.
Packaging and Labeling	Study intervention will be provided in carton. Each carton will be labeled as required per country requirement.
SRSD	J-PI for Actemra

* In Japan, this product is considered as IMP.

Tocilizumab has been approved for treatment of CRS induced by tumor-specific T cell infusion therapy, and the use of tocilizumab to CRS induced by CD3 bispecific antibody has not been approved in Japan. Pfizer will supply tocilizumab to Japan study sites. The data related to tocilizumab from this study may be used for supplemental NDA of tocilizumab in Japan. Therefore, in this study, tocilizumab is a non-IMP, but considered as IMP in Japan.

Tocilizumab should be managed in accordance with IP manual.

10.13. Appendix 13: Summary of Safety Stopping Rules

Safety stopping rules were derived based on posterior probability of 0.90 in Protocol Amendment 5. Per US FDA recommendation, safety stopping rules were updated based on posterior probability of 0.80.

10.13.1. Treatment-Related Grade 3-4 GBS (Including Variants) per posterior probability 0.80 vs 0.90

Number of Evaluable Participants	Minimum Number of Evaluable Participants With Treatment-Related Grade 3-4 GBS (Including Variants)	
	Posterior Probability ≥0.90	Posterior Probability ≥0.80
20-27	2	2
28-39	3	2
40-47	3	3
48-64	4	3
65-70	4	4
71-90	5	4
91-93	5	5
94-116	6	5
117-118	6	6
119-143	7	6
144	8	6
145-150	8	7

Criteria for 151 or more evaluable participants will be calculated based on the posterior probability of ≥0.90 and ≥0.80 respectively

10.13.2. Treatment-Related Grade 4 SN/IR Neurologic AEs (Excluding ICANS)/Treatment-Related Grade 3-4 Motor Neuropathy Events per posterior probability 0.80 vs 0.90

	Minimum Number of Evaluable Participants With Treatment-Related Grade 4 SN/IR Neurologic AEs (Excluding ICANS)/Treatment-Related Grade 3-4 Motor Neuropathy Events that would Prompt Temporary Enrollment Hold	
	Posterior Probability ≥0.90	**Posterior Probability ≥0.80**
20-21	4	4
22-27	5	4
28	5	5
29-35	6	5
36	6	6
37-43	7	6
44-51	8	7
52	9	7
53-59	9	8
60	10	8
61-67	10	9
68-69	11	9
70-75	11	10
76-78	12	10

Criteria for 79 or more evaluable participants will be calculated based on the posterior probability of ≥0.90 and ≥0.80 respectively.

10.14. Appendix 14: Anti-infectious Prophylaxis and Monitoring Recommendation

Participants should receive antimicrobial prophylaxis as per the recommendations below.

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	Administer for participants with ANC <1000/ µL	Administer for 14 days for ANC <1000/ µL. 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 ANC <500/µL for >7 days --- Prolonged ANC <500/µL for >3 weeks	Until neutropenia resolution (ANC ≥500/µL). Prophylaxis may be extended at the discretion of the investigator as clinically indicated. --- Until neutropenia resolution (ANC ≥500/µl)
Anti-viral	Acyclovir or alternative	Initiate antiviral prophylaxis to prevent herpes zoster reactivation	Continue for 3 months following the end of treatment
CMV	On study CMV testing by PCR should be performed on a monthly to every three-month schedule depending on risk factors. Valganciclovir 900 mg PO BID Alternative (ganciclovir i.v., foscarnet i.v.) or other approved agents.	For participants with CMV copy number ≥1000/mL, or per local standard of care, initiation of antiviral treatment is recommended (other risk factors including the rise in CMV copy number should be considered) Treatment is required for symptomatic participants irrespective of viral load	Continue therapy until two consecutive measurements at least 14 days apart show viral load < 1000/mL and resolution of symptoms (if present)
Pneumocystis jirovecii Pneumonia (PJP)	Trimethoprim-sulfamethoxazole DS – 1 tablet PO daily, three times per week	For participants CD4 cell count < 200/µL or unknown	Suggested duration: until CD4 count ≥200 cells/µL based on 2 consecutive measurements at least 14 days apart.

Prophylaxis	Therapy	Start	Stop
	Alternatives: Pentamidine (or alternative), or Dapsone – 100 mg PO daily or 50 mg PO BID, or Atovaquone – 1500 mg PO daily		Prophylaxis may be extended at the discretion of the investigator as clinically indicated.
Hypogammaglobulinemia/ Subcutaneous or 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	Prophylactic or therapeutic administration of G-CSF in participants with severe neutropenia or with serious neutropenic complications should be considered by investigators consistent with the ASCO guidelines (Smith et al, 2015) in order to decrease the risk of neutropenia specifically in participants with baseline extensive BM involvement and/or low neutrophil counts.	For participants with ANC <1000/µL	Until resolution of neutropenia.

Dimopoulos et al, 2021; NCCN 2022b NCCN 2022c; NCCN 2022a; Smith et al, 2015; Raje et al, 2022.

10.15. Appendix 15: 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
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen-presenting cell
ASCO	American Society of Clinical Oncology
ASCT	allogeneic stem cell transplant
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUCτ	area under the serum concentration-time curve from time zero to time τ
AV	Atrioventricular
AxMP	auxiliary medicinal product
BCMA	B-cell maturation antigen
β–hCG	beta-human chorionic gonadotropin
BICR	blinded independent central review
BID	twice a day
BM	bone marrow
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BMMC	bone marrow mononuclear cells
BOR	best overall response
bpm	beats per minute
BsAb	bispecific antibody
BUN	blood urea nitrogen
C	Cycle
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T-cell therapy
CB	clinical benefit
CD#	cluster of differentiation and number (eg, CD38)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase

Abbreviation	Term
C_{max}	maximum concentration
CMV	cytomegalovirus
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
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
CXDX	Cycle X Day X
CYP	cytochrome P450
D	Day
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOCR	duration of complete response
DOR	duration of response
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
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EM	Extramedullary
EMD	extramedullary disease
EMG	Electromyography
EORTC MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma module

Abbreviation	Term
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 Questionnaire–30 (items)
EOS	end of study
EOT	end of treatment
EQ-5D	EuroQoL 5 Dimensions
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (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
G-CSF	granulocyte colony stimulating factor
gDNA	genomic DNA
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
GVHD	graft versus host disease
HA	Health Authority
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
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 of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Term
ICU	intensive care unit
ID	identification
Ig#	immunoglobulin (eg, IgM, IgA, etc)
IMiD	immunomodulatory drug
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IR	Immune-related
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
ISS	International Staging System
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
IWR	interactive Web-based response
J-PI	Japan prescribing information
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
MHRA	Medicines and Healthcare products Regulatory Agency
MM	multiple myeloma
MQI	medically qualified individual
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

Abbreviation	Term
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NCV	Nerve conduction velocity
NDA	New drug application
NGS	next generation sequencing
NIMP	noninvestigational medicinal product
NSAID	non-steroidal anti-inflammatory drug
OR	objective response
ORR	objective response rate
OS	overall survival
$PaCO_2$	partial pressure of arterial carbon dioxide
PJP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	oral (orally)
POEMS	polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	preferred term; prothrombin time
PVC	premature ventricular contraction/complex
QT	time from the beginning of the QRS complex to the end of the T wave
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
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

Abbreviation	Term
RP2D	recommended Phase 2 dose
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sBCMA	soluble BCMA
SC	subcutaneous(ly)
sCR	stringent complete response
SMQ	standardized MedDRA queries
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
TNFr SF 17	tumor necrosis factor receptor superfamily 17
TTR	time to response
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VAS	visual analogue scale
VHP	voluntary harmonization procedure
VGPR	very good partial response
WBC	white blood cell
WOC	withdrawal of consent
WOCBP	woman/women of childbearing potential

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