MAGNETISMM-2

A PHASE I, OPEN LABEL STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETIC OF ELRANATAMAB (PF-06863135), A B-CELL MATURATION ANTIGEN (BCMA) - CD3 BISPECIFIC ANTIBODY, AS A SINGLE AGENT IN JAPANESE PARTICIPANTS WITH RELAPSED/REFRACTORY ADVANCED MULTIPLE MYELOMA

Study Intervention Number:	PF-06863135
Study Intervention Name:	Elranatamab
US IND Number:	N/A
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ClinicalTrials.gov NCT:	NCT04798586
Protocol Number:	C1071002
Phase:	1

Short Title: MAGNETISMM-2, A Phase 1 Study of Elranatamab (PF-06863135) in Japanese Participants with Multiple Myeloma

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	06 October 2020	N/A
Amendment 1	03 December 2020	The primary purpose of this amendment is to incorporate changes/clarifications requested by the PMDA following agency review. Objectives and Endopoints in Section 1.1. Synopsis and Section 3. Objectives and Endpoints: Corrected PK parameter of the secondary endpoint to V_z/F. Section 1.3.1 Schedule of Activities for Q1W Dose Interval and 1.3.2 Schedule of Activities for Q2W Dose Interval: Added HB viral load monitoring every 12 weeks for participants who are HBV DNA negative but HBsAb and HBcAb positive at screening. Added urine pregnancy test to the footnote. Section 1.3.2. Schedule of Activities for Q2W Dose Interval: Removed post-dose PK sampling from footnote 18 as a typo. Section 4.3.3. Dose Limiting Toxicity Definition: Clarified the DLT definition for dose delay. Section 5.2. Exclusion Criteria: Added clarification that known or suspected hypersensitivity to component of PF-06863135 is also excluded. Section 8.2.5. Clinical Safety Laboratory Assessments: Added HB viral load monitoring every 12 weeks for participants who are HBV DNA negative but HBsAb and HBcAb positive at screening and guidance when re-activaiton of HBV is suspected.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Section 8.3.5.1. Exposure During Pregnancy: Extended the reporting period of EDP from 28 days to 56 days from the last dose.  Section 9.4.1.2. Adverse Events and Section 9.4.1.3. Laboratory Test Abnormalities: Moved to the Section 9.4.2. Secondary Endpoint(s). Section 9.4.2.3. Best Overall Response: Corrected the definition of overall response and clinical benefit. Section 9.4.2.8. PF-06863135 Pharmacokinetic Analysis: Corrected PK parameter of the secondary endpoint to V_z/F and deleted $R_{ac.}$ Section 9.4.3.1 Electrocardiogram Analysis: Removed 'The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions.' as only QTcF will be analyzed. Section 10.4.1. Male Participant Reproductive Inclusion Criteria: Extended the required contraception period of EDP from 28 days to 56 days from the last dose. Section 10.4.2. Female Participant Reproductive Inclusion Criteria: Added

Document History		
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		clarification that women who are currently breastfeeding and intend to interrupt breastfeeding are excluded. Extended the required contraception period of EDP from 28 days to 56 days from the last dose. Section 10.4.4. Contraception Methods: Add clarification that oral progestogen only hormone contraception has not been approved in Japan. In addition, other clarifications, administrative, and typographical modifications were made.
Amendment 2	10 June 2021	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. Section 2.2.6: Additional information and updates were added based on Phase 1 results (C1071001). Section 2.3.1: Risk assessment was updated based on the current data. Section 6.5: Clarification and recommendation for administration of COVID-19 vaccines were added.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Section 6.5.2: Requirement of premedication for CRS mitigation was added. Section 8.3.1: 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. Section 8.3.5.1 and Section 10.4: Contraception use has been extended from 56 days to 90 days after the last dose of study intervention. Given the INN is established, PF-06863135 has been replaced with the INN name, elranatamab. Clarifications and typo corrections were made throughout.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: MAGNETISMM-2, A Phase 1 study of Elranatamab (PF-06863135) in Japanese Participants with Multiple Myeloma

Background and Rationale

Elranatamab is a bispecific monoclonal antibody targeting both B-cell maturation antigen (BCMA, also known as tumor necrosis factor receptor superfamily member 17 [TNFRSF17] or cluster of differentiation [CD] 269) on multiple myeloma (MM) cells and CD3 on T-cells. 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. Elranatamab is currently in clinical development for MM.

Study C1071001 is an ongoing Phase 1, first-in-human, open-label study to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacodynamics (PD) and clinical activity of elranatamab as monotherapy and in combination with other agents. The dose escalation phase of Study C1071001 is currently ongoing with doses up to 1000 µg/kg once weekly (Q1W) via subcutaneous (SC) administration have been evaluated. Once weekly (Q1W) intravenous (IV) dosing was also explored in earlier dose escalation part of the study. Dose-limiting toxicities (DLTs) of febrile neutropenia Grade 3 and electrocardiogram QT prolonged Grade 1 were observed at 30 and 50 µg/kg IV, respectively. However, no dose limiting toxicities (DLTs) were observed for all SC dose cohorts in Study C1071001. Based on the safety, tolerability, PK, PD, and clinical activity of elranatamab in non-Japanese population in Study C1071001, 1000 µg/kg SC Q1W have been selected as the recommended Phase 2 dose (RP2D) and regimen in non-Japanese population. While 1000 µg/kg SC showed tolerable and manageable safety profile, a priming dose approach may mitigate the consequences of CRS which is mainly observed after the initial dose, and a minimal impact on achieving efficacious exposure threshold is predicted in a priming dose approach. For further evaluation in elranatamab studies, a priming dose approach is planned to be used.

The primary purpose of this Phase 1 study (C1071002) is to confirm the safety and tolerability of elranatamab 1000 µg/kg SC Q1W with a priming dose of 600 µg/kg SC in Japanese participants. Japanese participants with relapsed or refractory MM will be enrolled to permit Japan participation in pivotal studies including but not limited to the phase 2 registrational study in participants with triple-class refractory MM.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability at the RP2D with a priming dose approach of single-agent elranatamab administered to Japanese participants	• First cycle including a priming dose (4 weeks) Dose Limiting Toxicities (DLTs)

Objectives	Endpoints
Secondary:	**Secondary:**
• To evaluate the overall safety profile	• Adverse events (AEs) as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. Severity of CRS and ICANS will be graded according to ASTCT grading criteria • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
• To evaluate the single-dose and multiple-dose PK of elranatamab	• PK parameters of elranatamab: Cycle 0 Day 1 (C0D1) dose, Cycle 1 Day 1 (C1D1) dose and Cycle 2 Day 1 (C2D1) dose maximum concentration (C_{max}), area under the concentration versus time curve from time zero to the last quantifiable time point prior to the next dose (AUC_{last}) and if data permit, apparent clearance (CL/F), apparent volume of distribution during terminal phase (Vz/F), and terminal elimination ($t_{1/2}$) • Pre-dose trough concentrations after multiple doses of elranatamab
• To evaluate the immunogenicity of elranatamab	• Incidence and titers of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) against elranatamab
• To evaluate preliminary anti-tumor activity	• Objective response rate (ORR) based on the IMWG response criteria for MM • Time to event endpoints: time to response (TTR), duration of response (DOR), progression free survival (PFS) and overall survival (OS), as assessed by IMWG criteria for response • Minimal residual disease (MRD) after treatment with elranatamab using IMWG MRD criteria
• To characterize the impact of elranatamab on systemic soluble immune factors	• Pre- and post-dose quantification of soluble cytokines in serum
[redacted]	

Overall Design

This is a Phase 1, open-label, multi-center study to evaluate the safety, tolerability, PK, PD, and clinical activity of elranatamab monotherapy. Approximately 4-6 Japanese participants are expected to be enrolled overall in this study, and the RP2D (1000 μg/kg) which was declared in non-Japanese participants in the study C1071001 with a priming dose (600 μg/kg) will be administered to each participant.

DLTs through the first dose (a priming dose) to the end of the first cycle (total 4 weeks) will be evaluated with the target DLT rate of 25%.

The study population consists of Japanese adult participants with relapsed or refractory MM who have received at least 3 prior therapies, including immunomodulatory drug (IMID), proteasome inhibitor (PI) and anti-CD38 antibody, with measurable disease based on IMWG guidelines, aged ≥20 years.

The study will be conducted with approximately 5 study sites in Japan.

Number of Participants

A maximum of approximately 6 participants will be enrolled to study intervention (see Section 9.2). However, the total number of participants will depend on the number of participants evaluable for DLT. A participant is classified as DLT-evaluable if he/she experiences a DLT (irrespective of whether they received all of the planned doses of investigational product and study intervention and scheduled safety assessments during the DLT window) or if he/she otherwise in the absence of a DLT receives all of the planned doses of investigational product and study intervention and has received scheduled safety assessments during the DLT window. If a participant fails to meet these criteria, he/she may be replaced.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. 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.

Intervention Groups and Duration

The initial dose will be 600 μg/kg SC which will be injected on Cycle 0 Day 1 (7 days prior to Cycle 1 Day 1) as a priming dose. During treatment cycle (full dose from Cycle 1 Day 1 and thereafter), 1000 μg/kg SC will be given weekly in 3 week cycles. Treatment will continue until progressive disease (PD), unacceptable toxicity, withdrawal from treatment, investigator decision, or study termination, whichever occurs first.

Dose modification information is provided in the Section 6.6.

Data Monitoring Committee or Other Independent Oversight Committee:

This study will not use a DMC.

Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor.

Sample Size Determination

The total number of participants will depend on the absence/presence of DLT in the initial 4 participants and the number of participants evaluable for DLT. Additional 2 participants will be enrolled to verify the toxicity in Japanese population if at least one DLT is observed in the initial 4 participants. Thus, maximum 6 evaluable participants may be enrolled in this study. The actual sample size may be smaller than 6 but not less than 4, depending on the underlying dose toxicity profile.

Although the sample size is not based on any statistical considerations, the study would have >55% chance to declare the RP2D determined in C1071001 with a priming dose to have exceeded the maximum tolerated dose (MTD) in Japanese participants if the true DLT rate for Japanese participants is over 30%. Especially, the study would have 74.6% and 87.5% chance if the true DLT rate is 40% and 50%, respectively. It is determined that the RP2D with a priming dose exceeds the MTD in the Japanese population if ≥2 DLTs are observed in this study.

Statistical Analysis for Primary Endpoint

DLT is the primary endpoint of this study. The occurrence of DLTs observed in the dosing cohorts is used to confirm the safety and tolerability of the RP2D with a priming dose. Adverse events constituting DLTs will be listed.

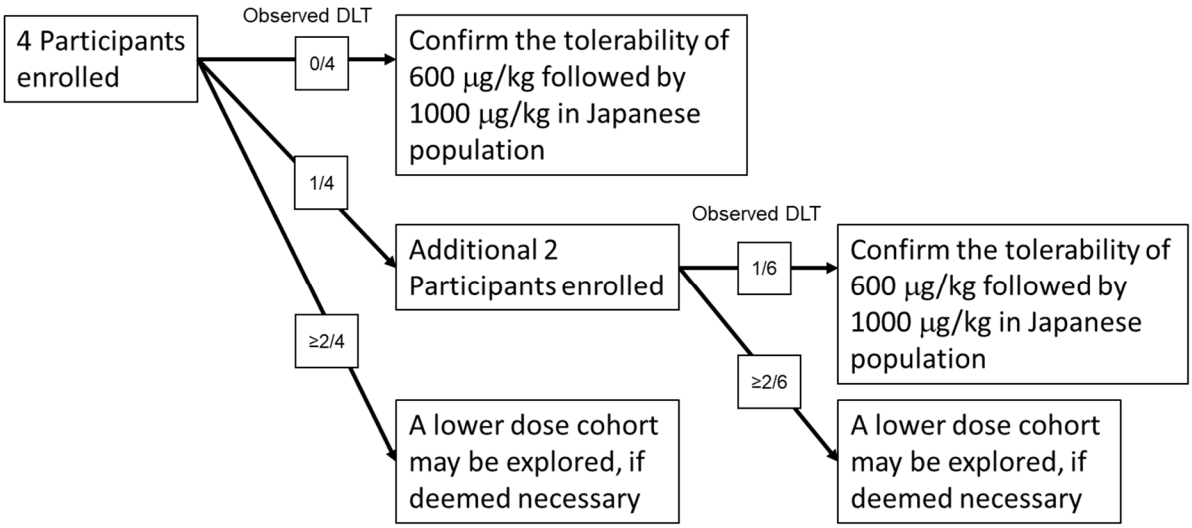
Confirmation of RP2D in Japanese participants

If there is either no DLT in the initial 4 participants or one DLT in 6 participants, the RP2D which were declared in non-Japanese participants with a priming dose will be confirmed to be tolerable in Japanese participants. If DLT is observed in ≥2 of the initial 4 participants or 6 participants, a lower dose cohort may be explored, if deemed necessary.

Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

1.2. Schema



600 μg/kg followed by1000 μg/kg will be dosed to each participant

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 assessment required for compliance with the protocol.

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

1.3.1. Schedule of Activities for Q1W Dose Interval

Schedule of Activities Visit Identifier[a]	**Screening[1]**	**Treatment Period**														**28 Days Follow-up [33]**	**Survival Follow-up [35]**
Study Day	**Within 28 days prior to treatment**	**Cycle 0 (single priming dose) (7 days)**				**Cycle 1 (1 Cycle = 3 weeks)**						**Cycle 2 onwards**			**EOT [34]**		
		1	**2**	**3**	**4***	**1**	**2**	**3**	**4***	**8**	**15**	**1**	**8**	**15**			
Visit Window (days)						±1				±3	±3	±3	±3	±3		+7	±14
Informed consent[2]	X																
Myeloma history[3]	X																
Medical history[4]	X																
Baseline signs and symptoms[5]	X																
Eligibility Criteria and Registration[6]	X																
Participant hospitalization[7]		X	X	X		X	X	X									
Clinical Evaluation																	
Physical examination[8]	X	X															
Brief physical examination[8]		X	X			X	X			X	X	X	X[8]	X[8]	X	X	
Neurological examination[9]	X	X	X			X	X			X	X	X	X	X	X	X	
Weight[10]	X	X				X						X			X		
Vital signs[11]	X	X	X			X	X			X	X	X	X	X	X	X	
ECOG performance status[12]	X	X				X				X	X	X			X		
(12 lead) ECG[13]	X	X	X		X	X	X		X	X	X	X	X[13]	X[13]	X		
Echo or MUGA[14]	X	If there is a history of cardiac events, perform when clinically indicated.													X		

Schedule of Activities Visit Identifier[a]	**Screening[1]**	**Treatment Period**														**28 Days Follow-up [33]**	**Survival Follow-up [35]**
Study Day	**Within 28 days prior to treatment**	**Cycle 0 (single priming dose) (7 days)**				**Cycle 1 (1 Cycle = 3 weeks)**						**Cycle 2 onwards**			**EOT [34]**		
		1	**2**	**3**	**4***	**1**	**2**	**3**	**4***	**8**	**15**	**1**	**8**	**15**			
Visit Window (days)						±1				±3	±3	±3	±3	±3		+7	±14
Hematology[15]	X	X	X			X	X			X	X	X	X[15]	X[15]	X	X	
Blood Chemistry[16]	X	X	X			X	X			X	X	X	X[16]	X[16]	X	X	
Coagulation[17]	X	X				X				X	X	X	X[17]	X[17]	X	X	
Hepatitis assessment[18]	X											X (If applicable)					
Urinalysis[19]	X	X													X	X	
Pregnancy test and contraception check[20]	X	X										X			X	X	X
Treatment																	
Treatment with elranatamab[21]		X				X				X	X	X	X	X			
Premedication for CRS[22]		X				X											
Disease assessments																	
Genetic analysis bone marrow aspirate[23]		X															
SPEP, SIFE, serum FLC ratio, beta-2 microglobulin (local)[24]	X	X				X						X			X		If obtained as SOC prior to subsequent treatment[35]
UPEP, UIFE (local)[25]	X	X				X						X			X		
Bone marrow collection and assessments-aspirates[26]		X	At 1, 3 and 9 months after C0D1, every 6 months thereafter, at suspected CR and optional at disease progression. Collection at 9 months after C0D1 and onwards will be optional for participants who experience a plateau or CR. Check for MRD at CR.														
Bone marrow collection and assessments-biopsies[26]		X	At 1, 3 (optional) and 9 (optional) months after C0D1, every 6 months thereafter (optional), at suspected sCR and optional at disease progression. Collection at 9 months after C0D1 and onwards will be optional for participants who experience a plateau or CR.														
Disease assessments by PET/ CT[27]	X		At 1, 3 and 9 months after C0D1 and every 6 months thereafter, and at suspected CR or PD, and when clinically indicated.												X		

Schedule of Activities Visit Identifier[a]	**Screening[1]**	**Treatment Period**														**28 Days Follow-up [33]**	**Survival Follow-up [35]**
Study Day	**Within 28 days prior to treatment**	**Cycle 0 (single priming dose) (7 days)**				**Cycle 1 (1 Cycle = 3 weeks)**						**Cycle 2 onwards**			**EOT [34]**		
		1	**2**	**3**	**4***	**1**	**2**	**3**	**4***	**8**	**15**	**1**	**8**	**15**			
Visit Window (days)						±1				±3	±3	±3	±3	±3		+7	±14
Other clinical assessments																	
Serious and nonserious AE monitoring[28]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant treatment(s)[29]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Local Site Injection Tolerability Assessment[30]		X				X				X	X						
Pharmacokinetic (PK) assessments																	
Blood sample for elranatamab		See Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments															
Immunogenicity assessments																	
Anti-drug antibodies and neutralizing antibodies against elranatamab		See Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments															
Pharmacodynamic assessments																	
CCI [redacted]		[redacted]															
CCI [redacted]																	
Bone marrow aspirate sample for NGS MRD determination[26]		X	At 1, 3 (optional) and 9 (optional) months after C0D1, every 6 months thereafter (optional), at suspected sCR and optional at disease progression if BM disease assessments are completed.														
Serum sample for circulating proteins CCI [redacted] analysis		X	See Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments														

Schedule of Activities Visit Identifier[a]	Screening[1]	Treatment Period														28 Days Follow-up [33]	Survival Follow-up [35]
Study Day	Within 28 days prior to treatment	Cycle 0 (single priming dose) (7 days)				Cycle 1 (1 Cycle = 3 weeks)						Cycle 2 onwards			EOT [34]		
		1	2	3	4*	1	2	3	4*	8	15	1	8	15			
Visit Window (days)						±1				±3	±3	±3	±3	±3		+7	±14
Other assessments																	
CCI [redacted]																	
Post Treatment																	
Survival follow-up[35]																	X

*Please see Schedule of Pharmacokinetic, Soluble Factor and Cytokine Assessments for additional assessments on Cycle 0 Day 4 (C0D4) and Cycle 1 Day 4 (C1D4).

a. Day relative to start of study intervention (Day 1).
b. 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.

Footnotes for Schedule of Activities

1. **Screening:** To be completed within 28 days prior to start of study treatment.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures, and be completed within 28 days prior to start of study treatment.
3. **Myeloma History:** will be collected within 28 days during screening prior to start of study treatment. Includes history of disease under study including details of primary diagnosis, biopsy information, and treatment history.
4. **Medical History:** Includes history of disease process other than the cancer under study (active or resolved) and concurrent illness. Includes prior treatments and any current medical treatments for any condition.
5. **Baseline Signs & Symptoms:** Participants will be asked about any signs and symptoms experienced within the 28 days prior to C0D1. During the study, any new or worsened conditions since baseline will be recorded on the Adverse Events (AE) case report form (CRF) page.
6. **Registration:** Participant number assigned by Pfizer Inc.
7. **Participant hospitalization:** All participants will be hospitalized for 72 hrs from C0D1 and C1D1. Hospitalization period may be extended if the participant experiences abnormal laboratory findings or ongoing adverse events that require further hospitalization.
8. **Physical examination (PE):** Physical examination will include height at screening. No need to repeat on C0D1 if screening assessment is performed within 3 days of dosing, including assessment of weight. **Brief Physical Examination including Baseline Signs and Symptoms:** A symptom directed exam and assessment for emergent toxicities or changes from prior visits, does not need to be repeated if done within 24 hours of C0D1. Assessment on Day 8 and Day 15 is not required in Cycle 3 onward.

9. **Neurological examination:** From Cycle 0 to Cycle 3, neurological examination should be performed on Day 1, Day 8 and Day 15. From Cycle 4 onward, it should be performed on Day 1. In addition, from Cycle 0 to Cycle 1, neurological examination should be performed on Day 2. See Section 8.2.1 for the required neurological examination.
10. **Weight:** Weight will be measured prior to dosing.
11. **Vital Signs:** Includes temperature, blood pressure (BP), and pulse rate to be recorded in the sitting position after 5 minutes of rest.
12. **Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Section 10.12.
13. **12-Lead electrocardiogram (ECG):** At each time point except at screening (see the schedule of activities), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTc interval. At screening, single 12-lead ECG will be performed. On C0D1 until C2D15, triplicate 12-lead ECGs will be performed to determine mean QTcF interval. On Day 1 of Cycle 0, Day 1, 8 and 15 of Cycles 1 and 2, ECGs will be performed prior to investigational product administration (and premedication), and the end of subcutaneous injection. From Cycle 3 onwards, single 12-lead ECG will be performed on Day 1 of each cycle prior to investigational product administration (and premedication, if applicable). When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. When CRS symptoms are observed, ECG should be skipped until the symptoms are resolved.
14. **Echocardiogram (Echo) or multigated acquisition scan (MUGA):** Echo or MUGA will be evaluated in participants with previous history of cardiac events. For these participants, an Echo or MUGA will be performed at screening, when clinically indicated and at the end of treatment (EOT) visit.
15. **Hematology:** No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. Assessment on Day 8 and Day 15 is not required in Cycle 3 onward. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Section 10.2 for Laboratory Tests list.
16. **Blood Chemistry:** No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. Assessment on Day 8 and Day 15 is not required in Cycle 3 onward. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Section 10.2 for Laboratory Tests list.
17. **Coagulation:** No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. Assessment on Day 8 and Day 15 is not required in Cycle 3 onward. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Section 10.2 for Laboratory Tests list.
18. **Hepatitis assessment:** Screening tests for hepatitis B (HBV) and C (HCV) should be performed including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb) and hepatitis C virus (HCV) antibody. In the case of apparent ongoing HBV or HCV infection, reflexive serum DNA or RNA viral load testing, respectively, will be performed. Participants with positive HBsAb and positive HBcAb are allowed to participate in the study if they have negative HBV DNA test at screening but HB viral load should be monitored for re-activation every 12 weeks. Participants with HBsAb positive who have been vaccinated with HBV are exempted from the testing of HB viral load. See Section 10.2 for Laboratory Tests list.
19. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. Following C0D1, only obtain as clinically indicated until EOT. See Section 10.2 for Laboratory Tests list.
20. **Pregnancy Test and contraception check:** Serum or urine pregnancy test for females of childbearing potential (see Pregnancy Testing Section 8.2.6). Contraception use for males and women of childbearing potential (WOCBP) will be checked to confirm that contraception is used consistently and correctly.
21. **Treatment with investigational product elranatamab:** Investigational product as a priming dose will be administered on C0D1 (7 days prior to C1D1). After the priming dose, investigational product as a full dose of 1000 µg/kg will be administered Day 1, 8 and 15 of each cycle (see Administration Section 6.1). If a participant has received treatment with every week dosing (Q1W) elranatamab for at least 6 months, and disease assessments have remained stable

over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks after consultation with sponsor. If the participant subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing. If the dose intervals is increased from weekly to every 2 weeks, see Schedule of Activities for Q2W for subsequent cycles.

22. **Premedication for CRS:** Must be administered 60 minutes (±15 minutes) prior to elranatamab dose, See Section 6.5.2.
23. **Genetic Analysis:** Bone marrow aspirates taken on C0D1 will be evaluated for t(4;14)(p16;q32), t(14;16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities, unless data is available from tests conducted within 6 months or less of participant enrollment. Sample for C0D1 may be taken up to 7 days before study treatment.
24. **Serum immunofixation electrophoresis (SIFE), serum protein electrophoresis (SPEP), serum free light chain analysis (FLC) tests and beta-2 microglobulin tests:** No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 8.1.1.1 for laboratory disease assessment tests list. Beta-2 microglobulin will only be collected on C0D1. Note that SIFE will be completed at baseline, when electrophoresis shows no measurable protein, at suspected CR/sCR, and at suspected progression (clinical or biochemical). When a CR/sCR or a clinical or biochemical progression is suspected, SPEP, SIFE, and serum free light chain analysis (FLC) tests will be repeated within 1 to 4 weeks. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered.
25. **24 hr urine immunofixation electrophoresis (UIFE), 24 hr urine protein electrophoresis (UPEP):** No need to repeat on C0D1 if baseline assessment performed within 3 days prior to that date. See Assessments Section 10.2 for laboratory tests list. Note that UIFE will be completed at baseline, when electrophoresis shows no measurable protein, at suspected CR/sCR, and at suspected progression (clinical or biochemical). When a CR/sCR or a clinical or biochemical progression is suspected, UPEP and UIFE will be repeated within 1 to 4 weeks. If samples collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration.
26. **Bone Marrow Collection and Assessments:** For C0D1 and on-treatment bone marrow collections and assessments, see Section 8.1.1.2. Sample for C0D1 may be taken up to 7 days before study treatment. Bone marrow collections and local plasma cell assessments should be fixed according to the calendar, regardless of treatment delays. Bone marrow evaluation consisting of bone marrow aspirate and/or bone marrow biopsies will be performed to follow disease response. When bone marrow plasma cell infiltration is assessed by both bone marrow aspirate and by bone marrow biopsy, the highest value of bone marrow plasma cell infiltration should be utilized for response evaluation. Bone marrow aspirates will also be collected and plasma cells will be evaluated at time of suspected CR and optional at time of suspected disease progression. Bone marrow biopsy will also be collected and plasma cells will be evaluated when confirmation of sCR is required. For participants who experience a plateau or CR, additional bone marrow aspirates at 9 months after C0D1 and onwards will be optional. Optional bone marrow aspirate and biopsy samples will also be taken at disease progression if a sample was not taken within the past 4 weeks. Minimal residual disease (MRD) will be evaluated by high-throughput sequencing using a next generation sequencing (NGS) assay, if CR is observed; a sample taken on C0D1 will be used as a reference. Samples at 1 and 3 months after C0D1 will be collected ±7 days; samples at 9 months after C0D1 and later will be collected ±14 days.
27. **Disease assessments by fluorodeoxyglucose (FDG) positron emission tomography (PET)/ computed tomography (CT):** See Section 8.1.1.3. Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 28 days before C0D1, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given participant, and (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the participant's source notes. Images may also be required at suspected CR, when disease progression is suspected (eg, symptomatic deterioration), and when otherwise clinically indicated. Images at 1 and 3 months after C0D1 will be collected ±7 days; images at 9 months after C0D1 and later will be collected ±14 days. For participants with only skin involvement, skin lesions should be measured with a ruler.
28. **Adverse Event (AE) Assessments:** AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. However, the severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS) will be assessed according to the ASTCT grading[22] (See

Section 10.13) instead of CTCAE. 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 through and including a minimum of 28 calendar days after the last investigational product administration. If the participant begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

29. **Concomitant Treatments:** All concomitant medications and nondrug supportive interventions should be recorded on the CRF.
30. **Local Site Injection Tolerability Assessment:** Assessment of injection site should be conducted at 1 to 4 hours following treatment administration on Day 1 of Cycle 0, Day 1, 8 and 15 for the first cycle. If injection site pain or injection site reaction (ISR) characteristics continue to persist after the first cycle, local site injection tolerability assessments should continue until the symptoms resolve.

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33. **28 Days follow-up:** At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, participants will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related toxicity. Participants continuing to experience toxicity 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.
34. **End of Treatment (EOT) Visit:** Obtain these assessments if not completed in the last week (last 4 weeks for disease assessments).
35. **Survival follow-up:** Following discontinuation of study treatment (unless participants are lost to follow-up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected at visit or by telephone every 3 months until death, or at least 12 months after the first treatment of the last participant, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected. Any standard of care (SOC) disease assessments obtained between EOT and subsequent anti-cancer therapy will be collected. Information of AEs and contraception check will also be collected until the end of active AE reporting period as defined in Section 8.3.1, and contraception check period in Section 10.4.

Pharmacokinetic, Soluble Factor, Cytokine Activities CCI Sampling

The schedule of pharmacokinetic, soluble factor and cytokine activities table provides an overview of the protocol visits and procedures. The investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the wellbeing of the participant.

Visit Identifier	**Up to 7 days prior to C0D1**	**Treatment Period**																					**EOT**
		Cycle 0						**Cycle 1**											**Cycle 2**			**Cycle 3 onwards**	
Study Day		**D1**				**D2**	**D4**	**D1**				**D2**	**D4**	**D8**			**D15**		**D1**	**D8**	**D15**	**D1**	
Hours Pre/ after dosing†		**0**	**2***	**4**	**8**	**24**	**72**	**0**	**2***	**4**	**8**	**24**	**72**	**0**	**2***	**4**	**0**	**2***	**0**	**0**	**0**	**0**	
Visit window				±0.5 hr	±1 hr	±3 hrs	±24 hrs			±0.5 hr	±1 hr	±3 hrs	±24 hrs			±0.5 hr							
Serum sample for circulating proteins CCI CCI analysis [1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		3 (±7 days) and 9 months (±14 days) after C0D1. In addition, whenever CRS is suspected.	
Samples for elranatamab blood level[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X[2]	X
Blood samples for ADA and NAb[3]		X						X									X		X			X[3]	X
CCI																							

Abbreviations: ADA = Anti- elranatamab antibodies; BCMA = B-cell maturation antigen; CRS = cytokine release syndrome; D = Day; EOT = end of treatment; NAb = neutralizing antibodies.

*The 2-hour sample should be taken at 2 hours post-injection ±12 minutes.

† All efforts will be made to obtain the pharmacokinetic (PK) samples at the exact nominal time relative to dosing. However, samples obtained within the window specified will be considered acceptable.

Footnotes for Schedule of Pharmacokinetic, Soluble Factors and Cytokine Activities

1. **Serum sample for circulating proteins CCI analysis:** See Section 10.2 for a full list of cytokine assessments. All samples will be analyzed centrally. Collect approximately 4 mL of whole blood for processing into serum at indicated visits. All 0 hour samples will be collected within 2 hours prior to investigational product administration on days whereby investigational product is to be administered. If CRS is suspected, an adhoc cytokine sample will be collected (see Section 8.8.2). Should the site require cytokine information for participant management, the site will have the option of collecting an additional sample for local analysis. If a sample for cytokine panel evaluation is due to be collected on the same day as the day a suspected CRS event occurs, then an ad hoc sample for central analysis is not required/collected. However, an ad hoc sample for local analysis may still be collected for participant management.
2. **Blood sample for elranatamab blood level:** Approximately 5 mL sample of whole blood (to provide approximately 2 mL of serum) will be collected at each time point for PK analysis of elranatamab. After Cycle 8, pre-dose PK samples will be collected only on every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional PK sample should also be taken if CRS is suspected, and a PK sample is not already scheduled to be taken (eg, Cycle 3 onwards).
3. **Anti elranatamab Antibodies (ADA) and Neutralizing Antibodies (NAb):** Collection of two 1 mL pre-dose serum samples (from 5 mL total whole blood) to detect the presence of antibodies to elranatamab is to be obtained prior to the start of treatment. Participants having an unresolved adverse event 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 adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor. After Cycle 4, pre-dose ADA and NAb samples will be collected only on Cycles 6, 8, and every 4th cycle thereafter (Cycle 8, Cycle 12, Cycle 16, etc.).

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1.3.2. Schedule of Activities for Q2W Dose Interval

Schedule of Activities **Visit Identifier[a]**	**Treatment Period (at least 6 months after C1D1)** **1 Cycle = 4 weeks**		**EOT[24]**	**28 Days Follow-up[25]**	**Survival Follow-up[26]**
Study Day	**Day 1**	**Day 15**			
Visit Window (days)	–3/+7	–3/+7		+7	±14
Clinical Evaluation					
Brief physical examination	X		X	X	
Neurological examination	X				
Weight[1]	X		X		
Vital signs (BP/pulse rate/Temp)[2]	X	X	X	X	
ECOG performance status[3]	X	X	X		
(12 lead) ECG[4]	X		X		
Echo or MUGA[5]	If there is a history of cardiac events, perform when clinically indicated.		X		
Safety Laboratory					
Hematology[6]	X		X	X	
Blood Chemistry[7]	X		X	X	
Coagulation[8]	X		X	X	
Hepatitis assessment[9]	If applicable				
Urinalysis[10]	If clinically indicated		X	X	
Pregnancy test and contraception check[11]	X		X	X	X
Treatment					
Treatment with elranatamab[12]	X	X			
Disease assessments					
SPEP, SIFE, serum FLC ratio, beta-2 microglobulin (local)[13]			X		If obtained as SOC prior to subsequent treatment[26]
UPEP, UIFE (local)[14]			X		
Bone marrow collection and assessments- aspirates[15]	At 9 months after C0D1, every 6 months thereafter, at suspected CR and optional at disease progression. Collection at 9 months after C0D1 and onwards will be optional for participants who experience a plateau or CR. Check for MRD at CR.				

Schedule of Activities Visit Identifier[a]	Treatment Period (at least 6 months after C1D1) 1 Cycle = 4 weeks		EOT[24]	28 Days Follow-up[25]	Survival Follow-up[26]
Study Day	**Day 1**	**Day 15**			
Visit Window (days)	–3/+7	–3/+7		+7	±14
Bone marrow collection and assessments- biopsies[15]	At 9 months (optional) after C0D1, every 6 months thereafter (optional), at suspected sCR and optional at disease progression. Collection at 9 months after C0D1 and onwards will be optional for participants who experience a plateau or CR.				
Disease assessments by PET/ CT[16]	At 9 months after C0D1 and every 6 months thereafter, and at suspected CR or PD, and when clinically indicated.		X		
Other clinical assessments					
Serious and non-serious AE monitoring[17]	→	→	→	→	
Concomitant treatment(s)[18]	→	→	→	→	→
Pharmacokinetic (PK) assessments					
Blood sample for elranatamab[19]	X		X		
Immunogenicity assessments					
Anti-drug antibodies and neutralizing antibodies against elranatamab[20]	X		X		
Pharmacodynamic assessments					
CCI					
Bone marrow aspirate sample for NGS MRD determination[15]	At 9 months (optional) after C0D1, every 6 months thereafter (optional), at suspected sCR and optional at disease progression if BM disease assessments are completed.				
Serum sample for circulating proteins CCI CCI analysis[23]	9 months (±14 days) after C0D1. In addition, whenever CRS is suspected.				
Post- Treatment					
Survival follow-up[26]					X
a. Day relative to start of study intervention (Day 1).					

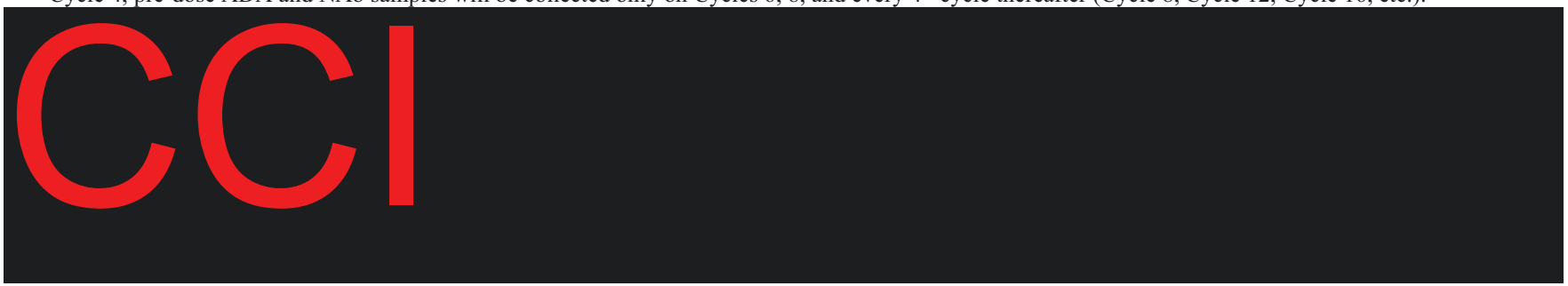
Footnotes for Schedule of Activities

1. **Weight:** Weight will be measured prior to dosing.
2. **Vital Signs:** Includes temperature, blood pressure (BP), and pulse rate to be recorded in the sitting position after 5 minutes of rest.

3. **Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) – see Section 10.11.
4. **12-Lead electrocardiogram (ECG):** From Cycle 3 onwards, single 12-lead ECG will be performed on Day 1 of each cycle prior to investigational product administration (and premedication, if applicabl). When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs may be performed as clinically indicated. When CRS symptoms are observed, ECG should be skipped until the symptoms are resolved.
5. **Echocardiogram (Echo) or multigated acquisition scan (MUGA):** Echo or MUGA will be evaluated in participants with previous history of cardiac events. For these participants, an Echo or MUGA will be performed at screening, when clinically indicated and at the end of treatment (EOT) visit.
6. **Hematology:** All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Section 10.2 for Laboratory Tests list.
7. **Blood Chemistry:** All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Section 10.2 for Laboratory Tests list.
8. **Coagulation:** All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. See Section 10.2 for Laboratory Tests list.
9. **Hepatitis assessment:** For participants with negative HBV DNA test but positive HBsAb and positive HBcAb at screening, HB viral load should be monitored for re-activation every 12 weeks. Participants with HBsAb positive who have been vaccinated with HBV are exempted from the testing of HB viral load.
10. **Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal. Obtain as clinically indicated until EOT. See Section 10.2 for Laboratory Tests list.
11. **Pregnancy Test and contraception check:** Serum or urine pregnancy test for females of childbearing potential (see Pregnancy Testing Section 8.2.6). Contraception use for males and WOCBP will be checked to confirm that contraception is used consistently and correctly.
12. **Treatment with investigational product elranatamab:** Investigational product will be administered on Day 1 and 15 of each cycle (see Administration Section 6.1). Cycles would remain the same length with any skipped weekly doses noted. If the participant subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.
13. **SIFE, SPEP, FLC tests and beta-2 microglobulin tests:** See Assessments Section 8.1.1.1 for laboratory disease assessment tests list. Beta-2 microglobulin will only be collected on C0D1. Note that SIFE will only be completed at baseline, when electrophoresis shows no measurable protein, at suspected CR/sCR, and at suspected progression (clinical or biochemical). When a CR/sCR or a clinical or biochemical progression is suspected, SPEP, SIFE, and serum free light chain analysis (FLC) tests will be repeated within 1 to 4 weeks. All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered.
14. **24 hr UIFE, 24 hr UPEP:** See Assessments Section 10.2 for laboratory tests list. Note that UIFE will only be completed at baseline, when electrophoresis shows no measurable protein, at suspected CR/sCR, and at suspected progression (clinical or biochemical). When a CR/sCR or a clinical or biochemical progression is suspected, UPEP and UIFE will be repeated within 1 to 4 weeks. If samples collection day coincides with days whereby investigational product is to be administered, samples will be collected prior to investigational product administration.
15. **Bone Marrow Collection and Assessments:** See Section 8.1.1.2. Bone marrow collections and local plasma cell assessments should be fixed according to the calendar, regardless of treatment delays. Bone marrow evaluation consisting of bone marrow aspirate and/or bone marrow biopsies will be performed to follow disease response. When bone marrow plasma cell infiltration is assessed by both bone marrow aspirate and by bone marrow biopsy, the highest value of bone marrow plasma cell infiltration should be utilized for response evaluation. Bone marrow aspirates will also be collected and plasma cells will be evaluated at time of suspected CR and optional at time of suspected disease progression. Bone marrow biopsy will also be collected and plasma cells will be evaluated when confirmation of sCR is required. For participants who experience a plateau or CR, additional Bone marrow aspirates at 9 months after C0D1

and onwards will be optional. Optional bone marrow aspirate and biopsy samples will also be taken at disease progression if a sample was not taken within the past 4 weeks. Minimal residual disease (MRD) will be evaluated by high-throughput sequencing using a next generation sequencing (NGS) assay, if CR is observed; a sample taken on C0D1 will be used as a reference. Samples at 1 and 3 months after C0D1 will be collected ±7 days; samples at 9 months after C0D1 and later will be collected ±14 days.

16. **Disease assessments by PET/ CT:** See Section 8.1.1.3. Images may also be required at suspected CR, when disease progression is suspected (eg, symptomatic deterioration), and when otherwise clinically indicated. Images at 1 and 3 months after C0D1 will be collected ±7 days; images at 9 months after C0D1 and later will be collected ±14 days. For participants with only skin involvement, skin lesions should be measured with a ruler.
17. **AE Assessments:** AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. However, the severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS) will be assessed according to the ASTCT grading[22] (See Section 10.13) instead of CTCAE. 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 through and including a minimum of 28 calendar days after the last investigational product administration. If the participant begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
18. **Concomitant Treatments:** all concomitant medications and nondrug supportive interventions should be recorded on the CRF.
19. **Blood sample for elranatamab blood level:** Approximately 5 mL sample of whole blood (to provide approximately 2 mL of serum) will be collected at each time point for PK analysis of elranatamab. After Cycle 8, pre-dose PK samples will be collected only on every 4th cycle (Cycle 8, Cycle 12, Cycle 16, etc.). An additional PK sample should also be taken if CRS is suspected, and a PK sample is not already scheduled to be taken (eg, Cycle 3 onwards).
20. **Anti-drug antibodies and neutralizing antibodies against elranatamab:** Collection of two 1 mL pre-dose serum samples (from 5 mL total whole blood) to detect the presence of antibodies to elranatamab is to be obtained prior to the start of treatment. Participants having an unresolved adverse event 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 adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor. After Cycle 4, pre-dose ADA and NAb samples will be collected only on Cycles 6, 8, and every 4th cycle thereafter (Cycle 8, Cycle 12, Cycle 16, etc.).



23. **Serum sample for circulating proteins CCI [redacted] analysis:** See Section 10.2 for a full list of cytokine assessments. All samples will be analyzed centrally. Collect approximately 4 mL of whole blood for processing into serum at indicated visits. All 0 hour samples will be collected within 2 hours prior to investigational product administration on days whereby investigational product is to be administered. If CRS is suspected, an adhoc cytokine sample will be collected (see Section 8.8.2). Should the site require cytokine information for participant management, the site will have the option of collecting an additional sample for local analysis. If a sample for cytokine panel evaluation is due to be collected on the same day as the day a suspected CRS event

occurs, then an ad hoc sample for central analysis is not required/collected. However, an ad hoc sample for local analysis may still be collected for participant management.

24. **End of Treatment (EOT) Visit:** Obtain these assessments if not completed in the last week (last 4 weeks for disease assessments).
25. **28 days follow-up:** At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, participants will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related toxicity. Participants continuing to experience toxicity 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.
26. **Survival follow-up:** Following discontinuation of study treatment (unless participants are lost to follow-up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected by telephone every 3 months until death, or at least 12 months after first treatment of the last participant, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected. Any standard of care (SOC) disease assessments obtained between EOT and subsequent anti-cancer therapy will be collected. Information of AEs and contraception check will also be collected until the end of active AE reporting period as defined in Section 8.3.1, and contraception check period in Section 10.4.

2. INTRODUCTION

Elranatamab is a bispecific monoclonal antibody against B-cell maturation antigen (BCMA, also known as tumor necrosis factor receptor superfamily member 17 [TNFRSF17] or cluster of differentiation [CD] 269) and CD3 that is currently being investigated in adult participants with relapsed or refractory multiple myeloma (MM). 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.

2.1. Study Rationale

The purpose of the study is to confirm safety and tolerability at the RP2D of elranatamab with an initial single priming dose administered subcutaneously on weekly dosing schedule (Q1W) in monotherapy setting in Japanese participants with relapsed or refractory MM.

2.2. Background

2.2.1. Multiple Myeloma

MM is a hematological malignancy that is characterized by uncontrolled expansion of bone marrow plasma cells. Approximately 114,000 new cases of MM are diagnosed worldwide each year, and 80,000 patients will die from their disease.[1] In Japan, 7,880 cases were newly diagnosed as MM in 2017 and the mortality of patients with MM were 4,209 in 2018.[2]

MM is a disease that evolves from a pre-malignant stage of monoclonal gammopathy of undetermined clinical significance (MGUS), to asymptomatic smoldering myeloma, to symptomatic active myeloma.[3] During the active stage of disease, a majority of patients develop painful bone lesions and organ dysfunction, leading to anemia, renal insufficiency and hypercalcemia. Whilst patients with smoldering myeloma do not require primary therapy, the treatment regimen for patients with active disease is currently dependent on the patient's eligibility to receive an autologous stem cell transplant (ASCT). For patients <70 years old with no comorbidities, induction therapy (either proteasome inhibitor-based or immunomodulation-based regimens) combined with an ASCT is the suggested approach, with 2-year survival achieved in 80% of patients.[3,4] Still, even in this younger age group, the rate of toxicity following transplant is high, with 5% mortality due to adverse events reported in clinical studies.[5] In older patients ie, those >70 years, adverse event related mortalities following ASCT is a staggering 19%.[5] Though in theory allogeneic stem cell transplant has a curative potential, it is not a recommended regimen for this population as no survival advantages have been demonstrated in randomized studies due to increased toxicities.[6] For transplant ineligible patients, immunomodulation based regimen of bortezomib, lenalidomide, and dexamethasone is the primary preferred treatment option as it was demonstrated in the Phase III Southwest Oncology Group (SWOG) S0777 study that an objective response rate (ORR), of 71%, and progression free survival (PFS) of 43 months can be achieved.[4,7] However, toxicity remains to be a concern, with Grade 3 or higher neuropathy reported in 24% of patients.

Despite a number of recent advances, the majority of patients are expected to relapse, even for those who respond initially to treatment. Even for patients who are eligible to receive

autologous stem cell transplants (ASCTs), the median time to relapse was 17.2 months.[8] Similarly, for patients that are treated with novel proteasome inhibitor-based or immunomodulation-based combination regimens as front line treatment, the median time to relapse is 16.4 months.[9]

Patients with relapsed or refractory MM who respond poorly to proteasome inhibitor-based or immunomodulation-based regimens show a median overall survival (OS) of only 1.5 years.[10] In this relapsed setting, approximately 50% treatment-related adverse events (AE) and 20% serious adverse events (SAE) have been reported.[11] Furthermore, each subsequent line of therapy renders the patient more refractory to treatment. For example, patients who are double-refractory to proteasome inhibitor-based or immunomodulation regimens have a median OS of 9 months.[12] It is therefore clear that additional treatment approaches are required for relapsed/refractory MM.

2.2.2. Bispecific Antibodies

Functional local and systemic immunity is often suppressed in a MM patient. Impaired immunity results from the disruption of normal hematopoiesis following bone marrow invasion by plasma clones. The potential for T-cell based immunotherapy for MM has been highlighted by the ability for graft immune reactive T-cells to eradicate myeloma cells following allogeneic stem cell transplantation.[13] It may therefore be possible to restore immune-reactive T-cells, prevent malignant cell growth and decrease disease recurrence with immunotherapeutic approaches.

Bispecific antibodies offer a novel immunotherapeutic approach that allows the direct targeting of cytotoxic T-cells to tumor cells. These antibodies are engineered with two separate antigen recognition domains; one that recognizes a tumor antigen and another that recognizes CD3 expressed on T-cells. Simultaneous binding of CD3 and the tumor antigen initiates a cytotoxic response towards the bound tumor cell. Unlike normal T-cell cytotoxicity, bispecific antibody mediated cytotoxicity is independent to the presence of antigen presenting cells (APCs), expression of major histocompatibility complex (MHC) I molecules by the tumor, and the presence of costimulatory molecules. Blinatumomab, a CD19/CD3 bispecific antibody, was the first bispecific antibody to be approved by the United States (US) Food and Drug Administration (FDA).[14] In a Phase 2 trial of relapsed or refractory B cell acute lymphoblastic leukemia (ALL) patients, 33% achieved complete response (CR) and 10% achieved CR with incomplete hematological recovery.[14] It may therefore be possible to use the same approach for MM with a myeloma-restricted antigen.

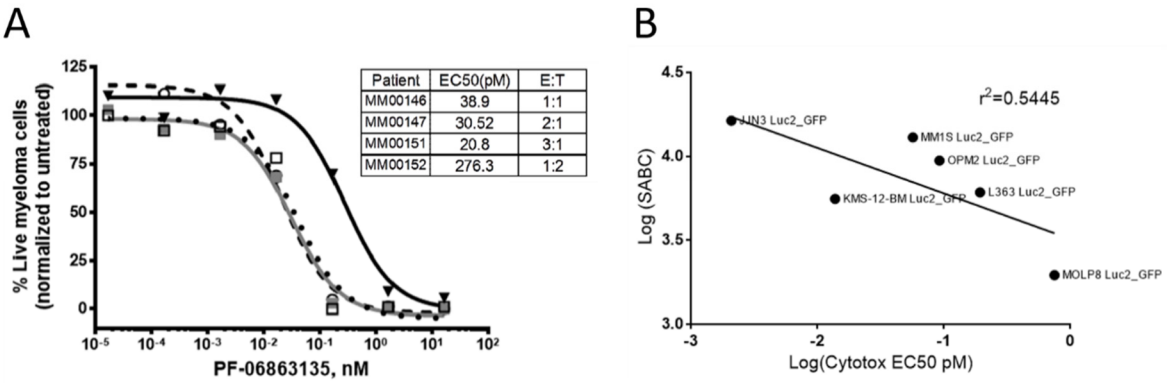
BCMA is a candidate for bispecific antibody-based immunotherapy. BCMA expression is upregulated during B-cell maturation into plasma blasts and plasma cells, but it is not expressed on naïve B cells, hematopoietic stem cells or normal tissues such as the heart, lung, kidney, or tonsil.[15,16] BCMA knockout mice show normal development, and are able to elicit a normal humoral immune response.[17,18] In MM, BCMA expression was identified at each disease stage, and on patients with differing cytogenetic risks.[15] Furthermore, BCMA expression was not influenced by treatment with ASCT or chemotherapy.[15,16] In vivo, bispecific antibodies against BCMA have been shown to induce T-cell activation, reduce tumor burden and prolong survival.[19,20,21]

Elranatamab is a heterodimeric humanized full-length bispecific antibody comprised of one BCMA binding arm and one CD3 binding arm paired through hinge mutation technology. It utilizes a modified human IgG2Δa fragment crystallizable (Fc) region. The half-life of elranatamab was 3 days in a non-human primate model, and elranatamab has a projected terminal half-life of 10 days in humans.

2.2.3. Nonclinical Pharmacology

Using fresh bone marrow aspirates from myeloma patients, elranatamab eliminated myeloma cells in a dose-dependent manner (see Figure 1A). There was a modest correlation between effective concentration 50 (EC50) and number of BCMA receptors on the cell surface when MM cell lines with varying BCMA cell surface receptor levels were used in a cytotoxicity assay (Figure 1B). BCMA is shed from the surface of myeloma cells, and soluble BCMA in patient serum may decrease activity of elranatamab by acting as a sink. Bone marrow stromal cells are known to protect MM cells from drug treatment and induce myeloma cell growth. In the case that either of these suppressive mechanisms negatively impact elranatamab activity.

Figure 1. Elranatamab Activity In Vitro



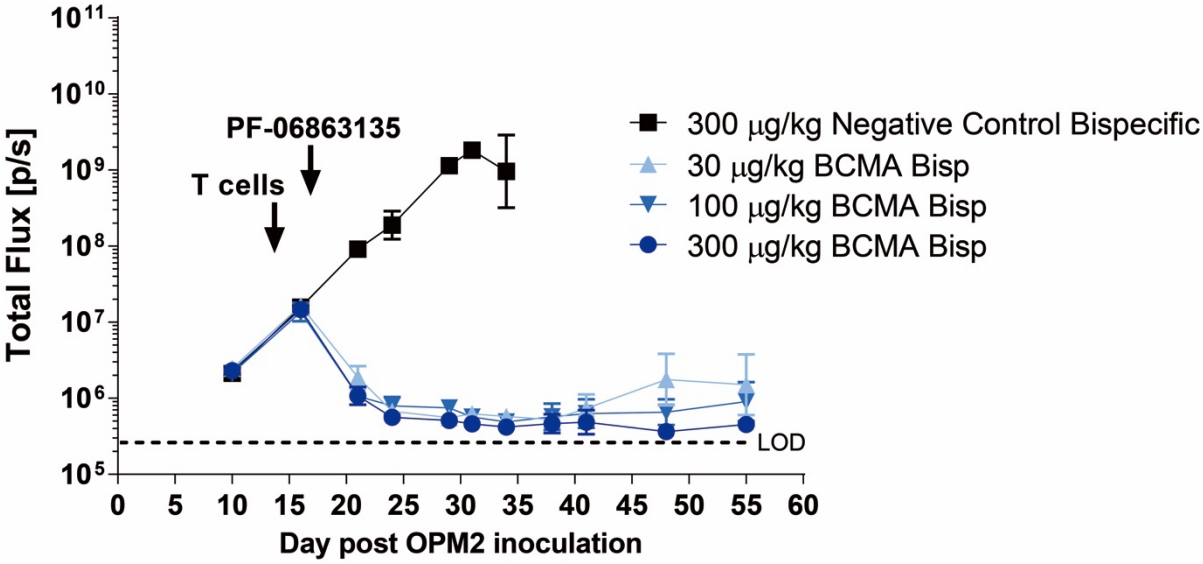
Abbreviations: EC50 = half maximal effective concentration; E:T = effector (T-cells) to target (myeloma cells) ratio; nM = nanomolar; pM = picomolar; sABC = specific antibody-binding capacity

2.2.3.1. Anti-tumor Efficacy of Elranatamab in Orthotopic Multiple Myeloma Models Tumor Models

Activity of elranatamab was also evaluated in MM orthotopic tumor models. MM cell line (OPM-2), myeloma cells were injected into NOD scid gamma (NSG) mice. Fourteen days following OPM-2 injection, the mice received an intraperitoneal injection of CD3+ T-cells and a single dose of elranatamab two additional days later. As shown in Figure 2, elranatamab dose dependently inhibited tumor growth, and elimination of myeloma cells was observed on Day 24. At the highest dose level of 300 μg/kg, tumor growth reduction was sustained up to Day 55 when the study was terminated. Similar results were observed using MM1.S (a glucocorticoid sensitive MM cell line) and MOLP-8 (a MM cell line with t(11;14)(q13;q32) chromosomal abnormality and negative for CD28) tumor models.

Elranatamab also showed enhanced tumor activity in the combination with anti-PD-1 antibody or lenalidomide, suggesting the potential for synergy in the human setting.

Figure 2. Elranatamab Activity in an OPM-2 MM Orthotropic Tumor Model



2.2.4. Nonclinical Pharmacokinetics and Metabolism

Single-dose pharmacokinetics (PK) and repeat-dose toxicokinetics were evaluated in cynomolgus monkeys following intravenous (IV) and subcutaneous (SC) dosing of elranatamab. After single IV dosing up to 0.01 mg/kg, the PK of elranatamab in cynomolgus monkeys were characterized by low clearance (CL), and low volume of distribution (V_{ss}), resulting in mean terminal elimination half-life (t½) values ranging from approximately 4 to 6 days. After once weekly IV dosing at doses 0.01 elranatamab to 0.3 mg/kg, systemic exposure increased with increasing doses and was higher after repeat dosing.

After once weekly SC dosing of elranatamab at 0.3 mg/kg, the mean T_{max} values on Day 1 and 22 were 56 and 25 hours, respectively. In general, there were no apparent sex-related differences in exposure. Induction of anti-drug antibodies (ADA) was observed in 1 animal after repeated dosing.

See Section 5.2 of the elranatamab Investigator's Brochure (IB) for detailed information on nonclinical studies.

2.2.5. Nonclinical Safety

In nonclinical safety studies conducted in cynomolgus monkeys with elranatamab administered by either the IV or SC route for up to 1-month in duration, the key effects were cytokine elevations that were occasionally accompanied by emesis during the first 6 hours after the first drug administration and minimal to moderate inflammation at the injection site. Decreases in B cells and plasma cells as well as fluctuations in peripheral T-cell numbers were observed in IV studies where immunophenotyping measurements were included. All of these effects were considered related to the mechanism of action. In addition, red skin

discoloration was noted in a subset of animals administered elranatamab by the IV route. None of the effects were considered adverse. Thus, the no-observed-adverse-effect level (NOAEL) in the pivotal toxicity study was ≥0.3 mg/kg in monkeys [highest dose tested; maximum concentration (C_{max}) of 10.4 µg/mL and area under the curve (AUC_{168}) of 715 µg·h/mL]. A detailed summary of the nonclinical safety programs is provided in the current IB.

2.2.6. Clinical Overview

Elranatamab is being evaluated as a single agent in Study C1071001. Part 1 dose escalation includes monotherapy (IV and SC) and Part 1.1 includes 2 priming cohorts (SC only). As of 04 February 2021, 53 participants were enrolled in Part 1 with 23 participants in the range of 0.1 to 50 µg/kg Q1W IV cohort and 30 participants in the range of 80 to 1000 µg/kg Q1W SC cohort. DLTs of febrile neutropenia Grade 3 and electrocardiogram QT prolonged Grade 1 were observed at 30 and 50 µg/kg IV, respectively. However, there were no DLTs observed in the SC dosing cohort across the dose range from 80 to 1000 µg/kg. There was no maximum tolerated dose (MTD) identified. Given the acceptable safety profile observed at the 1000 µg/kg Q1W together with encouraging clinical activity, this dose level was selected as the RP2D for further exploration in subsequent pivotal trials. More details on the safety profile during dose escalation is provided in the Investigator Brochure.

Priming Cohorts:

Part 1.1 in Study C1071001introduced a priming strategy to mitigate CRS which involves a single lower priming dose (600 µg/kg) followed by maintenance dosing starting 1 week later at the RP2D (1000 µg/kg) on either a QW or Q2W schedule. As of 04 February 2021, 20 participants have been treated in the Part 1.1 SC priming cohorts.

Preliminary data are available from 2 priming cohorts (Part 1.1, cutoff date: 04 February 2021). Across the Part 1.1 priming cohorts (n=20), the most common TEAEs regardless of causality included CRS (all grades 100%, Grade ≥3 0%), neutropenia (all grades 65%, Grade ≥3 45%), thrombocytopenia (all grades 45%, Grade ≥3 15%), injection site reaction (all grades 45%, Grade ≥3 0%), and anemia (all grades 40%, Grade ≥3 20%) (Table 1). According to ASTCT criteria, both CRS (Grade 1 55%, Grade 2 45%) and ICANS (Grade 1 5%, Grade 2 10%) were limited to Grade ≤2 with median duration of 2.5 and 3 days, respectively. Additional Grade ≥3 TEAEs regardless of causality occurring in ≥10% of participants included lymphopenia (Grade 3 0%, Grade 4 20%), leukopenia (Grade 3 10%, Grade 4 5%), AST increased (Grade 3 15%, Grade 4 0%), ALT increased (Grade 3 10%, Grade 4 0%), hypophosphatemia (Grade 3 10%, Grade 4 0%), and plasma cell myeloma (Grade 5 10%). Grade ≥3 infections regardless of causality included 1 event of sepsis (Grade 5) which was not related to study treatment by investigator. Treatment-emergent SAEs regardless of causality included CRS (n=3), hypercalcemia (n=2), plasma cell myeloma (n=2), and 1 each for acute kidney injury, asthenia, and sepsis; with the exception of CRS, none of these SAEs were judged by investigators as related to study treatment. Fatal TEAEs included plasma cell myeloma (n=2) and sepsis (n=1), none of which was considered related to study treatment by the investigator. With the introduction of a priming dose, the median duration of CRS decreased by 37.5% (from 4 days to 2.5 days) compared to that observed in

the 1000 μg/kg SC cohort with no priming dose. CRS incidence has been limited to the priming (Grade 1 55%, Grade 2 45%) and the initial full doses (Grade 1 10%). For participants receiving doses ≥ 600 μg/kg including the dose escalation cohorts (600 and 1000 μg/kg cohorts) and the 2 priming cohorts, CRS was observed in 97% of participants (61% Grade 1 and 35% Grade 2).

CRS began within the first 3 days of dosing in all participants with CRS. In participants experiencing CRS events across both IV and SC cohorts (n = 54), CRS occurred on Day 1 (n = 40, 74%), Day 2 (n = 13, 24%), and Day 3 (n = 1, 2%) after the first dose indicating the onset of CRS is predominantly within the first 2 days. In the SC cohort, only 1 participant experienced CRS after the second dose and no CRS events were observed after the third or later doses.

In summary, all cases of CRS during dose escalation or in the 2 priming cohorts were either Grade 1 or 2 according to ASTCT criteria, were managed by supportive care, and none resulted in permanent treatment discontinuation or dose reductions.

Peripheral Neuropathy including Guillain Barré Syndrome (GBS)

Peripheral neuropathy (including GBS) is considered an important potential risk of elranatamab. Between March and April 2021, 3 participants treated in Phase 1 Study C1071001 experienced serious adverse events of Grade 3 peripheral neuropathy, which was reported in 1 case as a variant of GBS, in 1 case as peripheral motor neuropathy and in 1 case as muscular weakness. Two of these participants had received elranatamab in combination with pomalidomide, and 1 participant had received elranatamab as single agent. For these 3 participants, they first experienced sensory neuropathy and subsequently experienced motor neuropathy involving the lower extremities. Time to onset of lower extremity weakness was approximately 3 to 8 weeks. All 3 participants showed evidence of anti-myeloma response which, based on changes in paraprotein levels, was evident as early as 1 week after initiation of study treatment. All participants were hospitalized for diagnostic evaluation. The participant diagnosed with GBS received empiric treatment with IV immunoglobulins with improvement of peripheral neuropathy to Grade 2; 1 participant had peripheral neuropathy improved to Grade 2; and 1 participant has stable peripheral neuropathy (at time of this amendment). Study treatment was permanently discontinued in the participant diagnosed with GBS and in the participant with muscular weakness.

The pathophysiology of peripheral neuropathy for these 3 participants remains to be elucidated. However, the 3 participants have some common features: all had pre-existing peripheral neuropathy, had received extensive prior treatment with IMiDs and proteasome inhibitors, had anti-myeloma response to elranatamab in combination with pomalidomide (2 participants) or as a single agent (1 participant), and had recent infections treated with antibiotics that are known to cause peripheral neuropathy (ciprofloxacin, levofloxacin, nitrofurantoin) less than a month before the onset of the peripheral neuropathy.

See Section 6.5.2 for additional guidance for peripheral neuropathy.

Table 1. Table 3. Study C1071001: TEAEs Occurring in >15% of SC Participants[a] (All Causalities by MedDRA PT and Maximum CTCAE Grade by Part 1 SC Cohorts; Safety Analysis Set)

	Part 1 SC Cohorts QW Dosing (N=30)						Part 1.1 SC Priming Cohorts (N=20)					
Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	0	0	7 (23.3)	20 (66.7)	3 (10.0)	30 (100.0)	0	3 (15.0)	8 (40.0)	7 (35.0)	2 (10.0)	20 (100.0)
Lymphopenia	0	0	6 (20.0)	18 (60.0)	0	24 (80.0)	0	1 (5.0)	0	4 (20.0)	0	5 (25.0)
CRS[b]	17 (56.7)	5 (16.7)	0	0	0	22 (73.3)	11 (55.0)	9 (45.0)	0	0	0	20 (100.0)
Anaemia	0	3 (10.0)	14 (46.7)	0	0	17 (56.7)	1 (5.0)	3 (15.0)	4 (20.0)	0	0	8 (40.0)
Injection site reaction	14 (46.7)	2 (6.7)	0	0	0	16 (53.3)	8 (40.0)	1 (5.0)	0	0	0	9 (45.0)
Thrombocytopenia	3(10.0)	2 (6.7)	5 (16.7)	6 (20.0)	0	16 (53.3)	2 (10.0)	4 (20.0)	2 (10.0)	1 (5.0)	0	9 (45.0)
Neutropenia	0	0	5 (16.7)	9 (30.0)	0	14 (46.7)	0	4 (20.0)	6 (30.0)	3 (15.0)	0	13 (65.0)
Leukopenia	3 (10.0)	2 (6.7)	5 (16.7)	1 (3.3)	0	11 (36.7)	0	1 (5.0)	2 (10.0)	1 (5.0)	0	4 (20.0)
Nausea	7 (23.3)	3 (10.0)	1 (3.3)	0	0	11 (36.7)	3 (15.0)	3 (15.0)	0	0	0	6 (30.0)
AST increased	5 (16.7)	2 (6.7)	3 (10.0)	0	0	10 (33.3)	2 (10.0)	1 (5.0)	3 (15.0)	0	0	6 (30.0)
ALT increased	5 (16.7)	1 (3.3)	3 (10.0)	0	0	9 (30.0)	2 (10.0)	2 (10.0)	2 (10.0)	0	0	6 (30.0)
Diarrhoea	6 (20.0)	2 (6.7)	1 (3.3)	0	0	9 (30.0)	5 (25.0)	2 (10.0)	0	0	0	7 (35.0)
Decreased appetite	5 (16.7)	2 (6.7)	0	0	0	7 (23.3)	3 (15.0)	1 (5.0)	0	0	0	4 (20.0)
Vomiting	6 (20.0)	1 (3.3)	0	0	0	7 (23.3)	5 (25.0)	1 (5.0)	0	0	0	6 (30.0)
Hypokalaemia	2 (6.7)	4 (13.3)	1 (3.3)	0	0	7 (23.3)	0	5 (25.0)	1 (5.0)	0	0	6 (30.0)
Arthralgia	3 (10.0)	2 (6.7)	1 (3.3)	0	0	6 (20.0)	2 (10.0)	0	0	0	0	2 (10.0)
Dry skin	4 (13.3)	2 (6.7)	0	0	0	6 (20.0)	4 (20.0)	0	0	0	0	4 (20.0)
ICANS	3 (10.0)	3 (10.0)	0	0	0	6 (20.0)	1 (5.0)	2 (10.0)	0	0	0	3 (15.0)
Hypophosphataemia	0	2 (6.7)	2 (6.7)	1 (3.3)	0	5 (16.7)	0	4 (20.0)	2 (10.0)	0	0	6 (30.0)
Urinary tract infection	0	5 (16.7)	0	0	0	5 (16.7)	0	1 (5.0)	0	0	0	1 (5.0)
Fatigue	1 (3.3)	2 (6.7)	1 (3.3)	0	0	4 (13.3)	3 (15.0)	4 (20.0)	0	0	0	7 (35.0)
Hypomagnesaemia	4 (13.3)	0	0	0	0	4 (13.3)	7 (35.0)	0	0	0	0	7 (35.0)
Musculoskeletal chest pain	0	1 (3.3)	0	0	0	1 (3.3)	1 (5.0)	4 (20.0)	0	0	0	5 (25.0)
Back pain	0	3 (10.0)	0	0	0	3 (10.0)	0	3 (15.0)	1 (5.0)	0	0	4 (20.0)

a. >15% in Part 1 SC cohorts and/or Part 1.1 SC Priming Cohorts
b. CRS grading based on modified ASTCT criteria (Lee, 2019)[22]; all AEs according to NCI CTCAE v4.03.
Cut-off date : 04 Feb 2021.

As of 04 February 2021, 1 participant in the 50 µg/kg IV cohort achieved a CR, and 2 participants in the IV cohorts achieved a MR (1 at 3 µg/kg IV and 1 at 50 µg/kg IV). CCI [redacted] CCI [redacted] Out of 30 treated participants in the SC cohorts, 6 participants achieved CCR (2 sCRs at 215 µg/kg SC, 1 sCR at 360 µg/kg SC, 2 sCRs at 600 µg/kg SC and 1 CR at 1000 µg/kg SC), 7 participants achieved a VGPR (2 at 360 µg/kg SC, 2 at 600 µg/kg SC and 3 at 1000 µg/kg), 2 participant achieved a PR (1 at 215 µg/kg SC, and 1 at 1000 µg/kg SC) and 1 participant achieved a minimal response at 215 µg/kg SC. Three participants with a response had received prior BCMA-antibody drug conjugate (ADC) and/or BCMA chimeric antigen receptor T-cell (CAR-T) therapy (1 VGPR at 360 µg/kg SC, 1 sCR at 600 µg/kg SC and 1 PR at 1000 µg/kg SC).

CCI [redacted]

Single- and multiple-dose PK of elranatamab are being evaluated in the ongoing study (C1071001). Preliminary PK data were available from 53 participants from IV (0.1 to 50 µg/kg) and SC cohorts (80 to 1000 µg/kg) in the dose escalation part of the study C1071001. The SC route was employed in this study given the potential to reduce the C_{max}.

SC dose administration resulted in a lower dose normalized C_{max} relative to IV administration. Elranatamab maximum serum concentrations within 24 hours after the first dose (ie, C_{max}-24h) were shown to be associated with all Grade and Grade ≥2 CRS. The 24-hour timepoint coincides with onset of CRS symptoms in the majority of participants. Exposure to total elranatamab increased with dose in an approximately dose-proportional manner. SC dose administration resulted in a prolonged absorption phase with median time to reach C_{max} (T_{max}) ranging from 3 to 7 days. Based on the available SC data, the model-predicted SC bioavailability is approximately 65% (95% CI: 61%, 68%).

Preliminary immunogenicity data available from 50 ADA-evaluable participants suggests low (14%) overall incidence of ADAs against elranatamab. The overall incidence of ADA appeared comparable between the IV (18.2%) and SC (10.7%) routes. Also, there appears to be no impact of the presence of ADA on the PK profiles by visual inspection and population PK analysis.

Preliminary population PK analysis based on data from 53 participants from IV and SC cohorts suggests that body weight (range: 42 to 120 kg) does not appear to be a clinically meaningful covariate on elranatamab exposure. This may support the use of fixed dosing approach for further clinical development. Age, sex, and race were not clinically meaningful covariates on elranatamab exposure.

2.3. Benefit/Risk Assessment

Based on the clinical data available to date, the conduct of the trial with the proposed single agent elranatamab doses and regimens is considered justifiable.

The clinical safety data available to date, in participants with relapsed or refractory MM, has suggested an acceptable safety profile of elranatamab in SC administration. The safety profile of elranatamab is acceptable and manageable. There were no DLTs observed in the SC dosing cohort across the dose range from 80 to 1000 μg/kg. In addition, measures including guidelines for treatment interruption and permanent discontinuation in case of toxicities, guidelines for steroid treatment, have been implemented. Furthermore, encouraging clinical activity of elranatamab has been observed in Study C1071001.

These data currently observed in the ongoing Phase 1 trial C1071001, support the hypothesis that elranatamab may represent an important therapeutic approach in participants with relapsed or refractory MM. Thus, the projected benefit/risk of C1071001 is favorable for investigation in this participant population.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of elranatamab may be found in the elranatamab IB, which is the single reference safety document (SRSD) for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) 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. Phase 1 results to date indicate that only Grade 1 and 2 CRS were observed with both IV and SC administration. No Grade ≥3 CRS events have been reported (see Table 1).	Participants will be hospitalized for at least 3 days after the C0D1 dose and C1D1 dose for safety surveillance. (see Schedule of Activities). The priming regimen is expected to mitigate 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 Section 10.13. Dose modification/discontinuation in the setting of Grade ≥2 AEs (including CRS) is described in Section 6.6.3. 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 Section6.5.2).
ICANS	A known toxicity of therapeutics that function by activation of immune effector cells. Phase 1 safety results suggest ICANS is infrequent and Grade ≤2.	Participants will be hospitalized for at least 3 days after the C0D1 dose and C1D1 dose for safety surveillance. (see Schedule of Activities). The priming regimen is expected to mitigate rate, duration, and severity of ICANS (see Section 4.3). Regular neurologic examinations will be performed by the investigator or designee (Section 8.2.1). Guidance for monitoring, grading, and management of ICANS per ASTCT criteria and guidelines is included in Section 10.13.

Peripheral neuropathy	In the Phase 1 study (C1071001), Grade 3 peripheral neuropathy has been observed with elranatamab.	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 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 (Section 6.5) Participants should be closely monitored for signs and symptoms of neuropathy following infections or following the administration of any vaccine. Work-up recommendations for new or worsening peripheral neuropathy (Grade ≥2) is described in Section 6.5.2. Dose modification/discontinuation for peripheral neuropathy is described in Section 6.6.3.
Study Procedures		
Bone marrow aspirate and biopsy	The risks associated with bone marrow aspiration and biopsy include pain or discomfort during the biopsy, including slight, stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness at the biopsy site. Other risks can include bleeding, swelling, scarring, bruising, nerve damage and infection, which can be life-threatening or fatal in rare cases.	To reduce these risks, the site of the biopsy will be numbed and sterile techniques will be used.

2.3.2. Benefit Assessment

Elranatamab is a bispecific monoclonal antibody against BCMA and CD3 and has demonstrated potent single agent anti-tumor activities in both preclinical studies as well as in the clinical study of C1071001.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with elranatamab are justified by the anticipated benefits that may be afforded to participants with relapsed or refractory MM.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To assess the safety and tolerability at the RP2D with a priming dose approach of single-agent elranatamab administered to Japanese participants	• First cycle including a priming dose (4 weeks) Dose Limiting Toxicities (DLTs)
Secondary:	**Secondary:**
• To evaluate the overall safety profile	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. Severity of CRS and ICANS will be graded according to ASTCT grading criteria • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing
• To evaluate the single-dose and multiple-dose PK of elranatamab	• PK parameters of elranatamab: C0D1 dose, C1D1 dose and C2D1 dose maximum concentration (C_{max}), area under the concentration versus time curve from time zero to the last quantifiable time point prior to the next dose (AUC_{last}) and if data permit, apparent clearance (CL/F), apparent volume of distribution during terminal phase (V_z/F), and terminal elimination ($t_{1/2}$) • Pre-dose trough concentrations after multiple doses of elranatamab
• To evaluate the immunogenicity of elranatamab	• Incidence and titers of ADA and NAb against elranatamab
• To evaluate preliminary anti-tumor activity	• ORR based on the IMWG response criteria for MM • Time to event endpoints: TTR, DOR, PFS and OS, as assessed by IMWG criteria for response • MRD after treatment with elranatamab using IMWG MRD criteria
• To characterize the impact of elranatamab on systemic soluble immune factors	• Pre- and post-dose quantification of soluble cytokines in serum

Objectives	Endpoints
CCI	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, multi-center study to evaluate the safety and PK of elranatamab in Japanese adult participants with relapsed or refractory MM who have received at least 3 prior therapies, including immunomodulatory drug (IMID), proteasome inhibitor (PI) and anti-CD38 antibody. Approximately 4-6 participants are expected to be enrolled overall in this study, and the RP2D which was declared in the study C1071001 with a priming dose will be administered to each participant.

Treatment with study intervention will continue until either disease progression, withdrawal from treatment, or unacceptable toxicity occurs, whichever occurs first.

The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on the emerging safety and PK data.

CCI

4.2. Scientific Rationale for Study Design

The primary purpose of the Phase 1 is to evaluate the safety and tolerability of elranatamab 1000 µg/kg SC Q1W with a priming dose of 600 µg/kg SC in Japanese participants. Participants with relapsed or refractory MM will be enrolled to permit Japan participation in pivotal studies, currently under development.

Studies to evaluate the developmental toxicity of elranatamab have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Section 10.4).

CCI

CCI

4.3. Justification for Dose

In the SC cohort in the dose escalation part of C1071001, no DLT was observed at all evaluated dose levels (80 to 1000 µg/kg SC Q1W). SC dose administration resulted in a lower dose-normalized C_{max} relative to IV administration and a prolonged absorption phase with median time to reach C_{max} (T_{max}) ranging from 3 to 7 days. Despite achieving higher exposure levels (AUC_t) 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. Although 2 DLTs were observed in IV cohorts (febrile neutropenia Grade 3 [30 µg/kg] and electrocardiogram QT prolonged Grade 1 [50 µg/kg]), no DLT were observed in all SC cohorts. Based on the safety, tolerability, PK, PD, and clinical activity ofelranatamab in non-Japanese population in the SC cohort of Study C1071001, 1000 µg/kg SC Q1W have been selected as the RP2D in non-Japanese population. While 1000 µg/kg SC showed tolerable and manageable safety profile, a priming dose approach may mitigate the consequences of CRS which is mainly observed after the initial dose. The priming dose approach has been commonly employed for other T-cell engaging bispecifics to mitigate CRS. For further evaluation in elranatamab studies, a priming dose approach is planned to be used, and a minimal impact on achieving efficacious exposure threshold is predicted in a priming dose approach. In this study (C1071002), 600 µg/kg SC will be used as a priming dose for the first week followed by 1000 µg/kg SC weekly. In 600 µg/kg SC and 1000 µg/kg SC cohorts of Study C1071001, -elranatamab 600 µg/kg SC Q1W and 1000 µg/kg SC Q1W have shown tolerable and manageable safety profile in addition to encouraging clinical activity in participants with MM.

4.3.1. Starting Dose

The starting dose will be 600 µg/kg SC for the first week as a priming dose, then 1000 µg/kg SC will be given weekly in 3-week cycles.

4.3.2. Criteria for Dose Escalation

Dose escalation beyond 1000 µg/kg SC Q1W is not planned for this study. Initially, 4 participants will be enrolled to the study and each participant will receive elranatamab 1000 µg/kg SC Q1W with a priming dose of 600 µg/kg SC 7 days prior to the first cycle. If DLT is observed in 1 of 4 participants, additional 2 participants will be enrolled. If DLT is observed in ≥2 of the initial 4 participants or ≥2 of the 6 participants, a lower dose cohort may be explored, if deemed necessary.

4.3.3. Dose Limiting Toxicity Definition

A participant is classified as DLT-evaluable if he/she experiences a DLT (irrespective of whether they received all of the planned doses of investigational product and study intervention and scheduled safety assessments during the DLT window) or if he/she otherwise in the absence of a DLT receives all of the planned doses of investigational product and study intervention and has received scheduled safety assessments during the DLT window. If a participant fails to meet these criteria, he/she may be replaced.

The DLT observation period will include a priming dose and the first cycle (throughout Cycle 0 to Cycle 1, 4 weeks in total) of treatment in each participant.

Significant adverse events considered to be related to the study intervention or treatment under investigation that occur after the DLT observation period will be reviewed in context of all safety data available. That review may result in re-evaluation of the dosing level or regimen.

Severity of AEs except for CRS and ICANS will be graded according to CTCAE version 5.0. CRS and ICANS will be graded according to ASTCT grading criteria (see Section 10.13). Any of the following AEs occurring in Cycle 0 and Cycle 1 will be classified as DLTs:

Hematological:

- Grade 4 neutropenia lasting >7 days.
- Febrile neutropenia (defined as an absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of >38.3°C [101°F], or a sustained temperature of ≥38°C [100.4°F] for more than one hour). If fever is determined to be a symptom of CRS confirmed by clinical course and cytokine levels and resolves in a manner consistent with CRS, this would no longer be considered a DLT, and the participant may resume treatment.
- Grade ≥3 neutropenia with infection.
- Grade 4 thrombocytopenia (unless the study entry baseline count was ≥25,000 and <50,000 to take into account bone marrow suppression due to MM, in this case Grade 4 thrombocytopenia needs to be accompanied by ≥ Grade 2 bleeding to be a DLT). For participants who experience a platelet count <10,000/mm^3, this is considered a DLT irrespective of other factors.
- Grade 3 thrombocytopenia with ≥ Grade 2 bleeding.

Non-hematological:

- Grade 4 Adverse Events (AEs).

- Grade 3 AE lasting ≥5 days despite optimal supportive care, with the exception of AE attributed to a CRS event (ie, Grade 3 transaminitis).

- Grade 3 CRS, except those CRS that have i) not been maximally treated (ie, lack of administration of standard of care treatment per the institution's, Investigator's, or treating physician's guidelines for the management of CRS) or ii) improved to ≤ Grade 1 within 48 hours.

- Grade 4 CRS.

- Confirmed drug-induced liver injury (DILI) meeting Hy's law criteria outlined in Section 10.6.

- Grade 4 laboratory abnormalities deemed clinically significant by the investigator shall be reported as Grade 4 AE.

Clinically important or persistent toxicities (eg, toxicities leading to dose interruption for ≥7 days including skipping planned dose during the DLT observation window) that are not included in the above criteria may also be considered a DLT following review by the investigators and the Sponsor. All DLTs need to represent a clinically significant shift from baseline.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset or deemed not clinically insignificant by the investigator.

- Grade 3 injection site reactions (ISR), allergic reaction or anaphylaxis will not be considered as DLTs but may be a reason for study discontinuation and will be reviewed with the sponsor's medical monitor.

4.3.4. Maximum Tolerated Dose Definition

MTD estimation is not planned for this study. However, if DLT is observed in ≥2 of the initial 4 participants or ≥2 of the 6 participants at the 1000 μg/kg dose level with a priming dose of 600 μg/kg SC, this dose level will be determined to be above MTD for the Japanese population.

4.3.5. Recommended Phase 2 Dose Definition

The target DLT rate is 25%. If no DLT is observed in the initial 4 participants or one DLT is observed in 6 participants, it will be concluded that the RP2D defined in the study C1071001 in non-Japanese population with a priming dose is tolerable in the Japanese population. If DLT is observed in ≥2 of the initial 4 participants or ≥2 of the 6 participants, a lower dose cohort may be explored, if deemed necessary.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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:

1. Females and/or male participants age ≥20 years.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

2. Participants with relapsed or refractory MM, as defined by the international myeloma working group (IMWG) criteria 2014 (see Section 10.9)

3. Participants who have measurable disease as defined by one or more of the abnormalities listed below:

    a. Serum myeloma (M)-protein ≥0.5 g/dL (5 g/L).

    b. Urine M-protein ≥200 mg/24 h.

    c. Serum free light chain (FLC) >100 mg/L (10 mg/dL) with abnormal kappa:lambda ratio.

4. Participants must have progressed on or been intolerant of at least 3 prior therapies. The prior therapy includes proteasome inhibitor, IMID drug and anti-CD38 antibody, either in combination or as a single agent. Participants who are determined to be inappropriate for those standard therapies by the investigator may be eligible.

5. ECOG PS 0, 1 or 2. PS 3 is permitted if PS is due solely to bone pain.

6. Adequate Bone Marrow Function, including:

- ANC ≥1,000/mm^3 or ≥1.0 x 10^9/L;
- Platelets ≥25,000/mm^3 or ≥25 x 10^9/L (transfusion support is permitted if completed prior to planned start of dosing);
- Hemoglobin ≥8.0 g/dL (transfusion support is permitted if completed prior to planned start of dosing).

7. Adequate Renal Function, including:
   - Estimated creatinine clearance (CrCl) ≥30 mL/min as calculated using the method standard for the institution. (If an estimated CrCl is believed to be inaccurate for a participant, 24-hour urine collection with actual assessment of CrCl is allowed);
   - Serum creatinine ≤2.5 mg/dL;
8. Adequate Liver Function, including:
   - Total serum bilirubin ≤2.0 mg/dL, except in participants with Gilbert Syndrome who must have a total bilirubin less than 3.0 mg/dL;
   - AST and ALT ≤2.5 x ULN; ≤5.0 x ULN if there is liver involvement by the tumor;
   - Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN in case of bone metastasis).
9. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment.
10. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
11. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

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

1. Participants with POEMS syndrome
2. Participants with 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.
3. Major surgery within 4 weeks prior to study entry.

4. Donor Lymphocyte Infusion (DLI) within 30 days prior to study entry.

5. Radiation therapy within 2 weeks prior to study entry (bone lesions requiring radiation may be treated with limited [ie, ≤25% of bone marrow in field] radiation therapy during this period) (see Section 10.8 Bone Marrow Reserve in Adults).

6. History of active autoimmune disorders (including but not limited to: Crohn's disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave's disease) and other conditions that compromise or impair the immune system.

7. Any form of primary immunodeficiency (such as Severe Combined Immunodeficiency Disease).

8. History of CTCAE Grade ≥3 immune-mediated adverse event (including hepatitis, pancreatitis, colitis, pneumonitis, carditis, and CRS) that was considered related to prior immune-modulatory therapy (exceptions: immune-related adverse events secondary to checkpoint inhibitors- that have been appropriately managed or --resolved such as hypophysitis and hypothyroidism).

9. Ongoing Grade ≥2 peripheral sensory or motor neuropathy.

10. Participant with history of GBS or GBS variants, history of any Grade ≥3 peripheral motor polyneuropathy, or history of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy.

11. Stem cell transplant within 12 weeks prior to enrollment or active graft versus host disease (GVHD) with other than Grade 1 skin involvement, or GVHD requiring immunosuppressive treatment.

12. Requirement for systemic immune suppressive medication [eg, ≥10 mg of prednisone or equivalent (≥1.5 mg of dexamethasone)].

13. Participant known to be refractory to platelet or red blood cell transfusions.

14. Current requirement for chronic blood product support.

15. Participants with active, uncontrolled bacterial, fungal, or viral infection, including HBV, HCV, known HIV or AIDS related illness and SARS-CoV2. In equivocal cases, participants whose viral load is negative, may be eligible after discussion with the sponsor's medical monitor. HIV seropositive participants who are healthy and low-risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV-positive participants should be evaluated and discussed with sponsor's medical monitor, and will be based on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions (eg, opportunistic infections), and status of HIV treatment. Also the potential for drug-drug interactions will be taken into consideration. Active infections must be resolved at least 14 days prior to enrollment.

16. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >470 msec unless a cardiac rhythm device/pacemaker is placed and eligibility is approved by the sponsor's medical monitor, complete left bundle branch block (LBBB), signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of active myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >470 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants. Cases must be discussed in detail with sponsor's medical monitor to judge eligibility.

17. Any of the following in the previous 6 months: myocardial infarction, long QT syndrome, Torsade de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation), serious conduction system abnormalities (eg, left anterior hemiblock), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), New York Heart Association class III or IV, cerebrovascular accident, transient ischemic attack, symptomatic pulmonary embolism, and/or other clinical significant episode of thrombo embolic disease. Ongoing cardiac dysrhythmias of NCI CTCAE ≥ Grade 2, atrial fibrillation of any grade. If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 msec, the participant can be considered eligible. Participants with cardiac rhythm device/pacemaker must be discussed in detail with sponsor's medical monitor to judge eligibility.

18. Hypertension that cannot be controlled by medications (eg, >150/100 mmHg).

19. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry. Participant may be included if 5 times elimination half-life of drug has passed.

20. Known or suspected hypersensitivity to component of elranatamab, murine and bovine products.

21. Live attenuated vaccine within 4 weeks of the first dose of study intervention

22. Other medical or psychiatric condition 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.

23. 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.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

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) may be rescreened if the participant do not meet a specific modifiable factor (eg, lab abnormality).

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 describe specific investigational product.

6.1. Study Intervention(s) Administered

Intervention Name	Elranatamab Solution for Injection
Type	Biologic
Dose Formulation	solution for injection
Unit Dose Strength(s)	40 mg/mL
Dosage Level(s)	600 µg/kg and 1000 µg/kg
Route of Administration	SC
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor Refer to the Product Specific IP manual.
Packaging and Labeling	Study intervention will be provided in 1vial/carton. Each vial and carton will be labeled as required per country requirement in an open-label manner.
[Current/Former Name(s) or Alias(es)]	N/A

Elranatamab 40 mg/mL solution for injection is presented as a sterile solution for SC administration. Each vial of elranatamab aqueous buffered solution, is sealed with a coated stopper and an overseal, and is labeled according to local regulatory requirements.

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, the number of injections may increase to accommodate this difference in volume to ensure the correct final dose is delivered.

Study drug should be administered to the abdomen (with preference given to the lower quadrants when possible). Refer to Section 10.14 for details on administration of multiple injections to the abdomen. Study staff should refer to the investigational product (IP) manual for specific instructions on the handling and preparation of study drug.

The first dose of study intervention will be 600 µg/kg, which will serve as a priming dose and will be administered 7 days prior to Day 1 of the first cycle (C0D1). In a treatment cycle, 1000 µg/kg will be administered in weekly schedule. Each cycle will be 3 weeks in duration, and each participant will be treated 3 times during each cycle, unless dose delays or interruptions occur (a minimum of 6 days should be maintained between doses). On C0D1 and C1D1, elranatamab will be administered on an inpatient basis. On all other days, elranatamab will be administered on an outpatient basis.

Details for preparation of elranatamab SC injection are provided in the current elranatamab IP manual. All participants should be weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of elranatamab required for dose preparation. The decision to recalculate elranatamab dose based on the weight obtained at each cycle can be in accordance with institutional practice; however, if the participant experienced either a weight loss or gain >10% compared to the weight used to calculate the prior dose, the amount of

elranatamab required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained.

Each participant may receive elranatamab until disease progression, unacceptable toxicity, withdrawal from treatment, participant no longer willing to participate in trial, investigator decision, or study termination. If a participant has received treatment with Q1W elranatamab for at least 6 months, and disease assessments have remained stable over at least 2 months, consideration may be given to increasing dose intervals from weekly to every 2 weeks after consultation with sponsor's medical monitor. If the participant subsequently begins to have increase of disease burden, dose intervals should return to weekly dosing.

6.2. Preparation/Handling/Storage/Accountability

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.

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.

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.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

Study interventions should be stored in their original containers.

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.

Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is

authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

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

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 biologic agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Participants will be enrolled to the study after participants have given their written informed consent and have completed the necessary baseline assessments. The site staff will fax/e-mail a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a participant identification (ID) number and supply this number to the site. The participant ID number will be used on all study-related documentation at the site.

No participant will receive study intervention until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the participant's enrolment;
- Specification of the dose level for that participant and;
- Permission to proceed with dosing the participant.

Study intervention will be injected at the study visits summarized in the SoA.

6.4. Study Intervention Compliance

When participants are dosed at the site, they 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 case report form (CRF). The dose of study intervention and study participant ID 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.

6.5. Concomitant Therapy

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions (eg, paracentesis) received by participants from screening until the end of treatment visit will be recorded on the CRF.

All COVID-19 vaccines are permitted and should be recorded as concomitant medications (standard AE collection and reporting processes should be followed). For participants in screening, the timing of vaccine dosing relative to the dosing of study drug on planned C0D1 is at the discretion of the investigator although it may be best to avoid the 7 days prior to C0D1 (priming dose) and consider the potential for vaccine-related adverse events, if applicable. For patients under the study treatment, the timing of vaccine dosing relative to the dosing of study drug is at the discretion of the investigator, although it may be best to avoid the DLT observation period (inclusive of Cycle 0 and Cycle 1; 28 days) and especially within 48 hours of C0D1 or C1D1 and to administer the vaccine during scheduled dosing holidays, if applicable.

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 bispecific antibodies.

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 including a priming dose. If the use of warfarin is clinically necessary, caution and additional INR monitoring are 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.

6.5.1. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not

permitted. Palliative radiotherapy on study 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 that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of elranatamab with radiotherapy, elranatamab treatment should be interrupted during palliative radiotherapy, stopping 7 days before and resuming treatment after 7 days.

6.5.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines.

Allopurinol/rasburicase may be administered as needed for tumor lysis prophylaxis or treatment.

Supportive Care for Cytokine Release Syndrome:

Symptoms associated with CRS vary greatly and may be difficult to distinguish from other conditions. The more common symptoms include fever, nausea, headache, tachycardia, hypotension, rash and shortness of breath. The severity of symptoms can be mild to life-threatening and thus there should be a high suspicion for CRS if these symptoms occur. If CRS is suspected, cytokines will be analyzed at central laboratories to determine if cytokine elevation consistent with CRS is observed (see Section 8.2.5). The severity of CRS will be assessed according to the modified grading described by Lee et al (2019).[22] A suggested treatment algorithm for the management of CRS is also provided in Section 10.13; however, if local standard of care is a different regimen this should be utilized.

For the priming dose (C0D1) and first full dose (C1D1), 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 label are permissible.

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

The pre-treatment medication will not be supplied by Pfizer.

Supportive Care for Injection Site Reactions (ISR)

ISR is a type of hypersensitivity reaction that may be immediate, although it usually appears within 24-48 hours after injection. ISR, by definition, includes the following erythema,

pruritus, pain, inflammation, rash, induration, itching and edema at the injection site. To evaluate ISRs, site tolerability assessments will be performed per the SoA.

Immune Effector Cell-Associated Neurotoxicity Syndrome ICANS:

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.[22] It has been observed following administration of some CAR-Ts and bispecific antibodies and can occur independently of CRS. The severity of ICANS should be graded according to the ASTCT consensus criteria,[22] and management guidelines are provided in the Section 10.13.[23,24]

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.[25] Recently, peripheral neuropathy has been described following administration of BCMA-directed bispecific T-cell engagers.[26]

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), nerve conduction velocity (NCV)/electromyographies (EMGs), and lumbar puncture to assess cerebrospinal fluid (CSF). In consultation with the 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.

Tumor Lysis Syndrome (TLS)

Tumor lysis is a group of metabolic complications that can occur after treatment of cancer. Tumor lysis syndrome (TLS) occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hypophosphatemia, and hypocalcemia. These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures, and death due to multi-organ failure. The

incidence and severity of the TLS depend on the cancer mass, the potential for lysis of tumor cells, the characteristics of the participant, and supportive care.

Optimal management of TLS should involve preservation of renal function. Management should also include prevention of dysrhythmias and neuromuscular irritability. All participants who are at risk for TLS should receive intravenous hydration to rapidly improve renal perfusion and glomerular filtration and to minimize acidosis. Reducing the level of uric acid, with the use of allopurinol and particularly with the use of rasburicase, can preserve or improve renal function and reduce serum phosphorus levels as a secondary beneficial effect.

Hyperkalemia remains the most dangerous component of TLS because it can cause sudden death due to cardiac dysrhythmia. Participants should limit potassium and phosphorus intake during the risk period for TLS. Frequent measurement of potassium levels (every 4 to 6 hours), continuous cardiac monitoring, and the administration of oral sodium polystyrene sulfonate are recommended in participants with TLS and acute kidney injury. Hypocalcemia can also lead to life-threatening dysrhythmias and neuromuscular irritability; controlling the serum phosphorus level may prevent hypocalcemia. Symptomatic hypocalcemia should be treated with calcium at the lowest dose required to relieve symptoms. Hypocalcemia not accompanied by signs or symptoms does not require treatment.

6.5.3. Hematopoietic Growth Factors

Primary prophylactic use of colony stimulating factors is not permitted during the first 28 days from Cycle 0 Day 1, but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines[27] and Japan guidelines[28]. During the screening window (ie, 28 days prior to Day 1), Granulocyte colony stimulating factors are not permitted to qualify a participant with low white blood cell (WBC) counts.

6.5.4. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor's medical monitor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section.

6.5.5. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section.

6.5.6. Corticosteroids

Chronic systemic corticosteroid use (prednisone >10 mg/day or equivalents) for palliative or supportive purposes is not permitted. However, systemic corticosteroid use at a low dose for a short duration (eg, 5 mg q.d. of prednisone, for 2 weeks) as symptomatic treatment on individual basis and upon discussion with the sponsor's medical monitor. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.5.7. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and elranatamab required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping elranatamab is recommended at least 7 days prior to surgery. Postoperatively, the decision to reinitiate elranatamab treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6.5.8. Transfusion

Primary prophylactic use of transfusion support for anemia is allowed to treat anemia.

Primary prophylactic use of transfusion support for thrombocytopenia is allowed during screening if the transfusion is completed prior to planned study treatment start. Primary prophylactic use of transfusion support for thrombocytopenia is allowed to treat thrombocytopenia.

6.5.9. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with elranatamab; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in one of three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

6.6.1. Dosing Interruptions

With respect to study intervention, participants experiencing the following adverse events should have their treatment interrupted. Participants experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in Section 6.6.2.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the participant missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Section 6.6.3, unless expressly agreed otherwise following discussion between the investigator and the sponsor's medical monitor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >3 weeks, treatment resumption will be decided in consultation with the sponsor's medical monitor.

6.6.2. Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- ANC ≥1,000/mm^3
- Platelets count ≥25,000/mm^3
- Nonhematologic toxicities have returned to baseline or Grade ≤1 severity (or, at the investigator's discretion, Grade ≤2 if not considered a safety risk for the participant).
- For any dosing day (start of cycle or during a cycle), no ongoing CRS or ICANS
- Recovery of treatment-emergent peripheral neuropathy to Grade ≤1 severity.

If a treatment delay results from worsening of hematologic or biochemical parameters, the frequency of relevant blood tests should be increased as clinically indicated.

If these conditions are met within 3 weeks of treatment interruption, elranatamab may be resumed. Refer to the Dose Reductions section for adverse events requiring dose reduction at the time of treatment resumption.

If participants require discontinuation of elranatamab for more than 42 days at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the Sponsor's medical monitor.

If a treatment interruption continues beyond Day 21 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle.

6.6.3. Dose Reductions

Following dosing interruption or cycle delay due to toxicity, the elranatamab dose may need to be reduced when treatment is resumed.

No dose reductions are planned for patients experiencing toxicities other than those listed as DLTs. No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity except for peripheral neuropathy. However, investigators should always manage their participants according to their medical judgment based on the particular clinical circumstances.

Participants experiencing recurrent and intolerable Grade 2 toxicity may resume dosing at the next lower dose level once recovery to Grade ≤1 or baseline is achieved.

Dose reduction of elranatamab by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Participants requiring more than 2 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor's medical monitor. All dose modifications/adjustments must be clearly documented in the participant's source notes and CRF.

Once a dose has been reduced for a given participant, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intraparticipant dose re-escalation is not allowed.

Table 2. Available Dose Levels

Dose Level	Study Intervention A
+1	1000 µg/kg
0	600 µg/kg
-1	360 µg/kg*

*Dose de-escalation below 360 µg/kg is not allowed.

Participants experiencing a DLT may resume dosing at the next lower dose level (if applicable) once adequate recovery is achieved, and in the opinion of the investigator and the sponsor's medical monitor, the participant is benefiting from therapy. Participants experiencing a DLT of prolonged myelosuppression (>42 days) may not resume treatment even if adequate recovery is achieved.

Recommended dose reductions for study intervention are described in Table 3.

Table 3. Dose Modifications for Study Intervention-Related Toxicity and for Sensory or Motor Peripheral Neuropathy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nonhematologic (excluding peripheral neuropathy)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level.*	Permanently discontinue.*
Peripheral sensory or motor neuropathy (all causality)	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**. If Grade ≥2 neuropathy reoccurs, permanently discontinue elranatamab.	Permanently discontinue elranatamab.	Permanently discontinue elranatamab
Hematologic***	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.**** If toxicity reoccurs, dosing may be reduced by 1 dose level. If toxicity reoccurs after a maximum of 2 dose level reductions, participant may be permanently discontinued from treatment. For platelets, withhold dose if toxicity ≤25,000mm^3 and re-start when platelets have returned to ≥25,000mm^3 or baseline.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then reduce the dose by 1 level and resume treatment.*** If toxicity reoccurs despite dose reduction, dosing may be reduced by 1 more dose level. If toxicity reoccurs, participant may be permanently discontinued from treatment.

* Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification.
** Consider additional diagnostic work-up (see Section 6.5.2).
*** For Grade 3 or 4 lymphopenia not associated with clinical events (eg, opportunistic infection), elranatamab treatment may continue without dose reduction and interruption.
**** Cycle will not be extended to cover for the missing doses.
In case of ongoing CRS or ICANS of any grade on any dosing day, dosing will be held until resolution.

6.7. Intervention After the End of the Study

No study treatment will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy or begins breastfeeding;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death;

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 survival. See 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, posttreatment 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 and contraception check (see Schedule of Activities 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).

Survival follow-up:

Following discontinuation of study treatment (unless participants are lost to follow-up, consent is withdrawn, or study is discontinued by the sponsor), survival status will be collected at visit or by telephone every 3 months after the follow-up visit until death, or at least 12 months after first treatment of the last participant, whichever comes first. Subsequent anti-cancer therapies and relevant transplant information will also be collected. Any standard of care (SOC) disease assessments obtained between EOT and subsequent anti-cancer therapy will be collected. Information of AEs and contraception check will also be collected until the end of active AE reporting period as defined in Section 8.3.1, and contraception check period in Section 10.4.

ECG Changes

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study intervention. If the mean QTcF intervals rise above 500 msec, during the monitoring for the QTcF prolongation,

- the QTcF interval has still not decreased to ≤480 msec after 2 weeks.
- at any time a participant has a QTcF interval >515 msec, or
- becomes symptomatic

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.1. Request to Continue Study Intervention

If the investigator feels the participant is still deriving benefit from treatment, following discussion with the sponsor the participant may have an option to continue dosing at the same dose or one dose lower, as long as the criteria below are met, until such benefit no longer exists.

Criteria that must be met to ensure that participants are not exposed to unreasonable risks by continued use of the investigational agent in spite of progression of disease. Such criteria may include the following:

- Absence of symptoms and signs indicating clinically significant progression of disease.

- No decline in ECOG PS.
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression).

At the time of progression of disease, obtain the re-consent of participants using a written ICD that details all approved therapy, and potential clinical benefit, that the participant may be foregoing in order to continue receiving the investigational product.

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 may include:

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

The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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 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 Schedule of Activities. 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 well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

8.1. Efficacy Assessments

8.1.1. Disease Response Assessment

Anti-cancer assessments and response will be assessed according to the International Myeloma Working Group (IMWG) response criteria for MM (See Section 10.10).[29]

Disease assessment will be assessed at baseline, during treatment as specified in the schedule of activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment.

If imaging is used in disease assessment, the same imaging technique used to characterize each identified and reported lesion at baseline will be employed in post-baseline disease assessments.

All participants' files and radiologic images and pathology samples must be available for source verification.

8.1.1.1. Laboratory Evaluation of Disease Response

Laboratory tests for disease response will be used to explore early signals of anti-cancer activity (see Section 10.10).[29,30] These laboratory tests will be completed per SoA, including assessments at suspected CR, whenever disease progression is suspected (eg, symptomatic deterioration), and at withdrawal from treatment if not done in the previous 4 weeks. Assessments will include:

- Serum protein electrophoresis (SPEP) for the measurement of serum M-proteins.
- Serum immunofixation electrophoresis (SIFE) for definitive identification of specific M-proteins (including immunoglobulin [Ig]G, IgA, IgM, and two light chains kappa

and lambda). SIFE will only be completed at baseline, when electrophoresis shows no measurable protein, at suspected CR/sCR, and at suspected progression (clinical or biochemical).

- 24 hr urine protein electrophoresis (UPEP) for the measurement of urine M-proteins.

- 24 hr urine immunofixation electrophoresis (UIFE) for definitive identification of specific M-proteins (including IgG, IgA, IgM, and two light chains kappa and lambda). UIFE will only be completed at baseline, when electrophoresis shows no measurable protein, at suspected CR, and at suspected progression (clinical or biochemical).

- Involved and uninvolved serum free light chain analysis (FLC) 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 should be recorded. If participants were treated with daratumumab less than 114 days prior to planned treatment day, daratumumab will interfere with SPEP, UPEP, SIFE and UIFE assays. Therefore, for these participants, FLC assay should be completed at screening, C0D1, and all subsequent disease assessments. Serum and urine M-spike if measurable at baseline in these participants should also be followed at the same timepoints as FLC with the most representative marker of disease status used for determination IMWG assessment.

- Beta-2 microglobulin. This will only be collected on the first day of treatment.

All samples will be collected prior to investigational product administration on days whereby investigational product is to be administered. In participants with two M-protein bands at the start of therapy, 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. When a complete response (CR), or a clinical or biochemical progression is suspected, SPEP, serum SIFE, UPEP, UIFE and FLC tests will be repeated within 1 to 4 weeks.

Note that if a participant had measurable serum or urine M-spike at baseline, unless the band is due to daratumumab or measurement of M-spike is confounded by the presence of daratumumab or other therapeutic mAb, progression 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.

8.1.1.2. Bone Marrow Plasma Cell Evaluation and Bone Marrow Sample Collection

Bone marrow evaluation of plasma cells in bone marrow aspirate and/or bone marrow biopsies will be performed to follow disease response.

Unilateral bone marrow aspirate samples will be collected and the percentage of plasma cells will be evaluated at the following times:

a. First pre-dose first day of study treatment or up to 7 days before study treatment;

b. At 1 month after C0D1 ±7 days;

c. At 3 months after C0D1 ±7 days;

d. When participant is found immunofixation negative in both serum and urine to confirm any complete response (CR);

e. At time of suspected disease progression (optional);

f. At 9 months after C0D1 and every 6 months thereafter unless a plateau or CR is observed. For participants who experience a plateau or CR, additional samples at 9 months after C0D1 and onwards will be optional. A ±14 day window applies for these collections.

Bone marrow biopsies will also be collected and the percentage of plasma cells within the biopsy samples will also be evaluated at the following times:

a. First day of study treatment (or up to 7 days before study treatment);

b. At 1 month after C0D1 ±7 days;

c. At 3 months (optional) after C0D1 ±7 days;

d. At 9 months ± 14 days (optional) after C0D1 and every 6 months ±14 days thereafter (optional);

e. At suspected stringent Complete Response (sCR);

f. At time of suspected disease progression (optional).

Assessments should be fixed according to the calendar, regardless of treatment delays. When bone marrow plasma cell infiltration is assessed by both bone marrow aspirate and by bone marrow biopsy, the highest value of bone marrow plasma cell infiltration should be utilized for response evaluation.

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

CCI
CCI In addition, if a participant is immunofixation negative in both serum and urine and flow cytometry is not available, biopsy sample will be required for immunohistochemistry (IHC) staining to assess clonality.

Bone marrow aspirates will also be evaluated centrally for minimal residual disease (MRD, see Section 10.11) by high-throughput sequencing using next generation sequencing (NGS) if there is evidence of CR. Results from central NGS assay may not be utilized if assay validation does not meet local policies and regulations. In this case, local validated assays may be utilized.

8.1.1.3. Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/Computed Tomography (CT) Imaging

Fluorodeoxyglucose-PET/CT (^{18}F-FDG-PET/CT) imaging will be used to explore early signals of anti-cancer activity. FDG-PET/CT is a functional imaging method in which the uptake of 18F-FDG by cells reflects the tissue uptake of glucose, thus revealing specific types of tissue metabolism. In MM, functional imaging on hybrid scanners (combination of PET and CT imaging) rather than on PET scanners alone are required. The association of abnormal FDG uptake provided by PET imaging and the assessment of bone structure provided by CT imaging leads to an optimal evaluation of disease.

Imaging studies will be collected per SoA at screening, at suspected CR, when disease progression is suspected (eg, symptomatic deterioration), when clinically indicated and at end of treatment visit (if not done in the previous 4 weeks). The screening PET/CT will be used to determine evaluable index lesions for each participant. Tumor background ratios (TBRs) and development of new sites of abnormality will be recorded.

If imaging is used in disease assessment, the same imaging technique used to characterize each identified and reported lesion at baseline will be employed in post-baseline disease assessments. Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring; otherwise, the participant will be classified as unevaluable. For participants with only skin involvement, skin lesions should be measured with a ruler at timepoints specified in Schedule of Activities. Plasmacytoma that has been irradiated will not be suitable for response assessment; however, it must be monitored for progressive disease.

Radiographic studies are not required to satisfy response and MRD requirements, except if CR or imaging MRD-negative status is suspected (see Section 10.11).

All participants' files and radiologic images and pathology samples must be available for source verification and for potential peer review.

Radiographic assessments obtained per the patient's standard of care prior to enrollment into the study 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 treatment, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given participant, and (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the participant's source notes.

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.

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, ECG (12-lead), laboratory assessments, including pregnancy tests, Echo or multigated acquisition scan (MUGA) and verification of concomitant treatments.

8.2.1. Physical Examinations

Participants will have a physical examination to include weight, vital signs, assessment of ECOG PS and height; height will be measured at Screening only.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen) and neurological system.

Neurological examinations include assessment of mental state, motor function, sensory function, gait, deep tendon reflexes, cranial nerve function, station and coordination.

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.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will be measured with the participant in the sitting position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

Vital signs should be monitored at least every 4 hours (±15 minutes) during the first 48 hours after first dose of study intervention (C0D1) and 24 hours after second dose of study intervention (C1D1) (see Section 10.13).

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

At each time point (see Schedule of Activities), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTc interval. To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. In addition, if verified QTc values continue to exceed the criteria above, immediate correction for reversible causes including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval should be performed.

If the QTc interval reverts to less than the threshold criteria listed above, and in the judgment of the investigator(s) and sponsor, it is determined that the cause(s) of QTc prolongation is something other than study intervention, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above the threshold values, the study intervention will be held until the QTc interval decreases to below the threshold values. Participants will then restart the study intervention at the next lowest dose level. If the QTc interval has still not decreased to 480 msec after 2 weeks, or if at any time a participant has a QTcF interval >515 msec or becomes symptomatic, the participant will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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 QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

Symptom of CRS including nausea, vomiting and diaphoresis may interfere with the accurate assessment of QTc. When CRS symptoms that indicate heightened autonomic tone are observed, ECG should be skipped until the symptoms are resolved.

If a participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Echocardiogram (Echo) or Multigated Acquisition Scan (MUGA)

Echo or MUGA will be evaluated in participants with previous history of cardiac events. For these participants, an Echo or MUGA will be performed at screening, when clinically indicated, and at the end of treatment visit. The following parameters will be evaluated: ventricular function (including left ventricular ejection fraction [LVEF], end systolic volume [ESV] and end diastolic volume [EDV]), qualitative evaluation of chamber size, and wall motion. A Doppler examination will be completed and should include an assessment of

mitral valve, atria, right ventricle, tricuspid valve, aortic valve, pulmonic valve, great vessels, and pericardium.

8.2.5. 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 DILI.

Participants with positive HBsAb and positive HBcAb are allowed to participate in the study if they have negative HBV DNA test at screening but HB viral load should be monitored for re-activation every 12 weeks. 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 elranatamab, 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.[31]

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in woman of childbearing potential (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 to the participant's receiving the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if

required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.7. Local Site Injection Tolerability Assessment

Assessments of the injection sites in the abdominal fat fold to monitor local tolerability to elranatamab SC injections will be performed for 1 to 4 hours following study drug administration in Cycle 0 and Cycle 1, as per the SoA. 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. Refer to Section 10.14 for more details.

Site tolerability assessments should continue at regularly scheduled visits if injection site pain or injection site reaction (ISR) characteristics continue to persist. The assessments should continue until the symptoms resolve. The injection sites will be assessed for erythema, induration, ecchymosis, injection site pain, injection site pruritus, or other observed characteristics after study drug dosing. Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported. When appropriate, at the discretion of the investigator, a participant with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. The dermatology consultation is expected to take place at the dermatologist's practice location, or may occur within the same institution where this study is conducted.

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/legally authorized representative 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.

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. 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 ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

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

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a

follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

8.3.5.3. Occupational Exposure

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.[22] See Section 10.13.

For the priming dose and first full dose, premedication for CRS is required (see Section 6.5.2).

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. 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 Section 10.13.All adverse events of special interest (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 according to SAE reporting procedur described in Section 10.3.4.

8.3.8.1. Lack of Efficacy

Not applicable because the study intervention has not approved for the treatment of MM and MM is life-threatening disease.

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.

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

Medication errors include:

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

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if

applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

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

8.4. Treatment of Overdose

For this study, any dose of elranatamab at each scheduled dosing greater than the assigned dose level will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of elranatamab (whichever is longer).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 2 weeks from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

8.5. Pharmacokinetics

Blood samples for the analysis of elranatamab concentrations will be collected into appropriately labeled tubes at the times specified in the SoA of the protocol. If CRS is suspected, and if a PK sample is not already scheduled to be taken (eg, from Cycle 3 onwards), a PK sample should also be taken. For each analysis, approximately 5 mL of blood samples will be collected to provide approximately 2 mL serum. The PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample for elranatamab should be collected from participants experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection should be documented in the CRF. Where noted in the SoA, blood samples for elranatamab concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples whenever possible.

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. The actual date and time of the sample collection will always be noted on the CRF. Samples obtained within the specified visit window will not be captured as a protocol deviation. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, participant and Sponsor.

Additional instructions for sample collection, processing, storage and shipping will be provided in the laboratory manual. The PK samples must be processed and shipped as indicated in the instructions provided to the investigator 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. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

PK samples will be assayed for -elranatamab using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

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8.7.1.1. Genetic Analysis

Bone marrow aspirates taken before the start of study treatment will be evaluated at local lab for t(4;14)(p16;q32), t(14;16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities as a disease characteristics. If some of these cytogenetic assessments cannot be done, site should provide participant's most recent cytogenetic testing results and enter into eCRF.

8.8.1. Bone Marrow Aspirate for NGS MRD

A 4 mL bone marrow aspirate sample (approximate volume) will be taken at the times specified in the Schedule of Activities. A sample taken pre-dose at screening or on C0D1 will

be used as a reference. MRD will be evaluated by high-throughput sequencing using a Next-Generation Sequencing (NGS) assay. Participants will be required to provide bone marrow aspirate samples for analysis of MRD as a key secondary efficacy endpoint whenever a bone marrow aspirate/biopsy sample is taken for disease response evaluation. A bone marrow collection will also occur following a CR, sCR or following disease progression. Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

8.9. Immunogenicity Assessments

Bioanalysis to assess for anti-drug (elranatamab) antibodies (ADA) will be performed. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs). All samples that are positive in a screening assay will be further characterized in terms of antibody specificity. A tiered approach to screening, confirmation and titer/quantitation will be utilized. A screening assay with competitive confirmatory steps followed by a titer assay will be used. Samples may also be analyzed in neutralizing antibody (NAb) assays. Participants found to have ADA at their final study visit and an ongoing AE possibly related to ADA will be asked to return to the clinic for ADA and

drug concentration blood sampling at approximately 3 month intervals until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

Blood samples (approximately 5 mL) to provide approximately 1 mL of serum each for ADA and NAb against elranatamab analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities of this protocol. The actual date and time (24-hour clock time) of each sample will be recorded. Additional instructions for sample collection, processing, storage, and shipping will be provided in the laboratory manual.

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. Any deviation from the specified sample handling procedure resulted in compromised sample integrity will be considered a protocol deviation.

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8.10. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic CCI measurements.

9.1. Statistical Hypotheses

There are no statistical hypotheses in this study so that no formal statistical testing will be performed.

9.2. Sample Size Determination

The total number of participants will depend on the absence/presence of DLT in the initial 4 participants and the number of participants evaluable for DLT. Additional 2 participants will be enrolled to verify the toxicity in Japanese population if at least one DLT is observed in the

initial 4 participants. Thus, maximum 6 evaluable participants may be enrolled in this study. The actual sample size may be smaller, depending on the underlying dose toxicity profile.

Although the sample size is not based on any statistical considerations, the study would have >55% chance to declare the RP2D determined in C1071001 study with a priming dose as it has exceeded the MTD for Japanese participants if the true DLT rate for Japanese participants is over 30%. Especially, the study would have 74.6% and 87.5% chance if the true DLT rate is 40% and 50%, respectively. It is determined that the RP2D with a priming dose exceeds the MTD in the Japanese participants if ≥2 DLTs are observed in this study.

Table 5. Detection Probablity of Over MTD

Total Sample Size	Number of DLTs Observed			True DLT Rate				
	Initial 4 Participants	Additional 2 Participants	Total	0.20	0.25	0.30	0.40	0.50
4	0	NA	0	40.96%	31.64%	24.01%	12.96%	6.25%
6	1	0	1	26.21%	23.73%	20.17%	12.44%	6.25%
6		≥1	≥2	14.75%	18.46%	20.99%	22.12%	18.75%
4	≥2	NA	≥2	18.08%	26.17%	34.83%	52.48%	68.75%
Detection Probability of Over MTD				32.83%	44.63%	55.82%	74.60%	87.50%

NA: Not Applicable

9.3. Analysis Sets

9.3.1. Full Analysis Set

The full analysis set includes all enrolled participants.

9.3.2. Safety Analysis Set

The safety analysis set includes all enrolled participants who receive at least 1 dose of study intervention. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.

9.3.3. Per Protocol Analysis Set (evaluable for RP2D)

The per protocol analysis set includes all enrolled participants who had at least 1 dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period.

9.3.4. PK Analysis Sets

The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest.

The PK concentration population is defined as all enrolled participants who are treated and have at least 1 analyte concentration.

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9.3.6. Immunogenicity Analysis Set

The immunogenicity analysis set includes all enrolled participants who receive at least one dose of study treatment and have at least one sample tested for ADA.

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. Primary Endpoint

9.4.1.1. Dose Limiting Toxicity

DLT is the primary endpoint of this study. The occurrence of DLTs observed in the dosing cohort is used to confirm the tolerability of the RP2D that was determined in non-Japanese population (C1071001) with a priming dose in Japanese population. The target DLT rate is 25%. Further, if a proportion of observed DLTs in this study is less than or equal to 30% derived from the upper boundary of equivalence interval in C1071001 study, the tolerability of the RP2D with the priming dose in Japanese population is considered to be confirmed. Adverse events constituting DLTs will be listed. Confirmation of the RP2D with the priming dose will be performed using the per protocol analysis set (evaluable for RP2D).

Confirmation of the RP2D with the Priming Dose

If there is either no DLT in the initial 4 participants or one DLT in 6 participants, the RP2D with the priming dose is confirmed. If DLT observed in ≥2 of the initial 4 participants or ≥2 of 6 participants, a lower dose cohort may be explored, if deemed necessary.

9.4.2. Secondary Endpoint(s)

9.4.2.1. Adverse Events

AEs (except CRS and ICANS) will be graded by the investigator according to the CTCAE version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). CRS and ICANS will be assessed according to the ASTCT grading[22] and coded using MedDRA. The focus of AE summaries will be on treatment-emergent AEs, those with initial onset or increasing in severity after the first dose of the study intervention. The number and percentage of participants who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 0, Cycle 1 and Cycles beyond 1).

9.4.2.2. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade (CTCAE version 5.0) observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 0, Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

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

9.4.2.3. Best Overall Response

Disease response will be presented in the form of patient data listings that include, but are not limited to starting dose, disease response at each visit, and best overall response. In addition, progression date, death date, date of the first response and the last disease assessment date, and the date of the last contact will be listed.

Best overall response (BOR) will be assessed based on reported overall responses at different evaluation time points using IMWG response criteria.

- Complete Response (CR) will encompass stringent Complete Response (sCR) and CR.
- Overall Response (OR) will encompass sCR, CR, very good partial response (VGPR), and partial response (PR) .
- Clinical Benefit (CB) will encompass sCR, CR, VGPR, PR, and minimal response (MR) .

A summary table of BOR will also be provided.

9.4.2.4. Progression Free Survival

Progression free survival (PFS) is the time from the first date of the study intervention to the date of the first documentation of progression, or death due to any cause. Progression is defined as the appearance of local, regional or distant disease of the same type after CR or progression of pre-existing lesions. It does not include second primary malignancies of unrelated types. A data listing of PFS will be provided. A summary table may be provided as appropriate.

9.4.2.5. Overall Survival

Overall survival (OS) is the time from the first date of the study intervention to the date of death due to any cause. A data listing of OS will be provided. A summary table may be provided as appropriate.

9.4.2.6. Time to Response

Time to response (TTR) is defined for participants with confirmed objective response (as defined above in overall response) as the time from the first date of the study intervention to

the date of the first documentation of objective tumor response. A data listing of TTR will be provided. A summary table may be provided as appropriate.

9.4.2.7. Duration of Response

Duration of Response (DOR) is defined for participants with confirmed objective response (as defined above in overall response) as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. A data listing of DOR will be provided. A summary table may be provided as appropriate.

9.4.2.8. Elranatamab Pharmacokinetic Analysis

The concentrations of elranatamab will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation (CV%), median, minimum maximum, geometric mean, and geometric CV%) by cycle, and nominal time. Individual participant and median profiles of the concentration-time data will be plotted by cycle using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

Individual concentration-time data of elranatamab following the Cycle 0 Day 1 dose, Cycle 1 Day 1 dose and Cycle 2 Day 1 dose will be analyzed separately using non-compartmental analysis to estimate the PK parameters. The PK parameters estimated will include C_{max}, time to maximum concentration (T_{max}), and concentration versus time curve (AUC_{last}). If data permit or if considered appropriate, minimum concentration (C_{min}), terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F) and apparent volume of distribution during terminal phase (V_z/F) will be also estimated for Cycle 0 Day 1, Cycle 1 Day 1 and Cycle 2 Day 1. Actual sample collection times will be used for the parameter calculations. The PK parameters will be summarized descriptively by cycle.

9.4.2.9. Analysis of Immunogenicity Data

For the immunogenicity data, the percentage of participants with 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 participants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described, if data permit. The potential impact of immunogenicity on PK and clinical response including pharmacodynamic markers, safety/tolerability and efficacy of ADA will be explored, if warranted by the data.

9.4.3. Other Safety Analyses

All safety analyses will be performed on the safety population.

Summaries and analyses of safety parameters will include all participants in the safety analysis set.

AEs, ECGs, BP, pulse rate, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of

participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.3.1. Electrocardiogram Analyses

The analysis of ECG results will be based on participants in the safety analysis set with baseline and on treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for HR (QTcF) using Fridericia's correction. Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF, and by dose. Individual QT (all evaluated corrections) intervals will be listed by time and dose. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by dose and time point.Details of additional analysis (if any) will be specified in SAP.

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

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

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single

observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor 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.

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative 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 or their legally authorized representative 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 or his or her legally authorized representative 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 or his or her legally authorized representative 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 ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

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.

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, 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 participants) 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

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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.

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.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data 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 (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 on-site monitoring), are provided in the monitoring plan.

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 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 on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

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. 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 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

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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 Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to

provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 6. Safety Laboratory Tests

Hematology	Chemistry	Serology	Coagulation	Urinalysis	Pregnancy Test	Ad hoc Central Lab Cytokine Analysis†
Hemoglobin	ALT	HBV	PT	Urine dipstick for urine protein: If positive, microscopy (Reflex Testing)	For female participants of childbearing potential, serum.	IL-6, IL-10, IL- 2, sIL2R, IL-12, IL-4, IL-5, IL-10, IL-13, IL-17, IL-1b, IL-8, IFNγ, and TNF-α
Platelets	AST	HCV	PTT/aPTT			
WBC	bicarbonate					
Absolute or % Neutrophils	CRP					
	Alk Phos					
Absolute or % Lymphocytes	Sodium					
	Potassium					
Absolute or % Monocytes	Magnesium					
	Chloride					
Absolute or % Eosinophils	Total calcium			Urine dipstick for urine blood: If positive, collect a microscopy (Reflex Testing)		
	Total bilirubin*					**Optional Ad hoc Local Lab Cytokine Analysis†**
Absolute or % Basophils						
	Total Protein					
	BUN					
	Creatinine					
	Uric Acid					IL-6
						IL-1β
	Glucose (nonfasted)					IL-10
						TNFα
	LDH					Other cytokines
	Albumin					
	Phosphorus or Phosphate					

* For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

† Cytokines for central lab evaluation will be collected if CRS is suspected. Local lab evaluation of cytokine is only required if the site require this information for participant management.

Investigators must document their review of each laboratory safety report.

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.

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, death due to progression of disease).

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, 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 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 make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

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 (see Section 10.13).

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 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 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

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 90 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding (women who are currently breastfeeding and intend to interrupt breastfeeding are excluded from participating), 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 90 days 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 not considered WOCBP:

1. 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.

2. 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 old and not using hormonal contraception or HRT. When there is a high FSH level, it should be confirmed that there is no other medical cause.
    - 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 (not approved in Japan).

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

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

    - Oral;

    - Intravaginal (not approved in Japan);

    - Transdermal (not approved in Japan);

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

    - Oral (not approved in Japan);

    - Injectable (not approved in Japan).

8. Sexual abstinence.

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

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

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide (all not approved in Japan);

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods) (all not approved in Japan)


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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.

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 >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants 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 participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

10.8. Appendix 8: Bone Marrow Reserve in Adults

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head :			136.6		
	Cranium	165.8	0.75	124.3	13.1	**13.1**
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs :			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	**10.2**
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar) :			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

10.9. Appendix 9: International Myeloma Working Group (IMWG) Multiple Myeloma Diagnosis Criteria

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

1. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

    a. Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL).

    b. Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL).

    c. Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L.

    d. Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT.‡

2. Any one or more of the following biomarkers of malignancy:

    a. Clonal bone marrow plasma cell percentage* ≥60%.

    b. Involved: uninvolved serum free light chain ratio§ ≥100.

    c. >1 focal lesions on MRI studies.¶

PET-CT=^{18}F-fluorodeoxyglucose PET with CT.

* Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

† Measured or estimated by validated equations.

‡ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§ These values are based on the serum freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

¶ Each focal lesion must be 5 mm or more in size.

Relapse is defined as progression of disease after an initial response to previous treatment, more than six months after cessation of treatment.

Refractory is defined as resistance to treatment due to lack of response or progression of disease during treatment or within six months after cessation of treatment.

10.10. Appendix 10: International Myeloma Working Group (IMWG) Response Criteria for Multiple Myeloma

All response categories require two consecutive assessments made any time before starting any new therapy. Participants must have measurable disease at enrolment (study entry).

Measurable disease is defined as:

- Serum M-protein ≥ 0.5 g/dL (5 g/L);
- Urine M-protein ≥ 200 mg/24 h;
- Serum FLC assay: involved FLC level ≥ 100 mg/L (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 lower or lowest level of response. Participants will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; participants cannot move to a lower response category.

Response	IMWG Criteria*
Stringent Complete Response (sCR)	• Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/ λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).[1] • In patients whereby the only measurable disease is by serum FLC levels, sCR is defined as normal FLC ratio of 0.26 to 1.65 plus absence of clonal cells in bone marrow as defined above.
Complete Response (CR)	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.[2] • In patients whereby the only measurable disease is by serum FLC levels, CR is defined as normal FLC ratio of 0.26 to 1.65 plus criteria listed above.
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. • In patients whereby the only measurable disease is by serum FLC levels, VGPR is defined as a ≥90% decrease in the difference between involved (tumor) and uninvolved (non-tumor) serum FLC levels.
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 FLC levels is required in place of the M-protein criteria.

	• If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. • In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)^3 of soft tissue plasmacytomas is also required.
Minimal Response (MR)	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a 50% reduction in the size (SPD)^3 of soft tissue plasmacytomas is also required.
No Change/Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR or progressive disease.
Progressive Disease (PD)	• Increase of ≥ 25% from lowest response value in any one or more of the following: o Serum M-protein (absolute increase must be ≥ 0.5 g/dL); o Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥ 5 g/dL; o Urine M-protein (absolute increase must be ≥ 200 mg/24 h; o In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); o In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); o Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD^3 of >1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis. o ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical Relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD^3 of the measurable lesion; • Hypercalcemia (>11 mg/dL); • Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein.

* All response categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. To confirm response or progressive disease, two discrete samples are required, and testing cannot be based upon the splitting of a single sample. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression free survival. Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.

[1] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/ λ /L ratio. An abnormal κ/ λ ratio by immunohistochemistry 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.

[2] Confirmation with repeat bone marrow biopsy is not required. Careful attention should be given to new positive immunofixation results appearing in patients who have achieved a complete response, when the isotype is different. This probably represents oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.

[3] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or dedicated CT scans where applicable. Measurement of tumor size will be determined by the SPD.

10.11. Appendix 11: IMWG MINIMAL RESIDUAL DISEASE (MRD) Criteria

MRD tests should be initiated only at the time of suspected complete response. Confirmation with two consecutive assessments is not required.

Response	IMWG Criteria
Sustained MRD-Negative[1]	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).
Flow MRD-negative[2]	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Imaging-negative MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.

CT = computed tomography; IMWG=International Myeloma Working Group; MRD = minimal residual disease; NGF = next-generation flow cytometry; NGS = next generation sequencing; PET = positron emission tomography; SUV = standardized uptake value.

Footnotes

1. Sustained MRD negativity, when reported, should also annotate the method used (eg, sustained sequencing MRD- negative).
2. Bone marrow multiparametric flow cytometry should follow NGF guidelines. The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The complete eight-color method should use a lyophilized mixture of antibodies. 5 million cells should be assessed. The method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

10.12. Appendix 12: ECOG Performance Status*

Grade	ECOG
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 house work, 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.

*As published in Am J Clin Oncol 5:649-655, 1982.

10.13. Appendix 13. CRS and ICANS Mitigation and Management

Participants are required to be hospitalized and monitored for CRS/ICANS for at least 3 days (72 hours) beginning on C0D1 and C1D1. For the priming dose (C0D1) and first full dose (C1D1), premedication for CRS is required (see Section 6.5.2)

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 (see Section 10.2) as long as the sampling does not interfere with the medical treatment of the participant.

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.

ASTCT CSR criteria[22] (Table 7) should be used only for the purposes of grading of CRS on the adverse event case report form (CRF) and management guidelines will follow ASTCT CRS grading. These treatment guidelines[23] may be modified as needed by the responsible investigators according to the best practices at their institute.

Table 7. ASTCT CRS Revised Grading System[22]

CRS parameter	Fever*	With Hypotension	And/or† Hypoxia
Grade 1	Temp. ≥38°C	None	None
Grade 2	Temp. ≥38°C	Not requiring vasopressors	Requiring low-flow‡ nasal cannula, low-flow‡ facemask or blow-by
Grade 3	Temp. ≥38°C	Requiring a vasopressor with or without vasopressin	Requiring high-flow‡ nasal cannula, high-flow‡ facemask, nonrebreather mask, or Venturi mask
Grade 4	Temp. ≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

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

* Fever is defined as temperature ≥38°C and not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine 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.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula 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 is defined as oxygen delivered at >6 L/min.

CRS management guidelines[23,24]

ASTCT Grade 1 CRS:

- Monitor vital signs for worsening of condition.

Fever

- Acetaminophen/paracetamol and hypothermia blanket for the treatment of fever.
- Non-steroidal anti-inflammatory drugs (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[1] 8 mg/kg IV or siltuximab[2] 11 mg/kg IV for persistent (lasting >3 days) and refractory fever.

ASTCT Grade 2 CRS:

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

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV fluid bolus of 500-1000 ml of normal saline. Can give second IV fluid bolus if systolic blood pressure 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 hrs if needed.
- If hypotension persists after 2 fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to intensive care unit (ICU), obtain echocardiogram (ECHO), and initiate other methods of hemodynamic monitoring.
- In patients at high-risk (bulky disease, older age 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.

ASTCT Grade 3 CRS:

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

[1] Tocilizumab is not approved in Japan for the treatment of CRS other than the events associated with chimeric antigen receptor T-cell (CAR-T) therapy.

[2] Siltuximab is not approved in Japan.

Fever

- Manage as in Grade 1 CRS.

Hypotension

- IV boluses, as needed, as recommended for Grade 2 CRS.
- Tocilizumab and 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.

ASTCT Grade 4 CRS:

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

Fever

- Manage as in Grade 1 CRS.

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.

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 delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and cerebral edema.[22] If ICANS is observed in relation to -elranatamab, the ASTCT criteria, its grading and management will be followed.[23,24] These treatment guidelines may be modified as needed by the responsible investigators according to the best practices at their institute.

Table 8. 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 9. ASTCT ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (unarousable and unable to perform ICE)
Depressed level of consciousness†	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 focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	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⁂	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate or decorticate posturing; or cranial nerve VI (abducens nerve) palsy; or papilledema; or Cushing's triad

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

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

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

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

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

ICANS management guidelines[23,24]

ASTCT ICANS Grade 1:

- Vigilant supportive care; aspiration precautions; intravenous (IV) hydration.
- Withhold oral intake of food, medicines, and fluids, and assess swallowing.
- Convert all oral medications and/or nutrition to IV if swallowing is impaired.
- Avoid medications that cause central nervous system depression.
- Neurology consultation.
- Evaluate elevated intracranial pressure (ICP), if suspected, with fundoscopic exam for papilledema and lumbar puncture for cerebrospinal fluid opening pressure.
- MRI of the brain with and without contrast; CT scan of the brain can be performed if MRI of the brain is not feasible.
- Daily 30 min electroencephalogram (EEG) until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam 750 mg every 12 hrs.
- Consider anti-IL-6 therapy with tocilizumab 8 mg/kg (maximum 800 mg) IV or siltuximab 11 mg/kg IV, if there is concurrent CRS.

ASTCT 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 hrs or methylprednisolone 1 mg/kg IV every 12 hrs if refractory to anti-IL-6 therapy, or for ICANS without concurrent CRS.
- Consider transferring patient to intensive care unit (ICU) if ICANS associated with grade ≥2 CRS.

ASTCT 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 intravenously (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 intensive care unit (ICU) and treat with phenobarbital loading dose of 60 mg IV.
  - Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 hrs for three doses; levetiracetam 1,000 mg IV every 12 hrs; phenobarbital 30 mg IV every 12 hrs.
  - Lacosamide may also be considered for treatment of seizures should the seizures persist but should not be used in patients 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 treatment at a loading dose of 15 mg/kg IV.
  - Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg IV every 8 hrs for three doses; levetiracetam 1,000 mg IV every 12 hrs; phenobarbital 1–3 mg/kg IV every 12 hrs.
  - Lacosamide may also be considered for treatment of seizures should the seizures persist but should not be used in patients with concurrent CRS in order to avoid arrhythmias and hypotension.

    - Continuous electroencephalogram 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.

ASTCT 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 methylprednisolone IV 1 g/day 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 hrs for 2 days, 125 mg every 12 hrs for 2 days, and 60 mg every 12 hrs for 2 days.

- For seizures, treat as described for grade 3 ICANS.

- MRI of the spine should be obtained for focal motor weakness.

- To manage elevated ICP:

    - Elevate head end of the patient'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 to lower.

    - 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.

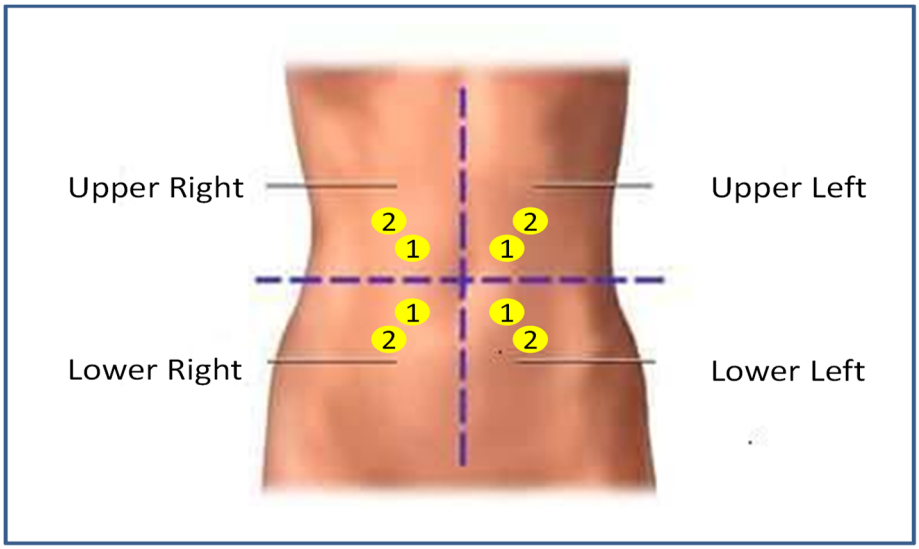
    - Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50–75 mL/h while monitoring electrolytes every 4 hrs, and withhold infusion if serum Na levels reach ≥155 mEq/L.

    - For patients with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 min, if needed.

- Consider neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema and IV anesthetics for burst-suppression pattern on EEG.

- Metabolic profiling every 6 hrs 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.

10.14. Appendix 14: Subcutaneous Injection Site Locations



Injection site locations include a maximum of 8 unique administration sites distributed across 4 abdominal quadrants with a possibility of up to 2 injection locations per quadrant. Location 1 is proximal to the umbilicus and Location 2 is distal to the umbilicus.

Administer the required number of injections in the following order:

1. Lower Left Quadrant Location 1;
2. Lower Right Quadrant Location 1;
3. Lower Left Quadrant Location 2;
4. Lower Right Quadrant Location 2;
5. Upper Right Quadrant Location 1;
6. Upper Left Quadrant Location 1;
7. Upper Right Quadrant Location 2;
8. Upper Left Quadrant Location 2.

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 ISR in the participant's source records and study CRF. Complete one CRF per injection.

10.15. Appendix 15: 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 globally 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).

10.15.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per exclusions criteria in this protocol. When the infection resolves, the patient may be considered for re-screening.

10.15.2. 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 (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Seciton 10.4 and Section 10.15.3.1 of this appendix regarding contraceptive guidance.

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

10.15.3. Alternative Facilities for Safety Assessments

10.15.3.1. 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:

- Hematology
- Blood chemistry
- Coagulation
- Urinalysis
- Pregnancy test

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 IU/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.

10.15.3.2. 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.

10.15.4. 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 elranatamab 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, elranatamab 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. Notify the study team when treatment is restarted.

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

10.15.5. Home Health Visits

A home health care service will be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Physical examination

- Vital signs

- ECOG PS

10.15.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or 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 study medical monitor.

10.16. Appendix 16: Condition to be discharged

When a participant is discharged from the hospital during the DLT evaluation period, the following conditions (tests, medical examination, etc.) should be performed on the day of the scheduled discharge by the investigators, and the propriety of discharge should be determined. The tests/medical examinations which are needed to confirm the participant's status will be conducted per clinical practice in the study site as appropriate.

- There is no current clinically significant adverse or side effects, including CRS, or medical reasons that requires monitoring in a hospital setting.

- If a clinically significant adverse or side effect has occurred or continues to be present, the investigator has determined that the event is manageable by appropriate treatment or prophylaxis in an out of the hospital setting.

- Overall physical condition is stable and acceptable.

- In case of emergency, the participant may return to the clinical study site or other medical institution. If participants go to a medical institution other than the clinical study site, the clinical study site asks that the participants contact the study site contact information and study investigator and the doctor at the medical institution will communicate to discuss appropriate treatments. A study site keeps flamework to ready for emergency situations that is available even during nights and holidays, and the sponsor will ensure that the selected study site will thoroughly follow all participants according to study procedures.

10.17. Appendix 17: Abbreviations

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

Abbreviation	Term
ADA	antidrug antibodies
ADC	antibody-drug conjugate
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen presenting cell
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ASCT	autologous stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BCMA	B-cell maturation antigen
BiPAP	biphasic positive airway pressure
BM	bone marrow
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C1D1	cycle 1 day 1
CAR-T	chimeric antigen receptor T-cell
CB	clinical benefit
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHF	congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
CR	complete response
CRAB	C = calcium (elevated), R = renal failure, A = anemia, B = bone lesions
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	c-reactive protein

Abbreviation	Term
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLI	donor lymphocyte infusion
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
EC	effective concentration
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EDV	end diastolic volume
EEG	electroencephalogram
EMA	European Medicines Agency
EMG	electromyography
EOT	end of treatment
ESV	end systolic volume
EU	European Union
EudraCT	European Clinical Trials Database
Fc	fragment crystallizable
FDA	Food and Drug Administration (United States)
FDG	fluorodeoxyglucose
FLC	free light chain
FSH	follicle-stimulating hormone
GBS	Guillain Barré Syndrome
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GVHD	graft versus host disease
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy

Abbreviation	Term
IB	investigator's brochure
ICANS	immune effector cell-associated neurotoxicity
ICD	informed consent document
ICE	Immune Effector Cell-Associated Encephalopathy
ICH	International Council for Harmonisation
ICU	intensive care unit
ICP	intracranial pressure
ID	identification
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMID	immunomodulatory drug
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
ISR	injection site reaction
IV	intravenous
IMWG	International Myeloma Working Group
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MGUS	monoclonal gammopathy of undetermined clinical significance
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NCV	nerve conduction velocity
NGF	next generation flow cytometry
NGS	next generation sequencing
NIMP	non-investigational medicinal product
NOAEL	no-observed-adverse-effect level

Abbreviation	Term
NSAID	non-steroidal anti-inflammatory drug
NSG	NOD scid gamma
OR	overall response
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
POEMS	polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
Q1W	once weekly
Q2W	every other week
QTc	corrected QT
QTcB	corrected QT (Bazett method)
QTcF	corrected QT (Fridericia method)
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SIFE	serum immunofixation electrophoresis
SPEP	serum protein electrophoresis
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SPD	sum of products of the maximal perpendicular diameters
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
SUV	tandardized uptake value
SWOG	Southwest Oncology Group
$t_{1/2}$	terminal elimination half-life
TBili	total bilirubin

Abbreviation	Term
TBR	tumor background ratio
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TNF	tumor necrosis factor
TTR	time to response
UIFE	24 hr urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	24 hr urine protein electrophoresis
US	United States
VGPR	very good partial response
Vss	volume of distribution
Vz	volume of distribution during terminal phase
WBC	white blood cell
WOCBP	woman of childbearing potential

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