MAGNETISMM-9

A PHASE 1/2, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE A DOSING REGIMEN WITH TWO STEP-UP PRIMING DOSES AND LONGER DOSING INTERVALS OF ELRANATAMAB (PF-06863135) MONOTHERAPY IN PARTICIPANTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Study Intervention Number:	PF-06863135
Study Intervention Name:	Elranatamab
US IND Number:	133,940
EudraCT Number:	2021-001371-16
ClinicalTrials.gov ID:	NCT05014412
Protocol Number:	C1071009
Phase:	1 /2
Sponsor Legal Address	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Learn About the Study Medicine (Elranatamab) in Participants With Multiple Myeloma That Has Come Back After Responding to Treatment or Has Not Responded to Treatment

Document History

Document	Version Date
Amendment4	20 Dec 2023
Amendment3	22Nov2022
Amendment2	10 June 2022
Amendment **1**	09 Jun 2021
Original orotocol	28 March 2021

This amendment inco1porates all revisions to date, including amendments made at the request of countiy health authorities and IRBs/ ECs and any protocol administl'ative clarification letter(s).

Protocol Amendment Summary of Changes Table

Amendment 4 (20 Dec 2023)

Overall Rationale for the Amendment:

The rima1 rationale for this amendment is to remove Pait 3 of the study CCI due to the evolving multiple myeloma ti·eatment landscape. As communicated to investigators via a letter dated 24 March 2023, the Sponsor's decision to no longer conduct Pait 3 of the study was not due to any safety issues or concerns. Some changes have been made to the infection prophylaxis guidance to align with pro ·run-level u dates and eh-anatainab dosin idance includin a new dosin fre uenc of CCI

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Removed any mention of previously planned Study Pait 3 throughout the protocol, updated title page (Study title and brief title), study schematic, removed Pait 3 SoA, edited exclusion criterion #13 related to CCI [redacted] removed figure 2 from Section 6, updated statistical section related to Pait 3.	To reflect the Sponsor's decision to no longer conduct Study Pait 3 due to the evolving multiple myeloma treatment landscape.	Title page (Study title and brief title), Section **1.1:** Synopsis, Section 1.2: Schema; Section 1.3: SoAs, Section 2.1: Study Rationale, Section 2.2.1: Multiple Myeloma (Table 3), Section 2.2.3.2: Clinical Overview (Sections 2.2.3.2.**1** 2.2.3.2.2 and 2.2.3.2.3), CCI [redacted] Section 2.3: Benefit/Risk Assessment, Section 2.3.1: Risk Assessment, Section 2.3.2: Benefit Assessment, Section 3: Objectives, Endpoints And Estimands, Section 4.1: Overall Design, Section 4.2: Scientific Rationale for Study Desi Section 4.3.3: CCI [redacted] Section 5.2: Exclusion criteria (exclusion criterion #13), Section 6: Study intervention(s) and Concomitant Therapy, Section 6.1: Study futervention s) Administered, CCI [redacted] (Figure 2), Section 6.3.1: Allocation to Study futeivention, 6.5.1.2: Dose Modifications for Ehanatamab-Related Toxicity and for Peripheral Neuro ath y, CCI [redacted] Section 6.7: Treatment of Overdose, Section 6.8.1:

Description of Change	Brief Rationale	Section # and Name
		Premedications Required for C okine Release Syndrome, CCI Section 8.6: B10mar ers, Section 8.6.8: B 1e for MRD (Pait 2 , Section 9: Statistical Considerations (Sections 9.1, 9.2, 9.3, 9.4 and 9.5
- Pait 1: removed option to return to 76 mg QW dosing after staiting 76 mg Q2W from C7 onwai·ds and removed option to return to 152 mg Q2W dosing after staiting 152 mg Q4W from C7 onwards (after RP2D was detennined) - Pait 2A DL2, Pait 2B and Pait 2C: removed option to return to 152 mg Q2W dosing after staiting 152 mg Q4W from C7 onwards	To remove the options to retmn to more frequent dosing (QW or Q2W) after staiting Q2W or Q4W dosing, as suppo1ted by mechanistic model simulations and expected reduction in disease burden.	Section 1.1: Synopsis (Overall Design), Section 1.3: SoA Pait 1, Section 4.1: Overall Design
CCI [redacted]	[redacted]	[redacted]
- Added pre-dose SARS-CoV-2 testing (at CXDl) - For pa1ticipants with SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the strut of symptoms or positive test result.	To avoid dosing paiticipants while an infection is ongomg.	Section 1.3: SoAs Pait 1 and Pait 2, Section 6.8.8: COVID-19, Section 10.2: Appendix 2- Clinical Laborato1y Assessments, Section 10.15: Appendix 15- Anti-infectious Prophylaxis and Monitoring

Description of Change	Brief Rationale	Section # and Name
- Edited text to clarify administrntion route for immunoglobulins - Require (instead of recommend) the use of PJP prophylaxis and antiviral prophylaxis - Added one column "Required/recommended" in Appendix 15	To clarify and align with program level infection guidance	Section 6.8.7- Infection Prophylaxis, Section 10.15: Appendix 15- Anti-infectious Prophylaxis and Monitoring
- Added that RP2D was selected after Pait 2A to be 152 mg Q2W, that the emollment is completed in all coho1ts and that Part 2C will not be explored, - CCI [redacted]	To info1m about the current study status at time of protocol amendment 4 and CCI [redacted]	Section 1.1: Synopsis, Section 4.1: Overall Design, Section 4.3.4: Defmition of RP2D for Pait 2B and Pait 1 FromC7
- Updated the dose modification rnles in case of intenuption > 4 weeks (if on Q2W dosing) or >8 weeks (if on Q4W dosing) or>12weeks (if on Q8W dosing) - Conected the guidance for QW and Q2Wregimen window± 3 da s) CCI [redacted] m case eh-anatamab cannot be administered on the planned window (window ± 6 days) - Clarified guidance regarding toxicity mana ement	To align with program level guidance and suppo1ted by mechanistic model simulations	Section 6.5.1.2- Dose Modifications for Eh-anatamab-Related Toxicity and for Peripheral Neuropathy
- Revised eh-anatamab contraception requirements WOCBP and men :	- To align with updated eh-anatamab PK data as described in last	Sections 1.3: SoAs Pait 1 and Pali 2, Section 4.2.3: Choice of Contrace tion/BaiTier

Description of Change	Brief Rationale	Section # and Name
Clarification for investigators via a letter dated 01 Febmaiy 2023. - Added the sentence: "The investigator or designee will advise the paiiicipant to seek advice about the donation and c1yopreservation of ge1m cells prior to the staii of study intervention, if a licable. "	eh-anatamab IB (WOCBP), to align with calculated safety mai·gin between seminal transfer and estimated MABEL (men) and to align with latest protocol template - To align with program level guidance	Requirements, Section 5.3.**1** Contraception, Section 10.4: Appendix 4- Contraceptive and BaiTier Guidance (Sections 10.4.1, 10.4.2 and 10.4.4).
Non-substantial Modification(s)		
- Revised eh-anatamab clinical study smnmai·ies, refen-ing protocol users to the IB for the most cmTent info1mation - Added rationale for the risk of infections with eh-anatamab in RRMM paiiici ants	To align with latest IB updates	Section 2.2.3.2: Clinical Overview, Section 2.3.1: Risk Assessment
Added that at the start of a cycle, pa1iicipant should have recovered from any lung infection or other serious infection to baseline	To avoid dosing paiiicipants while an infection is ongomg	Section 6.5.1.1: Redosing Criteria
CCI Physical Exam, Nemologic Exam, Vital Signs ai·e to be perfo1med every 2 c des - CCI and PK sainples that samples should be coll ected predose every 4 cycles CCI	CCI	Sections 1.3: SoAs Pa1i 1 and Pali2

Description of Change	Brief Rationale	Section # and Name
(only for pa1ticipants ah-eady dosed with 152 mg Q4W)		
Revised the guidance for Grade 3 PN in case of initial occmTence and recunent episode	To align with program level guidance	Section 6.5.1.2- Dose Modifications for Ehanatamab-Related Toxicity and for Peripheral Neuro ath - Table 6
CCI [redacted]	[redacted]	[redacted]
Added more detailed descriptions for when sennn FLC should be used to assess disease response and about repeat sampling for confmnation of disease pro ·ess1on	To better match descriptions in Section 10.10 (Appendix 10)	8.1.1. Laborato1y Assessment for Evaluation of Disease Response
Added that only ADA positive samples will be tested for NAb	To add clarity on the NAb samples that will be anal zed	Section 9.3.3.4. Immunogenicity Analyses
Removed that the study team should be notified when treatment is restaited after SARS-CoV-2 s toms have recovered	To align with program level guidance	Section 10.8.4. Study Intervention
Clarification of requirement for investigator adherence to European regulation 536/2014 and European Medical Device Regulation 2017/745.	To comply with cunent regulations	Section 10.1.1: Appendix l- Regulato1y and Ethical Considerations
- Clarification that a paiticipant's legally authorized representative can sign a statement of info1med consent and can be rovided with a co of	To comply with cunent regulations	Section 10.1.3: Appendix l- Info1med Consent Process

Description of Change	Brief Rationale	Section # and Name
the ICD(s) only if allowed by local regulations. - Clarification that documents used to reconsent participants or their legally authorized representative must be IRB/EC-approved, as required per local regulations.		
Added information on security measures and associated SOPs for information technology systems used to collect, process, and store study-related data	Added information on security measures and associated SOPs for information technology systems used to collect, process, and store study-related data	Section 10.1.4: Appendix 1- Data Protection
- Addition of CTIS and public websites to the locations where Pfizer discloses clinical study results. - Clarification that Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com and that CSR synopses will have personally identifiable information anonymized - Clarification that Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications, with specification of the document types. - Clarification that CSRs provided to researchers as part of data sharing will have personally	To comply with current regulations	Section 10.1.6: Appendix 1- Dissemination of Clinical Study Data

Description of Change	Brief Rationale	Section # and Name
identifiable info1mation anon ·zed.		
- Clarification that monitoring details are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee. - Clarification that the investigator must provide direct access to source records and documents	To comply with cunent regulations	Section 10.1.7: Appendix 1- Data Quality Assurance
- Updated the definition of the study sta1t date to be the date of the first paiticipant's first visit. - Updated some reasons at the sole discretion of the sponsor to close the study site or te1minate the study at an time	To comply with cunent regulations	Section 10.1.9: Appendix 1- Study and Site Stait and Closure
Updated the publication policies for study investigators and for Pfizer.	To comply with cunent regulations	Section 10.1.10: Appendix I- Publication Policy
Removed Tocilizumab from study intervention	Since the use of tocilizumab for CRS induced by anti-cancer treatment was approved in Japan, it is no longer IMP and there is no need of safety reporting in Japan	Section 10.14.1: Appendix 14- Japan
CCI [redacted]	[redacted]	[redacted]
Minor administrative, editorial, typographical, or fo1matting changes. U dated list of	Updated for grammatical conectness, consistency, and/or clarity.	Global

Description of Change	Brief Rationale	Section # and Name
abbreviations. Added new references		

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CCI [redacted]

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LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 1/2, open-label, multicenter study to evaluate a dosing regimen with 2 step-up priming doses and longer dosing intervals of elranatamab (PF-06863135) monotherapy in paiticipants with RRMM.

Brief Title: A Study to Learn About the Study Medicine (Elranatamab) in Paiticipants With Multiple Myeloma That Has Come Back After Responding to Treatment or Has Not Responded to Treatment.

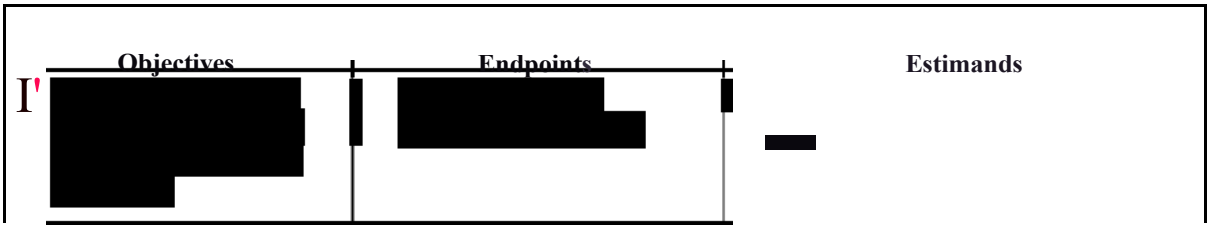
Rationale

The pmpose of the study (Pait 1 and Pait 2) is to evaluate the rate of Grade ::::: 2 CRS using a priming regimen that involves a premedication cocktail and 2 step-up priming doses to be administered within the first week of elranatamab ti·eatment. The study will also evaluate the safety, tolerability, PK, phaimacodynamics, and preliminaiy anti-myeloma activity of elranatamab full doses 76 mg and >76 mg with different dosing intervals.

Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Prima1-y		
Pa1·t 1 and Pa1·t 2		
• To assess the rate of Grade c:::2 CRS when eh-anatamab is administered with a dosing regimen of 2 step-up priming doses and premedication in participants with RRMM.	• Grade c:::2 CRS rate dming Cl.	• The prima1y estimand is rate of Grade c:::2 CRS dming Cl as assessed by ASTCT criteria. It will be estimated based on all enrolled RRMM participants who received at least 1 dose of study intervention regardless of duration on the study treatment.
Secondarv		
Pa1·t 1 and Pa1·t 2		
• To assess the safety and tolerability of eh-anatamab at doses >76 mg with a longer dosing interval (> 1 week) in order to identify the RP2D. **(Pa11 2A and 2C)**	• Incidence ofDLTs during DLT observation period.	• The secondruy estimand is DLT rate estimated based on data from DLT-evaluable pruticipants during the DLT observation period
• To evaluate the overall safety profile of eh-anatamab with 2 step-up priming doses and altemative dosing	• Adverse Events as characterized by type, frequency, severity as graded by NCI CTCAE version 5.0, timing, seriousness, and relationship to eh-anatamab.	• Not Applicable

Objectives	Endpoints	Estimands
regimens in pa1ticipants withRRMM	The severity of CRS and ICANS will be assessed according to ASTCT criteria; • Laborato1y abnonnalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	
• To evaluate the anti-myeloma activity of eh-anatamab with alternative dosing regimens in participants withRRMM	• ORR and CRR, per IMWG response criteria as determined by investigator; • Time to event endpoints: TIR, DOR, DOCR and PFS per IMWG response criteria as detennined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• Not Applicable
• To evaluate the PK of eh-anatamab	• Pre- and postdose concentrations of eh-anatamab.	• Not Applicable
• To evaluate immunogenicity of eh-anatamab	• Incidence and titers of ADA and NAb against eh-anatamab.	• Not Applicable
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



Overall Design

Study C1071009 is a prospective, open-label, multicenter, non-randomized Phase 1/2 study aimed to evaluate the safety (in paiticular the rate of Grade::::2 CRS) of a priming dose regimen of elranatamab that involves premedication and 2 step-up p1iming doses administered within the first week of treatment (Pait 1 and Pait 2). Study C1071009 will include RRMM paiticipants who are refracto1y to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb.

Part 1 and Part 2: the following dosing regimen will be evaluated in the first cycle (Cl) of elranatamab treatment:

- **C1D1:** Premedication + elranatainab 4 mg (hospitalization for at least 2 days, see Section 2.3.1)
- **C1D4:** Premedication + elranatainab 20 mg (hospitalization for at least 1 day, see Section 2.3.1)
- **C1D8:** Premedication + elranatainab 76 mg
- **C1D15 and C1D22:** elranatamab 76 mg QW

The first 2 doses of elranatamab on ClDl and C1D4 will serve as the step-up priming doses and will be administered on an inpatient basis to monitor paiticipants for CRS/ICANS. The dose of elranatamab should be increased to 20 and 76 mg on C1D4 and C1D8, respectively, as long as the paiticipant meets redosing criteria (Section 6.5.1).

All paiticipants emolled in Pait 1 and Pait 2 described below will contribute to the primaiy objective of the study, ie, assessing the rate of Grade ::::2 CRS dming Cl, asthe same dosing regimen is administered to all treatment groups dming the first cycle.

In addition, the study will evaluate the overall safety, tolerability, PK, phannacodynainics, and preliminaiy anti-myeloma activity of a regimen of elranatamab full dose of 76 mg QW for 6 cycles followed by Q2W or> 76 mg Q4W (Pait 1) and alternative regimens of elranatamab at dose levels >76 mg sta1ting from C2 with different dosing intervals (QW, Q2W, Q4W) (Pait 2).

The following dosing regimens will be assessed:

- **Part 1: Premedication, 2 step-up priming doses, and full dose 76 mg QW for 6 cycles followed by Q2W and/or RP2D (116 mg or 152 mg) Q4W as determined from Part 2A**

  Pait 1 aims to evaluate the overall safety, tolerability, PK, phannacodynamics, and preliminaiy anti-myeloma activity of the following regimen:

  C2 to C6: ehanatainab 76 mg QW

  C7 onwards: ehanatamab 76 mg Q2W (for participants with IMWG response of PR or better persisting for 2 months on QW)

  C7 onwards once the RP2D is identified in Part 2A: ehanatainab RP2D (116 mg or 152 mg) Q4W (for paiticipants with IMWG response of PR or better persisting for 2 months on QW or Q2W). An optional day of hospitalization may be considered for the first RP2D dosing (116 mg or 152 mg) Q4W depending on CRS profile observed in Pait 2A and Pait 2B.

  CCI [redacted]

- **Part 2: Premedication, 2 step-up priming doses, and full dose >76 mg** (ie, 116 and 152 mg) **at different dosing intervals**

  Pait 2 aims to evaluate the safety and efficacy of a regimen that includes premedication and a dosing regimen of 2 step-up primin_ do ses (Week 1) followed by full dose >76 mg with different dosing intervals starting from C2. CCI [redacted]

  Pait 2A dose detennination and Pait 2C tolerability evaluation will be based on a BLRM approach. The decision to strut emolling paiticipants in a new coho1t (Pait 2A Dose level 2, Pait 2B or Pait 2C) will be a joint decision to be detennined by the investigators and the sponsor in dose level review meetings.

Part 2A (Dose Detennination) will evaluate full ehanatamab doses >76 mg staiiing from C2 with a longer dosing interval (>1 week) to determine the potential RP2D to be finiher evaluated in Pa.ii 2B. Approximately 8 pai·ticipants will be enrolled at each dose level in Pa.ii 2A.

- **Dose level 1** will assess the following regimen:

  C2 to C6: elranatainab 116 mg Q2W. DLT observation period is C2 or 28 days staiiing from the first dose of 116 mg. Hospitalization on C2D1 or on the day of the first dose of 116 mg for at least 1 day is required, see Section 2.3.1. Ehanatamab 116 mg represents an ~ 50% increase in elranatamab dose versus 76mg.

  C7 onwards: ehanatamab 116 mg Q4W (for paiiicipants with IMWG response of PR or better persisting for 2 months on Q2W).

- If Dose level 1 is tolerable, **Dose level 2** will be initiated to assess the following regimen:

  C2 to C6: ehanatamab 152 mg Q2W. DLT observation period is C2 or 28 days staiiing from the first dose of 152 mg. Hospitalization on C2D1 or on the day of the first dose of 152 mg for at least 1 day is required, see Section 2.3.1. Ehanatamab 152 mg represents an ~ 30% increase in elranatamab dose versus 116 mg and will be the MAD in this study.

  C7 onwards: ehanatamab 152 mg Q4W (for pa1iicipants with IMWG response of PR or better persisting for 2 months on Q2W).

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The potential RP2D identified in Pa.ii 2A Dose level 1 or Dose level 2 will be fmiher evaluated and confnmed in Pali 2B.

Part 2B (Dose Expansion) will begin once the potential RP2D from Pa.ii 2A Dose level 1 or Dose level 2 is selected. Approximately 22 paiiicipants will be enrolled to confnm the safety and efficacy of the selected dosing regimen to have at least 15 paiiicipants treated for 2 cycles. Approximately a total of 30 pa1iicipants will be enrolled and treated at the potential RP2D, 8 from Pa1i 2A and 22 from Pa.ii 2B.

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fu Paiis 2B and 2C, hospitalization on C2Dl or on the day of the first dose of 116 mg or 152 mg may not be required depending on CRS profile observed in Pait 2A (See Section 2.3.1). This will be a joint decision to be detennined by the investigators and the sponsor before opening enrolhnent to Pait 2B and Pait 2C.

fu Pait 2 (A, B, and C), the ehanatamab dose may be escalated to 116 or 152 mg only in paiiicipants who have received at least 2 doses at 76 mg.

Pait 2 enrollment will staii after approximately 30 participants have been enrolled in Pa.ii 1. The decision to proceed with Pa.ii 2 of the study will be a joint agreement between the sponsor and the investigators based on the review of the available data, including CRS incidence and severity.

If neither Dose level 1 nor Dose level 2 in Pa.ii 2A proves to be tolerable, Pa1i 2C and Pa.ii 2B will not start and Pa.ii 1 will enroll approximately 68 participants for a total of 76 participants in the study.

At time of protocol amendment 4, Pait 1 and Pa.ii 2 (Pait 2A and Pa.ii 2B) were ongoing, and the enrollment is completed in all coho1is. Pait 2C will not be explored. The 152 mg Q2W dose was selected as the RP2D from Pa1i 2A, with a switch to 152 mg Q4W staiiing in C cle 7 for aiiici ants with an IMWG res onse of PR or better ersistin for 2 months).

CCI [redacted]

Number of Participants

Part 1 and Part 2:

Approximately 76 participants will be enrolled and treated across the study including: 30 participants in Pa.ii 1, 16 participants in Pa.ii 2A (n = 8 for each dose level), 22 pa1iicipants in Pa.ii 2B and 8 participants in Pa.ii 2C.

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

Study Population and Specific Inclusion/Exclusion Criteria

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Participants age ≥18 years (or the minimum country specific age of consent if >18).

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

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

3. Prior diagnosis of MM as defined according to IMWG criteria.[1]

4. Measurable disease based on IMWG criteria as defined by at least 1 of the following:

   a. Serum M-protein ≥0.5 g/dL by SPEP;

   b. Urinary M-protein excretion >200 mg/24 hours by UPEP;

   c. Serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

5. Refractory to at least 1 IMiD.

6. Refractory to at least 1 PI.

7. Refractory to at least 1 anti-CD38 antibody.

8. Relapsed or refractory to last anti-MM regimen.

   Note: Refractory is defined as having disease progression while on therapy or within 60 days of last dose in any line, or no response to therapy

9. ECOG performance status ≤1.

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

11. Adequate hepatic function characterized by the following:

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

    b. AST ≤2.5 x ULN; and

    c. ALT ≤2.5 x ULN

12. Adequate renal function defined according to local institutional standard method: eGFR ≥ 30 mL/min/1.73 m2 using CKD-EPI 2021 equation[2] or estimated creatinine clearance ≥ 30 mL/min using Cockcroft Gault formula. If both formulae are calculated, the higher of the 2 values may be used. A 24-hour urine collection for creatinine clearance may also be used in equivocal cases where amyloidosis is suspected.

13. Adequate BM function characterized by the following:

    a. ANC ≥1.0 × 10^9/L (use of G-CSF is permitted if completed at least 7 days prior to planned start of dosing);

    b. Platelets ≥25 × 10^9/L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and

    c. Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 14 days prior to planned start of dosing).

14. Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L).

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

16. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion Criteria

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

1. Smoldering MM

2. Active plasma cell leukemia

3. POEMS syndrome

4. Amyloidosis

5. Waldenström's macroglobulinemia

6. Known active CNS involvement or clinical signs of myelomatous meningeal involvement

7. Stem cell transplant within 12 weeks prior to enrollment or active GVHD

8. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:

   a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);

   b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);

   c. Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);

   d. Prolonged QT syndrome (or QTcF >470 msec at screening)

9. Ongoing Grade ≥ 2 peripheral sensory or motor neuropathy

10. History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy

11. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy

12. Active HBV, HCV, COVID-19/SARS-CoV-2, HIV or AIDS-related illness, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.

    COVID-19/SARS-CoV-2: While SARS-CoV-2 testing is not mandated for entry into this study, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV-2 infection within 14 days prior to enrollment, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, the participant is excluded.

    HBV:

    - This criterion excludes participants with a positive HBsAg (ie, either acute or chronic active hepatitis).

    - However, participants with HBV antibody positivity indicating immunity, either due to vaccination or prior natural infection, are eligible.

- Paiiicipants with positive anti-HBcAb but negative HBsAg and negative anti-HBsAb profile ai·e eligible if HBV DNA is not detected.

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

14. Any other active malignancy within 3 yeai·s prior to enrolhnent, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ or Stage 0/1 malignancy with minimal risk of recmrence per investigator

15. Other surgical (including major surge1y within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laborato1y abno1mality that may increase the risk of study paiiicipation or, in the investigator's judgment, make the pa1iicipant inappropriate for the study

16. Previous treatment with anti-BCMA bispecific antibody or CAR-T cell therapy

17. Live attenuated vaccine within 4 weeks of the first dose of study inte1vention.

18. Previous administration with an investigational dmg or vaccine within 30 days (or as dete1mined by the local requirement) or 5 half-lives preceding the first dose of study inte1vention used in this study (whichever is longer).

19. A paiiicipant may be eligible even if they are in the follow-up phase of an investigational study as long as they meet the criteria for time elapsed from previous administration of investigational product. Cases must be discussed with sponsor's medical monitor to judge eligibility.

20. fuvestigator site staff directly involved in the conduct of the study and their family members, site staff othe1wise supe1vised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their fainily members

Intervention Groups and Duration

Arm title	Description
Pait 1	Participants will receive eh-anatamab 4 mg on ClDl and 20 mg on ClD4 (2 priming doses) and then 76 mg QW for 6 cycles. Thereafter, pa1ticipants with PR or better response persisting for c:::2 months on QW will receive 76 mg Q2W and/or 116 mg or 152 mg Q4W from C7 and onwards. CCI [redacted]

Pa1t2A	Participants will receive eh-anatamab 4 mg on ClDl and 20 mg on ClD4 (2 priming doses) and then 76 mg QW for 1 cycle. Thereafter, paiticipant.s will receive: - **Dose level 1:** I16 mg Q2W for C2 to C6 and 116 mg Q4W from C7 and onwards (paiticipants with PR or better response persisting for:?:2 months on Q2W). - **Dose level 2:** 152 mg Q2W for C2 to C6 and 152 mg Q4W from C7 and onwards (participants with PR or better response persisting for ≥ 2 months on Q2W). CCI [redacted]
Pa1t2B	Pa1ticipants will receive eh-anatamab 4 mg on ClDI and 20 mg on CID4 (2 priming doses) and then 76 mg QW for I cycle. Thereafter, paiticipants will receive 116 or 152 mg Q2W for C2 to 6and116 mg or 152 mg Q4W from C7 and onwards artici ants with PR or better res onse persisting for:?:2 months on 2 W). CCI [redacted]
[redacted]	[redacted]

Each pa1ticipant should receive study intervention until confmned disease progression, unacceptable toxicity, withdrawal of consent, or study tennination.

The study will be completed when all paiticipants have been followed for OS for at least 2 years from the date of enrollment.

Data Monitoring Committee or Other Independent Oversight Committee: No.

Statistical Methods

A Bayesian dual-criterion design[3] will be used to estimate the primaiy endpoint of the tme Grade 2 CRS rate during Cycle 1 in Pait 1 and Pait 2.. With this design, the following criteria ai·e defined:

Part 1 and Part 2

- Bayesian statistical significance: Substantial evidence that the hue Grade 2 CRS rate exceeds a pre-specified value. For this study, Bayesian statistical significance will be achieved if the posterior probability of the hue Grade 2 CRS rate exceeding 35% is <10%;

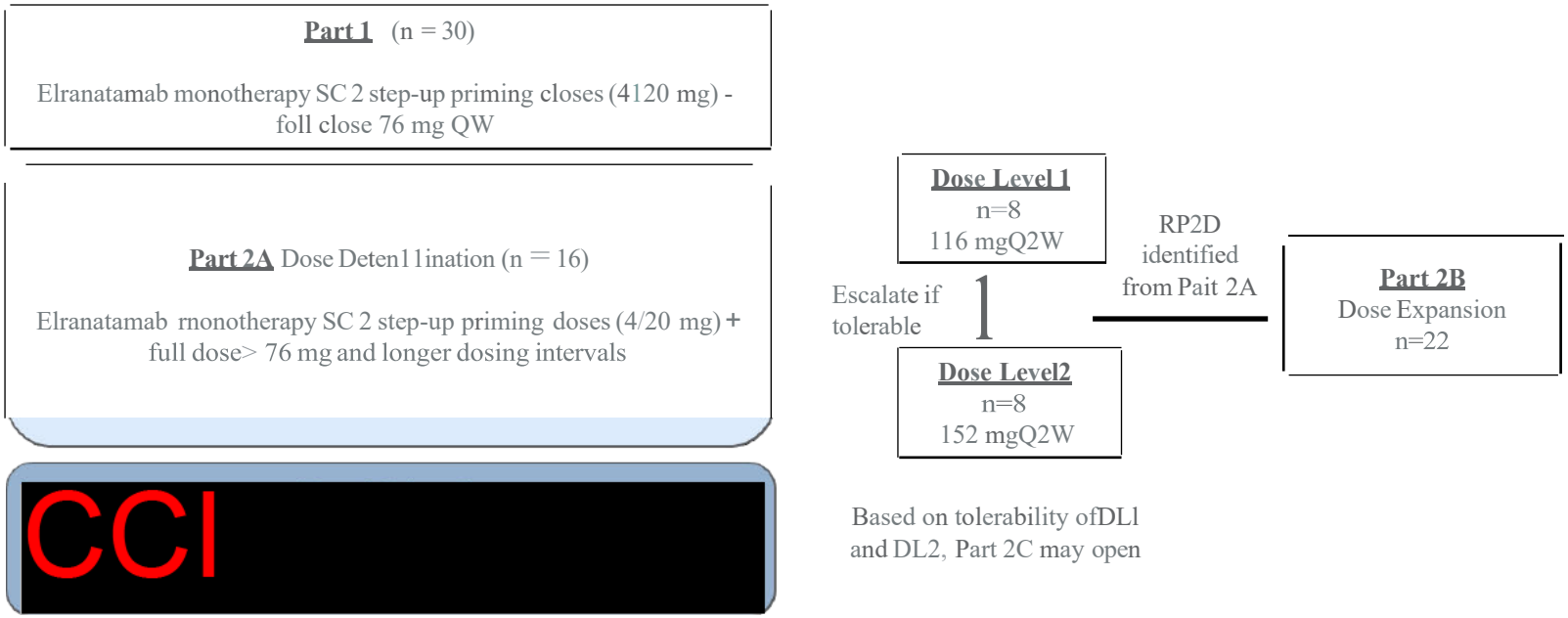
- Clinical relevance: The maximum number Grade ≥2 CRS events threshold that could justify further clinical development. For this study, it is defined as the median of the posterior distribution of the true Grade ≥2 CRS rate is ≤ 27%.

The analysis will use a Beta-binomial model (binomial sampling for number of Grade ≥2 CRS events and a beta prior distribution). A minimally informative beta prior distribution of the true Grade ≥2 CRS rate will be used. It is assumed a priori that the true mean Grade ≥2 CRS rate is 35%, so the prior distribution will be Beta (0.7, 1.3). Using this prior and based on the dual criteria defined above, approximately 76 participants will be enrolled and treated in Part 1 and Part 2 and a maximum of 20 participants with Grade ≥2 CRS events is allowed to meet the dual criteria in 76 participants. If exactly 20 participants in 76 participants experience Grade ≥2 CRS events, the observed Grade ≥2 CRS rate is 26.3% with median 26.3% and 90% credible interval of (18.7%, 35.0%) based on the posterior distribution.

The primary analysis will be conducted once all participants have completed C1 of study intervention or have otherwise discontinued the study intervention.

An interim analysis for non-binding futility will be conducted on the 30 participants enrolled and treated in Part 1 of the study.

1.2. Schema



QW:Once weekly
Q2W: Once every 2 weeks
SC: Subcutaneous
RP2D: Recommended Phase 2 Dose

All participants will be followed for OS for **at least 2 years** from the date of enrollment

Note: Premedications are administered on ClDl, ClD4, and ClD8 (refer to Section 6.8.1). The decision to proceed with Prut 2 of the study will be a joint agreement between the sponsor and the investigators based on the review of the available data, including CRS incidence and severity. If neither Dose level **1** or Dose level 2 in Pait 2A proves to be tolerable, Part 2B and Pait 2C will not stait and Part 1 will enroll approximately 68 pruticipants. In total, this study will enroll approximately 76 paiticipants.

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed info1mation on each assessment required for compliance with the protocol.

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

1.3.1. Part 1 Schedule of Assessments

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**	-	-1/+3 D	-1/+3 D	±3D	±3D	±3D	±3D	**14 Dpost-final dose**	**28 to 35 days post-final dose**	±14D	
Info1med consent	X											See Section 10.1.3.
Eligibility criteria	X											See Section 5.1 and Section 5.2.
Register with IRT	X											See Section 6.3.1.
Elll'ollment in IRT		X										See Section 6.3.1
Demography/ medical history	X											See Section 8.2.1.
Disease characteristics/ treatment history	X											See Section 8.2.1.
Clinical Procedures/Assessments - *Note:* Dmin2 the ti·eatment pe1iod, all assessments must be done within 72 hom·s p1ior to dosin2, except fo1·disease assessments which are to be done every 28 days from ClDl												
Physical exam	X	X	X				X	X•	X	X		

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycles 2-6 Dayl	Cycle 7 Onwards Dayl			Q12W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3D	±3D	±3D	±3D	14 Dpost-final dose	28 to 35 days post-final dose	±14D	
Neurologic exam	X	X	X	X	X	X	X	X•	X	X		Starting C2D1, neurological exam to be performed weekly (on D1, D8, D15 and D22) for cycles 2-3, then eve1y other week (on D1 and D15) for cycles 4-6, then every 28 days (on D1) from cycle 7 onwards. CCI
I E score		X										See Section 8.2.2.
CCI												
Height/weight	X											See Section 8.2.2.

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day 4	Day 8	Day 15	Day 22	Cycles 2-6 Dayl	Cycle 7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**±14D**	
Vital signs (temperature, HR, BP, and02 saturation)	X	X	X	X	X	X	X	X•	X	X		Pre-dose vital signs collected on ClDl, C1D4, C1D8, C1D15, and C1D22 should be repo,ted in the CRF. Vital signs monitored at least eveiy 4 hours (±30 minutes) during the first 48 hrs aftei·first (ClDl) and during 24 hrs after second dose of study intervention (C1D4) should be repoited in the CRF. If performed, abnormal vital signs associated with AEs (eg CRS or an infection) should be reported in the CRF
												CCI [redacted]
ECOGPS	X											See Section 8.2.8
CMVtesting (quantitative PCR)	X	X(See Notes)										Local laboratory. To be done prior to administration of study intervention (at screening or prior to first dose) and then either monthly or eve,y 1 to 3 cycles depending on risk factors and baseline CMV viral load as clinically indicated. See Section 6.8.7 and Appendix 15.

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day 4	Day 8	Day 15	Day 22	Cycles 2-6 Day 1	Cycle 7 Onwards Day 1			Q12W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**± 14D**	
												For participants already enrnlled and treated under Pait 1, a CMV testing should be pe,fonued as a baseline reference for CMV status at the next scheduled dosing visit and repeated either monthly or every 1 to 3 cycles depending on risk factors and baseline CMV viral load as clinically indicated.
SARS-CoV-2 test							X					Starting with protocol amendment 4, PCR or antigen test required predose on Day 1 (CXDl), upon suspected exposure to SARS-CoV-2 and at signs or symptoms of COVID-19 infection (see Appendix 2 and Appendix 15). For participants with SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms or positive test result. [redacted]

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day 4	Day 8	Day 15	Day 22	Cycles 2-6 Dayl	Cycle 7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**		-1/+3 **D**	-1/+3 **D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**± 14D**	
Triplicate 12-LeadECG	X (Singlet)	X					X (Cycle2 and4)		X			Single assessment at screening. Triplicate at all other time points. Predose ECG for all specified visits. Perform ECG prior to elrnnatamab administration (and premedication) and PK sample collection (if scheduled). ECG assessments should be skipped if CRS symptoms are ongoing. Additional ECGs should be performed as clinically indicated. See Section 8.2.4.
EC												See Section . . .
Premedication for CRS		**X**	**X**	**X**								Must be administered approximately 60 minutes (±15 min) prior to elranatamab dose. See Section 6.8.1.
Ekanatamab administration		**X**	**X**	**X**	X	X	X (QW)	X (Q2W or [redacted]				If participant has received QW dosing for at least 6 cycles and has achieved a PR or better persisting for:C::2 months the dose interval will be changed from QW to Q2W or Q4W when the RP2D is identified in Pait 2A [redacted]

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**	-	-1/+3 D	-1/+3 D	±3D	±3D	±3D	±3D	**14 Dpost-final dose**	**28 to 35 days post-final dose**	±14D	
Participant hospitalization		X	X					(X)				!Hospitalization requit·ed for at least 12 days on ClDl and 1 day overnight) for C1D4. !Hospitalization from ClDl to IDS may be considered. Optional 1t1ospitalization may be considered hen escalating to the RP2D (116 mg or 152 mg) Q4W depending on k:RS profile observed in Pait 2A and Pait 2B. See Section 2.3.1. and 4.1
AE monitoring	Assess Continuously											See Section 8.3
Concomitant therapy	Assess Continuously											See Section 6.8.
Subsequent anticancer therapies/date of progression									Assess continuously			See Section 7.1.
Survival status										X	X	Collected by telephone eve1y 12 weeks until death, or at least 2 years from the date of enrollment, whichever comes first.

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**	**-**	**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**±14D**	
Disease response assessment (per IMWG criteria)							X	X	X	X*	X*	To be conducted on a 28-day (±1 wk) interval whether dose given or not (ie, the 28-day interval (±1 wk) from ClDl should be maintained regardless of dose delays/intem1ptions). See Section 8.1. *For pa1ticipants who discontinue study intervention without PD: perform at EOT visit, then at least Q4W (±1 wk) until PD, withdrawal of consent, participant lost to follow-up, death or defined end of study. For additional details on IMWG response criteria, see Appendix 10.

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**	**-**	**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**±14D**	
SPEP, SIPE, serum FLC	X	X					X	X	X	X*	X*	Screening and CIDI (if not done within 72 hours prior to dosing). To be conducted on a 28-day (±I wk) interval whether dose given or not (ie, the 28-day interval (±I wk) from CIDI should be maintained regardless of dose delays/intem1ptions). *For pa1ticipants who discontinue study intervention without PD: perform at EOT visit, then at least Q4W (±I wk) until PD, withdrawal of consent, participant lost to follow-up, death or defined end of study. Except for sCR, semm FLC analysis is required when both serum and urine M-component levels are deemed non measm·able or uninterpretable (including at suspected CR). See Section 8.1.1.

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**	**-**	**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**±14D**	
UPEP, UIFE (24-hour urine collection required)	X	X					X	X	X	X*	X*	Screening and CIDI (if not done within 72 hours prior to dosing). To be conducted on a 28-day (±I wk) interval whether dose given or not (ie, the 28-day interval (±I wk) from CIDI should be maintained regardless of dose delays/intem1ptions). See Section 8.1. *For participants who discontinue study intervention without PD: perform at EOT visit, then at least Q4W (±I wk) until PD, withdrawal of consent, participant lost to follow-up, death or defined end of study. If an evaluable 24-hour urine collection is missed, another attempt for collection should be scheduled within 7 days of the missed assessment. See Section 8.1.1.

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**	**-**	-1/+3 **D**	-1/+3 **D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**±14D**	
Senuu quantitative immunoglobulins (IgG, IgM, IgA, IgD, IgE)	X	X					X	X	X	X*	X*	Screening and CIDI (if not done within 72 hours prior to dosing). For all participants, to be collected on a 28-day (±I wk) interval whether dose given or not (ie, the 28-day interval [±I wk] from CIDI should be maintained regardless of dose delays/intem1ptions). IgD or IgE only required if the heavy chain component of the disease is known to be D or E. See Section 8.1.1. *For pa1ticipants who discontinue study intervention without PD: perform at EOT, then at least Q4W (±I wk) until PD, withdrawal of consent, participant lost to follow-up, death, or defined end of study. For additional details, see Appendix I0

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**	**-**	**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**±14D**	
Imaging (PET/CT, CT or MRI)	**X**	Time points for disease assessments described in notes										At screening, as clinically indicated if EMD is suspected, and annually. For participants with measurable EMD (paramedulla1y disease or plasmacytomas associated with bone are not considered EMD) at screening, every 12 wks (±1 wk) and at suspected CR/sCR. Paiticipants with non-meastu·able EMD must be assessed at suspected CR/sCR. Once all EMD has resolved/disappeared, imaging can be conducted annually (or eai·lier if clinically indicated) and at suspected PD. For pa1ticipants w'ith only skin involvement, skin lesions should be measured with a mler eve1y 4 wks (+ 1 wk). Pe1fo1m until PD, withdrawal of consent, patticipant lost to follow-up, death, or defined end of study. See Section 8.1.3.

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycles 2-6 Day 1	Cycle 7 Onwards Day 1			Q12W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3D	±3D	±3D	±3D	14 Dpost-final dose	28 to 35 days post-final dose	± 14D	
[redacted]	I				[redacted]							[redacted]
[redacted]	I											[redacted]
[redacted]	I				[redacted]							[redacted]

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day4	Day8	Day15	Day22	Cycles 2-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	**Day-28 to Day-1**		-1/+3 **D**	-1/+3 **D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**±14D**	
Contraception check	X	X					X	X	X	X		Only required in WOCBP . Through *5* months post last dose of study intervention. See Section 5.3.1.
Pregnancy test	X	X					X	X	X	X		Only required in WOCBP. Also to be done whenever I menstmal cycle is missed dming the active treatment period (or when potential pregnancy is otheiwise suspected). Senun required at screening. See Section 8.2.7.
Hematology/chemistry	X	X	X	X	X	X	X	X	X	X		See Section 10.2. For CI D4, hematology only.
PT/INR	X											See Section 10.2.
Hepatitis B and C testing	X											Hepatitis B and C testing results will not be collected in the eCRF. See Section 10.2.
CCI												

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycles 2-6 Day 1	Cycle 7 Onwards Day 1			Q12W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3D	±3D	±3D	±3D	14 Dpost-final dose	28 to 35 days post-final dose	±14D	
CCI												

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycles 2-6 Dayl	Cycle 7 Onwards Dayl			Q12W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3D	±3D	±3D	±3D	14 Dpost-final dose	28 to 35 days post-final dose	± 14D	
CCI	I	I			I		+					
		I	I	I	I	I						
		I										
		I										
		I										

Table 1. Schedule of Assessments: Part 1

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day Cycle)		EOTVisit	FU Visit	LTFU	Notes/Protocol Section
		Dayl	Day 4	**Day 8**	**Day 15**	**Day** 22	Cycles 2-6 Day 1	Cycle 7 Onwards Day 1			Q12W	
Visit Window	Day-28 to Day-1		-1/+3 **D**	-1/+3 **D**	**±3D**	**±3D**	**±3D**	**±3D**	**14 Dpost-final dose**	**28 to 35 days post-final dose**	**± 14D**	
Phannacokinetics and Immunogenicity Assessments												
Blood sample for PK		X	X	X			**X** (C2, 4, 6)	**X•** (ClO, 16, etc.)	**X**			Predose, 24, and 48 hrs postdose on ClDl. Predose and 24 hon C1D4. Collect predose on C1D8, and Day **1** of C2, 4, 6, then at D1 of eveiy sixth cycle starting from ClO(ie, ClODl, C16D1, etc.). If CRS is suspected, additional PK samples should be collected if not ah-eady scheduled. [redacted]
Blood sample for ADAs and Nabs		**X**					**X** (C2, 4, 6)	**X** (ClO, 16, etc.)	**X**			Predose on ClDl, C2D1, C4D1, C6D1, and eve,y sixth cycle sta,ting ClO(ie, ClODl, C16D1, etc). If AE possibly related to ADA occurs, additional samples for ADA and PK should be collected if not scheduled. See Section 8.7.

1.3.2. Part 2 Schedule of Assessments

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day4	Day8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
Info1med consent	X												See Section 10.1.3.
Eligibility criteria	X												See Section 5.1 and Section 5.2.
Register with IRT	X												See Section 6.3.1.
Enrollment in IRT		**X**											See Section 6.3.1.
Demography/ medical history	X												See Section 8.2.1.
Disease characteristics/ treatment history	X												See Section 8.2.1.
Clinical Procedures/Assessments - *Note:* Dmin2 theh·eatment pe1iod, all assessments must be done within 72 hom·s p1ior to dosin2, except for disease assessments which are to be done eve1-y28 days from ClDl													
Physical exam	X	**X**	X				**X**	X	X*	X	**X**		
Neurologic exam	X	X	X	**X**	X	X	**X**	X	X*	X	X		Starting C2Dl up to end ofC6, neurological exam to be perfonued biweekly (on D1, D15), then eve1y 28 days
I E score													.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3 D	±3 D	± 3 D	±3D	±3D	14D post-fmal dose	28 to35 days post-final dose	±14D	
[redacted]	I	I			I		I	I	I	I	I		CCI [redacted]
[redacted]	I	I			I		I	I	I	I	I		[redacted]
Height/weight													See Section 8.2.2.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	-1/+3 **D**	±3 **D**	±3 **D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	± **14D**	
Vital signs (temperature, HR, BP and 02 saturation)	X	X	X	X	X	X	**X**	X	X*	X	**X**		Pre-dose vital signs collected on ClDl, C1D4, ClDS, ClD15, and C1D22 and C2Dl should be repo1ted in the CRF. Vital signs Monitored at least eveiy 4 hrs (± 30 min) during the first 48 hrs after first dose (ClDl), dtuing 24 hrs after second dose of study intervention (C1D4), and dming 24 hrs after study intervention administration on C2Dl should be repo1ted in the CRF (the latter may not be required for Pait 2B and Part 2C depending on whether CRS is observed after C2D1 dose in Pa1t2A). If pe1fo1med, abnonual vital signs associated with AEs (eg, CRS or an infection should be r . 01ted in the CRF. [redacted] CCI
ECOGPS	X												See Section 8.2.8.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	±3 **D**	±3 **D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	± **14D**	
CMVtesting (quantitative PCR)	X	X(See Notes)											Local laborato,y. To be done prior to administration of first study intervention (at screening or prior to first dose) and then either monthly or eveiy I to 3 cycles depending on risk factors and baseline CMV viral load as clinically indicated. See Section 6.8.7 and Appendix 15. For pa,ticipants akeady enrolled and treated under Part 2, a CMV testing should be pe1fo1med as a baseline reference for CMV status at the next scheduled visit and repeated eveiy I to 3 cycles depC11ding on risk factors and baseline CMV viral load
SARS-CoV-2 test							**X**	X	X*				Starting with protocol amendmC11t 4, PCR or antigen test required predose on Day I (CXDI), upon suspected exposure to SARS-CoV-2 and at signs or symptoms of COVID-19 infection (see AppC11dix 2 and Appendix 15). For pa,ticipants with SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms or positive test result. CCI [redacted]

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day4	Day8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
Triplicate 12-LeadECG	X (Singlet)	**X**					**X** (Predose and 24 hr postdose)	**X** (C4 and C6)		**X**			Single assessment at screening. Triplicate at all other time points. Predose ECG for all specified visits. Perform ECG prior to elranatamab administration (and premedication) and PK sample collection (if scheduled). Additional 24 hr postdose time point at C2D1 should be collected. ECG assessments should be skipped if CRS symptoms are ongoing. Additional ECGs should be pe1fo1med as clinically indicated. See Section 8.2.4.
ECHO/MUGA	**X**												See Section 8.2.5.
Premedication for CRS		**X**	**X**	**X**									Must be administered approximately 60 min (±15 min) prior to elranatamab dose. See Section 6.8.1.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	-1/+3 **D**	±3 **D**	±3 **D**	± **3 D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
Eh-anatamab administration		**X**	X	**X**	X	X	**X** (Q2W)	X (Q2W)	X iif				CCI [redacted] The switch to Q4W dosing interval at C7 or later will occur for participants who have achieved a response category of PR or better persisting for ≥ 2 months. CCI [redacted]
Participant hospitalization		**X**	X				**X**						Hospitalization requit·ed for at least 2 days on ClDl and 1 day (ovemight) on C1D4. Hospitalization from ClDI to ClDS may be considered. Hospitalization required for at least I day on C2D1 for Patt 2A. Hospitalization on C2D1 may not be required for Part 2B and Pait 2C dependmg on CRS profile observedm Patt 2A. See Section 2.3.1and 4.1.
DLT evaluation (Part 2A and 2C only)							X						See Section 4.3.3.
AE o 'to. g	sess Co t' uously												See Sect'o 8..
Concomitant therapy	Assess Contmuously												See Section 6.8.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day4	Day8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
Subsequent anticancer therapies/date of progression										Assess continuously			See Section 7.1.
Survival status											**X**	**X**	Collected by telephone eve,y 12 weeks until death, or at least 2 years from the date of enrolhnent, whichever comes first. See Section 7.I.
Disease response assessment (per IMWG criteria)							**X**	X	X	X	X*	X*	To be conducted on a 28-day (±I wk) interval whether dose given or not (ie, the 28-day interval (±I wk) from CIDI should be maintained regardless of dose delays/intem1ptions). See Section 8.1. *For pa,ticipants who discontinue study intervention without PD: pe1fo1m at EOT visit, then at least Q4W (±I wk) until PD, withdrawal of consent, pa,ticipant is lost to follow-up, death, or defined end of study. See Appendix I0.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day4	Day8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
SPEP, SIFE, serum FLC	X	**X**					**X**	X	**X**	X	X*	X*	Screening and CIDI (if not done within 72 hours prior to dosing). To be conducted on a 28-day (±I wk) interval whether dose given or not (ie, the 28-day interval (±I wk) from CIDI should be maintained regardless of dose delays/intem1ptions). *For pa1ticipants who discontinue study intervention without PD: pe1fo1m at EOT visit, then at least Q4W (±I wk) until PD, withdrawal of consent, pa1ticipant lost to follow-up, death. or defined end of study. Except for sCR, semm FLC analysis is required when both semm and tu-ine M-component levels are deemed non measm·able or uninte1pretable(including at suspected CR). See Section 8.1.1.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day4	Day8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
UPEP, UIFE (24-hotu·urine collection required)	X	**X**					**X**	X	**X**	X	X*	X*	Screening and CIDI (if not done within 72 hours prior to dosing). To be conducted on a 28-day (±I wk) interval whether dose given or not (ie, the 28-day interval (±I wk) from CIDI should be maintained regardless of dose delays/intem1ptions). "'For pa1ticipants who discontinue study intervention without PD: pe1fo1m at EOT visit, then at least Q4W (±I wk) until PD, withdrawal of consent, pa1ticipant lost to follow-up, death, or defined end of study. If an evaluable 24-hotu·urine collection is missed, another attempt for collection should be scheduled within 7 days of the missed assessment. See Section 8.1.1.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day4	Day8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
Senuu quantitative immunoglobulins (IgG, IgM, IgA, IgD, IgE)	X	**X**					**X**	X	**X**	X	X*	X*	For all participants, to be collected on a 28-day (±1 wk) interval whether dose given or not (ie, the 28-day interval [±I wk] from CIDI should be maintained regardless of dose delays/intem1ptions) . IgD or IgE only required if the heavy chain component of the disease is known to be DorE. See Section 8.1.1 '"For pa1ticipants who discontinue study intervention without PD: pe1fo1m at EOT, then at least Q4W (±I wk) until PD, withdrawal of consent, pa1ticipant lost to follow-up, death, or defmed end of study. See Appendix 10.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day4	Day8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	**-1/+3 D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
Imaging (PET/CT, CT or MRI)	X	Time points for disease assessments described in notes											At screening, as clinically indicated if EMD is suspected and annually. For pa1ticipants with measurable EMD (paramedullarydisease or plasmacytomas associated with bone are not considered EMD) at screening, every 12 wks (± 1 wk) and at suspected CR/sCR. Pa1ticipants w-ith non-measurable EMD must be assessed at suspected CR/sCR. Once all EMD has resolved/disappeared, intaging can be conducted annually (or earlier if clinically indicated) and at suspected PD. For participants with only skin involvement, skin lesions should be measured with a mler every 4 wks (+ 1 wk). Pe1form until PD, withdrawal of consent, participant lost to follow-up, death, or defined end of study. See Section 8.1.3.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	-1/+3 **D**	±3 **D**	±3 **D**	± **3 D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
[redacted]	I												
[redacted]	I												
[redacted]	I												
Contraception check	X	X					X	X	X	X	X		Only requit·ed in WOCBP. Through 5 months post last dose of study intervention. See Section 5.3.1.

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	-1/+3 **D**	±3 **D**	±3 **D**	± **3 D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
Pregnancy test	X	X					X	X	**X**	X	X		Only requit·ed in WOCBP. Also to be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Serum requit·ed at screening. See Section 8.2.7.
Hematology/ chemistiy	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		See Section 10.2. For Cl D4, hematology only.
PT/INR	**X**												See Section 10.2.
Hepatitis B and C testing	**X**												Hepatitis B and C testing results will not be collected in the eCRF. See Section 10.2.
CCI													

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			QI2W	
Visit Window	**Day-28 to Day-1**		**-1/+3 D**	-1/+3 **D**	**±3D**	**±3D**	**±3D**	**±3D**	**±3D**	**14D post-fmal dose**	**28 to35 days post-final dose**	**±14D**	
CCI	I	I	I	I			I	+		I			
		I	I	I	I	I		I	I	I			

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Q12W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3D	±3D	±3D	±3D	±3D	14D post-final dose	28to35 days post-final dose	±14D	
CCI	I						I	I	I	I			
	I	I			I		I	IIII					
		I	I	I	I	I							

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3 D	±3 D	± 3 D	±3D	±3D	14D post-fmal dose	28 to35 days post-final dose	±14D	
CCI		I											
		I											
		I											

Table 2. Study Schedule of Assessments: Part 2

Visit Identifier	Screening	Treatment Period Cycle 1					Treatment Period (each 28 Day cycle)			EOT Visit	FU Visit	LTFU	Notes/Protocol Section
		Day 1	Day 4	Day 8	Day 15	Day 22	Cycle2 Dayl	Cycles 3-6 Dayl	Cycle7 Onwards Dayl			Ql2W	
Visit Window	Day-28 to Day-1		-1/+3 D	-1/+3 D	±3 D	±3 D	±3D	±3D	±3D	**14D** post-**fmal dose**	**28 to35 days post-final dose**	± **14D**	
Phannacokinetics and Immunogenicity Assessments													
Blood sample for PK		X	X	X			**X**	X (C4 and C6)	X* (C8, 10, 13, etc.)	X			Predose, 24 and 48 hrs postdose on C1DI. Predose and 24 hon C1D4 and C2Dl. If no hospitalization required on C2Dl for Part 2B and Pait 2C, the 24 h postdose w-ill not be required. Collect predose on C1D8 and on DI ofC2, 4, 6, 8, then at Day 1 of eve1y third cycle starting ClO (ie, ClODl, Cl3Dl, etc). In the event of suspected CRS, unexpected or serious AE, or AE leading to discontinuation of study intervention, additional PK samples should be collected if not already scheduled. CCI [redacted]
Blood sample for ADAs and NAbs		**X**					**X**	X (C4 and C6)	ClO, 16, etc	X			Predose on ClDl, C2Dl, C4Dl, C6Dl and every sixth cycle sta1ting ClO(ie, ClODl, C16Dl, etc). If AE possibly related to ADA occurs, additional samples for ADA and **PK** should be collected if not scheduled. See Section 8.7.

2. INTRODUCTION

Elranatamab (PF-06863135), a heterodimeric humanized full-length bispecific IgG2 kappa antibody that targets both BCMA on MM cells and CD3 on T-cells (BCMA x CD3 bispecific antibody), is currently being developed for the treatment of participants with MM.

2.1. Study Rationale

The purpose of the study Part 1 and Part 2 is to evaluate the rate of Grade ≥ 2 CRS using a priming regimen that involves a premedication cocktail and 2 step-up priming doses to be administered within the first week of elranatamab treatment. The study will also evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary anti-myeloma activity of elranatamab full doses 76 mg and > 76 mg with different dosing intervals..

2.2. Background

2.2.1. Multiple Myeloma

MM is a hematological B-cell malignancy characterized by dysregulated proliferation of BM plasma cells. Globally, there are approximately 176,000 new cases and 117,000 deaths per year attributed to MM.[4] The American Cancer Society estimates that for the US in 2021, approximately 34,920 new MM cases will be diagnosed and approximately 12,410 MM-related deaths will occur.[5]

Despite recent advances in treatment, MM remains an incurable disease and almost all patients, even those who initially respond to treatment, are expected to relapse. Even for patients who receive ASCT, the median time to relapse is only 17.2 months.[6] Similarly, for patients who are treated with novel PI-based or IMiD-based combination regimens as frontline treatment, the median time to relapse is 16.4 months.[7]

Moreover, MM patients typically cycle through many lines of treatment, having become relapsed/refractory to various therapeutic approaches. Trials that have treated patients with BCMA-directed therapy in the RRMM population have included heavily pretreated patients; for example, 57% of patients studied by Trudel et al had received ≥5 lines of therapy[8] and other trials have included populations receiving a median of 6 (range 3-18) prior therapies[9] and a median of 5 (range 3 to 18) prior therapies.[10]

Outcomes in the RRMM population are quite poor; for example, patients with RRMM who respond poorly to PI-based or IMiD-based regimens show a median OS of 13 months (95% CI: 11, 15).[11] Newer and more effective therapies have substantially increased patient benefit; however, in this real-world setting (N=3449), the most recent 4-year survival is only 75%.[12] Results from 2 trials in patient populations similar to the current protocol are summarized in Table 3. The lack of effective and durable therapeutic options highlights the unmet medical need in the RRMM patient population.

Table 3. Efficacy Results for Available Therapies for Patients With Relapsed/ Refractory Multiple Myeloma Who Have Received at Least 2 Prior Therapies

Available Therapy	Prior Therapy for Eligibility	Median Number of Prior Therapies	ORR % (n/N)	mDOR (months)	Reference
Selinexor + dexamethasone	IMiD, PI, anti-CD38 mAb	8	25.3% (21/83)	3.8	XPOVIO® USPI
Belantamab mafodotin (belamaf)[a]	IMiD, PI, anti-CD38 mAb	7	32% (31/97)	11.0 months (95% CI, 4.2 months to not reached),	BLENREP USPI
Idecabtagene vicleucel[b]	IMiD, PI, anti-CD38 mAb	6 (3-6)	72% (72/100)[b]	11.0	ABECMA® USPI
Melphalan flufenamide + dexamethasone[c]	IMiD, PI, anti-CD38 mAb	6	23.7% (23/97)	4.2	PEPAXTO® USPI
Carfilzomib	IMiD, PI	5	23% (61/266)	7.8	KYPROLIS® USPI
Kd (carfilzomib + dexamethasone)	IMiD, PI	1-3	76.9% (357/464)	21.3	KYPROLIS® USPI (ENDEAVOR study)
Daratumumab	IMiD, PI	5	29.2% (31/106)	7.4	DARZALEX® USPI
Pomalidomide + dexamethasone	IMiD, PI	5	29.2% (33/113)	7.4	POMALYST® USPI
Ciltacabtagene autoleucel	IMiD, PI, anti-CD38 mAb	6	97.9% (95/97)	21.8 (21.8, NE)	CARVYKTI USPI

a. Blenrep® was withdrawn from the US market on 22 Nov 2022, based on the outcome of the DREAMM-3 phase III confirmatory trial[13].
b. ORR for the evaluable population; ORR for the mITT (N=135) was 64%.
c. Pepaxto® was withdrawn from the US market on 22 October 2021 due to an overall survival data (ie, lack of efficacy) in the ITT population of the Phase 3 OCEAN study [14].
[15-22]

2.2.2. BCMA and CD3

BCMA is a transmembrane glycoprotein belonging to the TNFr SF 17 superfamily. BCMA is normally expressed exclusively in lymphocytes of the B-cell lineage, including plasmablasts and differentiated plasma cells, where it is involved in the regulation of B-cell maturation. BCMA is widely expressed on malignant plasma cells collected from patients with MM whereas BCMA is detected in a very small proportion of normal BM mononuclear cells from healthy volunteers.[23] Cleavage of cell surface BCMA by γ-secretase releases sBCMA[24] which can act as a decoy for BCMA-directed antibodies. Inhibition of γ-secretase can reduce levels of sBCMA and increase activity of BCMA-directed therapies.[25] sBCMA levels in

serum are elevated in patients with MM and correlate with the proportion of MM cells in the BM microenvironment. sBCMA levels are independent of renal function, which permits its use as a biomarker in patients with renal insufficiency, and BCMA is detectable in the serum of patients with non-secretory disease.[26] Moreover, patients in 2 studies with high baseline levels of sBCMA appeared to have poorer clinical outcomes.[23,26]

T-cells are potent immune cells capable of mediating adaptive immunity through the expression of antigen receptor complexes (TCR), which comprise an antigen-specific alpha-beta heterodimer and a transmembrane CD3 protein and mediate receptor signaling and T-cell activation.[27] TCRs recognize specific protein fragments (ie, peptides) presented by MHC proteins on APCs, virally infected cells, and tumor cells. Triggering of CD3 signaling in a CD8+ T-cell synapsed with another cell presenting a target antigen can cause the T-cell to release perforin and granzyme B, resulting in cancer cell lysis and death. Cancer cells can avoid T-cell recognition and destruction by down-modulating peptide/MHC presentation. One way to remove dependence on peptide/MHC presentation is through direct bridging of a cell-surface antigen on a target cell with the extracellular CD3 on T-cells, leading to T-cell signaling equivalent to that generated by MHC/TCR-based engagement.

2.2.3. Elranatamab (PF-06863135)

Elranatamab is a heterodimeric humanized full-length bispecific IgG2 kappa mAb derived from 2 mAbs, the anti-BCMA mAb (PF-06863058) and the anti-CD3 mAb (PF-06863059).. Targeted T-cell-mediated cytotoxicity follows the binding of 1 epitope of elranatamab to CD3-expressing T-cells and a second epitope to BCMA-expressing MM cells.

2.2.3.1. Nonclinical Studies of Elranatamab

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

2.2.3.2. Clinical Overview

Elranatamab is being evaluated for the treatment of adult patients with RRMM or NDMM in 11 ongoing studies. For detailed information on these studies, refer to the IB (January 2023).

The safety, efficacy, and PK of elranatamab as a single agent were initially evaluated in a Phase 1 study (C1071001) as monotherapy (IV and SC) or in combination with lenalidomide or pomalidomide. This study is ongoing, and enrollment is complete. Results from the study were recently published by Bahlis et al, 2023 [28].

Enrollment in the Phase 2 study C1071003 completed in January 2022 with a total of 187 participants enrolled and treated. Study results on the safety, efficacy, clinical pharmacology and immunogenicity of elranatamab are provided in the IB and were recently published by Lesokhin et al, 2023 [29].

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Study Intervention: Elranatamab monotherapy
CRS	A known toxicity of therapeutics that function by activation of immune effector cells. Circulating cytokines are elevated after IV or SC administration of elranatamab. CRS signs and symptoms are expected mainly after the first and second dose and occasionally after the third or later doses of elranatamab. In the present study, elranatamab dose will be increased to> 76 mg starting from Cycle 2 either with longer dosing intervals in Patt 2A DLI, Patt 2A DL2, and Patt2B [redacted] For Part 2, the planned regimen would result in up to 2-fold higher Cmax on Cycle 2 Day 1 (152 mg Q2W) compat·ed to 76 mg QW. Higher Cma.x during the first 24 hours of the first	Patticipants will be hospitalized for at least 2 days after the CIDl dose and at least 1 day after the ClD4 dose for safety surveillance (Patt I, Part 2). Hospitalization from Cl DI to CID5 may be considered. Since CRS events occmTed after the first (predominantly within the first 2 days) and second dose of eh-anatamab, the planned 2-day hospitalization after the first dose allows for the detection of initial CRS signs and symptoms and enables timely management of these events according to the ASTCT management guidelines. The I-day hospitalization on CID4 is considered adequate given the anticipated lower incidence and grade CRS after the second step-up dose of 20 mg. For Patt 2A, participants will be hospitalized for at least 1 day also on C2Dl. For Part 2B and Patt 2C, hospitalization on C2Dl may not be required depending on CRS profile observed in Part 2A. For patticipants enrolled in Part 1 who would switch to the RP2D Q4W, optional hospitalizationmay be considered on the day of RP2D administration depending on CRS profile observed in Patt 2A and Patt 2B. The 2 step-up priming doses schema is expected to mitigate the rate and severity of CRS, which is mainly expected after the first 1 to 2 doses. To fwther mitigate the CRS risk, premedications will be administered prior to the first 3 doses on ClD I, CID4 and CID8 (see Section 6.8.I). No premedications will be administered on C2Dl for Part 2 as the risk of CRS after repeated eh-anatatnab administration, even with a higher eh-anatatnab dose, is considered low. Guidance for monitoring, grading, and management of CRS per ASTCT criteria and guidelines is included in Appendix 12. Dose modification/discontinuation in the setting of Grade c:::2 AEs (including CRS) is described in Section 6.5. This study will include only participants who are likely to tolerate potential events of CRS by excluding patticipants who at·e 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). Criteria for temporary study hold based on Grade c:::3 CRS events are described in Section 9.4.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	dose of elranatamab was associated with a higher risk of CRS (See Section 4.3). Despite the predicted higher C_{max} for C2D1 in Part 2, the risk of CRS events on C2D1 (ie, after 2 step-up priming doses, and 3 full doses of 76 mg in Cycle 1) is considered low. For further information, refer to the IB.	
ICANS	A known toxicity of therapeutics that function by activation of immune effector cells. Data from ongoing studies suggest ICANS is infrequent and most often Grade ≤2. For further information, refer to the IB.	Participants will be hospitalized for at least 2 days after the C1D1 dose and at least 1 day after the C1D4 dose for safety surveillance. Hospitalization from C1D1 to C1D5 may be considered. For Part 2A, participants will be hospitalized for at least 1 day also on C2D1. For Part 2B and Part 2C, hospitalization on C2D1 may not be required depending on CRS profile observed in Part 2A. For participants enrolled in Part 1 who would switch to the RP2D Q4W, optional hospitalization may be considered on the day of RP2D administration depending on CRS profile observed in Part 2A and Part 2B. The 2 step-up priming doses schema may mitigate the rate and severity of ICANS, which is mainly expected after the initial dose. Regular neurologic examinations will be performed by the investigator (or designee) (Section 8.2.2). Guidance for monitoring, grading, and management of ICANS per ASTCT criteria and guidelines is included in Appendix 12. Dose modification/discontinuation in the setting of Grade ≥2 AEs (including ICANS) is described in Section 6.5.1.2. Additional management for Grade ≥3 ICANS events is described in Section 10.12.2 Criteria for temporary study hold based on Grade ≥3 ICANS events are described in Section 9.4.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Peripheral neuropathy including GBS	Peripheral neuropathy is a complication of multiple myeloma and its treatment. In the Phase 1 study (C1071001) and Phase 2 study (C1071003, cohort A), 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 for emerging signs and symptoms of new or worsening peripheral neuropathy. The administration of drugs known to cause peripheral neuropathy should be carefully considered, and if possible, avoided by the investigator; effective treatment and prophylaxis for infections should be prioritized (Section 6.8). Participants should be closely monitored for signs and symptoms of neuropathy following infections or following the administration of any vaccine (Section 8.3.8). Dose modification/discontinuation for peripheral neuropathy is described in Section 6.5. Work-up recommendations for new or worsening peripheral neuropathy (Grade ≥2) is described in Section 8.3.8. Additional management for peripheral neuropathy is described in Section 9.4.1.
Infections	Infections are common in patients with RRMM due to underlying immunosuppression. As elranatamab causes plasma cell depletion, and likely contributes to worsening hypogammaglobulinemia and neutropenia, elranatamab treatment increases the risk of infections. For further information refer to the IB. (	See Section 6.8.8 and Appendix 15 for infection prophylaxis. Monitor participants, especially those with neutropenia, for signs of infection. See Section 6.5.1 for dose modifications for elranatamab.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Disease progression due to lower C_{trough} in Part 2A/Part 2B/Part 1 from C7	The elranatamab dose will be increased from Cycle 2 while increasing the dosing interval from QW to Q2W. Based on predictions from preliminary population PK analyses, switching the elranatamab dose to 152 mg Q2W starting from Cycle 2 are predicted to result in an average C_{trough} ~ 14 and ~10% lower compared to 76 mg QW for free and total elranatamab, respectively.	Understanding the association between C_{trough} and other exposure metrics on efficacy is evolving. While a dose > 76 mg with longer dosing intervals starting from Cycle 2 may be associated with a lower C_{trough}, the risk of increased disease burden is considered low given the similar overall dose intensity (eg, 76 mg QW versus 152 mg Q2W) and the potential for better saturation of the sBCMA across the dosing interval with doses > 76 mg even with longer dosing intervals.

2.3.2. Benefit Assessment

There are few viable treatment options for RRMM, especially for those patients who are refracto1y to Pls, IMiDs and anti-CD38 mAbs (see Section 2.2.1). Based on data from the ongoing Phase 1 study (C1071001) and Phase 2 study (C1071003), elranatamab monotherapy has the potential to provide clinical benefit to participants with RRMM (see IB).

The 2 step-up priming doses approach and premedication schema proposed in this study are expected to fmiher reduce the rate and severity of CRS (see Section 6.1).

The dosing regimen of 76 mg QW SC, as implemented in Pait 1 for the first 6 cycles and Pali 2 dming Cycle 1, is expected to result in clinical benefit and provide coverage for the majority of triple-class RRMM patients with a manageable safety profile.

In Pait 2, the administration of elranatamab doses> 76 mg with longer dosing intervals, eg, 152 4W, will mai ntain overall dose intensity/exposure (ie, AUC) similar to 76 mg QW and Q2W, respectively. CCI [redacted] he p anne regunens m Pait 2 B or C an m Pait 1 a er 6 eye es cou ui er saturate the sBCMA sink across the dosing interval especially in patients with relatively high sBCMA levels. Better satmation of sBCMA would result in higher unbound elranatamab exposme which is anticipated to derive, maintain and/or fiuther deepen clinical responses. In addition, less frequent dosing can increase patient convenience and improve compliance.

2.3.3. Overall Benefit/Risk Conclusion

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

More details on the safety, efficacy, clinical phaimacological and immunogenicity of elranatamab are provided in the IB.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Prima1-y		
Pa1·t 1 and Pa1·t 2		
• To assess the rate of Grade 2 CRS when eh-anatamab is administered with a dosing regimen of2 step-up priming doses and premedication in pa1ticipants with RRMM	• Grade2 CRS rate during Cl.	• The primary estimand is rate of Grade2 CRS during Cl as assessed by ASTCT criteria. It will be estimated based on all enrolled RRMM pa1ticipants who received at least 1 dose of study intervention regardless of duration on the study treatment.
Seconda1-y		
Part 1 and Part 2		
• To assess the safety and tolerability of eh-anatamab at doses >76 mg with a longer dosing interval(> 1 week) in order to identify the RP2D **(Part 2A and 2C)**	• Incidence ofDLTs during DLT observation period.	• The secondruy estimand is DLT rate estimated based on data from DLT-evaluable pruticipants during the DLT observation period
• To evaluate the overall safety profile of eh-anatamab with 2 step-up priming doses and alternative dosing regimens in participants with RRMM	• Adverse Events as chru·acterized by type, frequency, severity as graded by NCI CTCAE version 5.0, timing, seriousness, and relationship to elranatrunab. The severity of CRS and ICANS will be assessed according to ASTCT criteria; • Laborato1y abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing.	• Not Applicable
• To evaluate the anti-myeloma activity of eh-anatamab with alternative dosing regimens in pa1ticipants with RRMM	• ORR and CRR, per IMWG response criteria as determined by investigator; • Time to event endpoints: TTR, DOR, DOCR and PFS per IMWG response criteria as detennined by investigator, and OS; • MRD (assessed by central lab) negativity rate per IMWG sequencing criteria.	• Not Applicable

Objectives	Endpoints	Estimands
• To evaluate the PK of eh-anatamab	• Pre- and postdose concentrations of eh-anatamab.	• Not Applicable
• To evaluate immunogenicity of eh-anatamab	• Incidence and titers of ADA and NAb against eh-anatamab.	• Not Applicable
[redacted] CCI [redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

Study C1071009 is a prospective, open-label, multicenter, non-randomized Phase 1/2 study aimed to evaluate the safety (in paiticular the rate of Grade::::2 CRS) of a priming dose regimen of eh-anatamab that involves premedication and 2 step-up p1irning doses to be administered within the first week of treatment (Pait 1 and Pait 2). Study C1071009 will include RRMM paiticipants who are refracto1y to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb.

All participants emolled in Pait 1 and Pait 2 will contribute to the primaiy objective of the study, ie, assessing the rate of Grade ::::2 CRS during Cl, asthe same dosing regimen is administered to all treatment groups during the first cycle.

Overall, at time of protocol amendment 4, Pait **1** and Pait 2 (Pait 2A and Pait 2B) were ongoing, and the enrollment is completed in all coho1ts. Pait 2C will not be explored. The RP2D was detennined from Pait 2A and is described below.

Twelve pa1ticipants were enrolled and treated in Pait 2A DLI (116 mg Q2W from C2Dl) and 7 were DLT evaluable. There was one DLT event. Eleven paiticipants were enrolled and treated in Pait 2A DL2 (152 mg Q2W from C2D**1)** and 7 were DLT evaluable. There was one DLT event. During the dose level review meeting (DLRM), the 152 mg Q2W dose was selected as the RP2D with a switch to 152 mg Q4W sta1ting in Cycle 7 (for paiticipants with an IMWG response of PR or better persisting for 2 months). In addition, participants in Pait 1 dosed with 76 mg Q2W, with an IMWG response of PR or better persisting for 2 months were also pennitted to switch to 152 mg Q4W. RP2D is cmTently investigated in Pait 2B with a dosing of 152 mg Q2W or 152 mg Q4W (depending on IMWG response).

CCI [redacted]

All study pa1ts ai·e detailed below.

Part 1 and Part 2:

The following dosing regimen will be evaluated in the first cycle (Cl) of elranatamab treatment:

- **C1D1:** Premedication + elranatainab 4 mg (hospitalization for at least 2 days, see Section 2.3.1)
- **C1D4:** Premedication + elranatainab 20 mg (hospitalization for at least **1** day, see Section 2.3.1)
- **C1D8:** Premedication + elranatainab 76 mg
- **C1D15 and C1D22:** elranatainab 76 mg QW

The first 2 doses of elranatamab on ClDl and C1D4 will serve as the step-up priming doses and will be administered on an inpatient basis to monitor paiticipants for CRS/ICANS. The dose of elranatamab should be increased to 20 and 76 mg on C1D4 and C1D8, respectively, as long as the paiticipant meets redosing criteria (Section 6.5.1).

In addition, the study will evaluate the overall safety, tolerability, PK, phaimacodynainics, and preliminaiy anti-myeloma activity of a regimen of elranatainab full dose of 76 mg QW for 6 cycles followed by Q2W or> 76 mg Q4W (Pait 1) and alternative regimens of

ehanatamab at dose levels >76 mg staiting from C2 with different dosing intervals (QW, Q2W, Q4W) (Pait 2).

The following dosing regimens will be assessed: **Part 1: Premedication, 2 step-up priming doses, and full dose 76 mg QW for 6 cycles followed by Q2W and/or RP2D (116 mg or 152 mg) Q4W as determined from Part 2A.**

Pait 1 aims to evaluate the overall safety, tolerability, PK, phannacodynamics, and preliminaiy anti-myeloma activity of the following regimen:

- **C2 to C6:** ehanatainab 76 mg QW
- **C7 onwards:** ehanatamab 76 mg Q2W (for participants with IMWG response of PR or better persisting for 2 months on QW)
- **C7 onwards once the RP2D is identified in Part 2A:** ehanatainab RP2D (116 mg or 152 mg) Q4W (for paiticipants with IMWG response of PR or better persisting for 2 months on QW or Q2W). An optional day of hospitalization may be considered for the first RP2D dosing (116 mg or 152 mg) Q4W depending on CRS profile observed in Pait 2A and Pait 2B.
- CCI [redacted]

Part 2: Premedication, 2 step-up priming doses, and full dose> 76 mg (ie 116 and 152 mg) at different dosing intervals

Pait 2 aims to evaluate the safety and efficacy of a regimen that includes premedication and a dosing regimen of2 step-up priming doses (Week 1) followed by full dose >76 mg with different dosing intervals staiting from C2.

Pait 2 includes a dose detennination rut Pait 2A Dose level 1 and Dose level 2), a dose expansion pait (Pait 2B), Pait 2A dose detennination and Pait 2C tolerability evaluation will be based on a BLRM approach.

The decision to strut enrolling paiticipants in a new cohoit (Pait 2A Dose level 2, Pait 2B or Pait 2C) will be a joint decision to be detennined by the investigators and the sponsor in dose level review meetings.

Part 2A will evaluate full ehanatainab doses >76 mg staiting from C2 with a longer dosing interval (> 1 week) to determine the potential RP2D to be further evaluated in Pait 2B. Approximately 8 paiticipants will be enrolled at each dose level in Pait 2A.

Dose level 1 will assess the following regimen:

- **C2 to C6:** elranatamab 116 mg Q2W. DLT observation period is C2 or 28 days staiting from the first dose of 116 mg. Hospitalization on C2 DI or on the day of the first dose of 116 mg for at least 1 day is required, see Section 2.3.1. Ehanatamab 116 mg represents an ~ 50% increase in ehanatamab dose versus 76 mg.

- **C7 onwards:** eh-anatamab 116 mg Q4W (for paiticipants with IMWG response of PR or better persisting for 2 months on Q2W).

If Dose level 1 is tolerable, **Dose level 2** will be initiated to assess the following regnnen:

- **C2 to C6:** ehanatainab 152 mg Q2W. DLT observation period is C2 or 28 days staiting from the first dose of 152 mg. Hospitalization on C2 DI or on the day of the first dose of 152 mg for at least 1 day is required, see Section 2.3.1. Ehanatamab 152 mg represents an ~ 30% increase in ehanatamab dose versus 116 mg and will be the MAD in this study.

- **C7 onwards:** ehanatamab 152 mg Q4W (for participants with IMWG response of PR or better persisting for 2 months on Q2W).

- CCI [redacted]

The potential RP2D identified in Pait 2A Dose level 1 or Dose level 2 will be further evaluated and confomed in Pait 2B (dose expansion).

Part 2B will begin once the potential RP2D from Pait 2A Dose level 1 or Dose level 2 is selected. Approximately 22 pa1ticipants will be enrolled to confnm the safety and efficacy of the selected dosing regimen to have at least 15 pa1ticipants ti·eated for 2 cycles. Approximately a total of 30 paiticipants will be enrolled and ti·eated at the potential RP2D, 8 from Pait 2A and 22 from Pait 2B .

- CCI [redacted]

[redacted]

I [redacted]

ill Paits 2B and 2C, hospitalization on C2Dl or on the day of the first dose of 116 mg or 152 mg may not be required depending on CRS profile observed in Pait 2A (See Section 2.3.1). This will be a joint decision to be detennined by the investigators and the sponsor before opening enrollment to Pait 2B and Pait 2C.

ill Pait 2 (A, B, and C), the elranatamab dose may be increased to 116 or 152 mg only in paiticipants who have received at least 2 doses at 76 mg.

Pait 2 enrollment will stait after approximately 30 participants have been enrolled in Pait 1. The decision to proceed with Pait 2 of the study will be a joint agreement between the sponsor and the investigators based on the review of the available data, including CRS incidence and severity.

If neither Dose level 1 or Dose level 2 in Pait 2A proves to be tolerable, Part 2C and Pait 2B will not strut and Pait 1 will enroll approximately 68 paiticipants.

4.2. Scientific Rationale for Study Design

Elranatamab has the potential to provide clinical benefit to paiticipants with RRMM (Section 2.2.3.2). The totality of efficacy, safety, PK, phannacodynainics data, and exposme-response analyses from Study C1071001 suppo1ted the RP2D of 76 mg, fixed dose equivalent of 1000 µg/kg, QW administered as a SC injection with a priming dose of 44 mg, fixed dose equivalent of 600 µg/kg, for the first dose. The RP2D is expected to result in clinical benefit for the majority of triple-class RRMM patients, including those with relatively high levels of baseline sBCMA, which Inight have an impact on unbound elranatamab diug exposme in the circulation and hence Inight impact the probability of achieving responses.[27] Impo1tantly, the RP2D demonstrated a manageable safety profile.

ill Study C1071001, elranatamab has shown a manageable safety profile mainly characterized by Grade 1 or 2 CRS (refer to the IB). To fmther reduce the rate of CRS and in paiticulai·the rate of Grade 2 and higher CRS, the cunent study will evaluate a regimen that involves a premedication cocktail and 2 step-up priming doses to be administered within the first week of elranatamab treatment.

ill ongoing elranatainab clinical studies, paiticipants who received at least 6 cycles and have achieved response of PR or better with responses pe • rsisting for at least 2 cycles, the dosing interval is changed from 76 mg QW to 76 mgQ2W. CCI Pait 1 and Part 2 will evaluate this regimen of

ehanatamab full dose of 76 mg QW for 6 cycles followed by Q2W. However, the cmTent study will also evaluate the overall safety, tolerability, PK, phru.macodynamics, and preliminru.y anti-myeloma a f ehanatamab full doses> 76 mg with alternative dosing intervals (QW, Q2W, Q4W,-(refer toSection 4.3.2). Pru.t 2 includes a dose dete1mination pru.t (Pait 2A Dose level 1, 116 mg, and Dose level 2, 152 mg, which represent ~ 50% and 30% increases from 76 m and 116 m res ectively), a dose expansion pru.t (Pait 2B), CCI

CCI

4.2.2. Diversity of Study Population

Reasonable attempts will be made to emoll pru.ticipants in the US with the distribution of characteristics shown below (Table 4) to ensme the study population is representative of the patient population that will use ehanatamab in clinical practice.

Table 4. Relevant Population Metrics - US

Race	Prevalence Rate (%)
Black/African American	19
American Indian or Alaska Native	I

Table 4. Relevant Population Metrics - US

Race	**Prevalence Rate** (%)
Asian	6
Native Hawaiian or other Pacific Islander	Not available
White	72
Ethnicitv	
Hispanic or Latino(a) or of Spanish Origin	12
Not Hispanic or Latino(a) or of Spanish Origin	88
Sex	
Male	56
Female	44
Ae:e (years)	
18-39	I
40-64	36
>65	63

4.2.3. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of eh-anatamab have not been conducted. Therefore, the use of a highly effective method of contraception is required for WOCBP (see Appendix 4). There are no contrnception requirements for male pa.iiicipants who receive eh-anatamab, as the calculated safety ma.i·gin is l 00-fold between the estimated maternal exposure due to seminal transfer and the estimated MABEL used as conservative estimate of exposure that may result in serious manifestations of developmental toxicity.

[redacted]

4.3. Justification for Dose

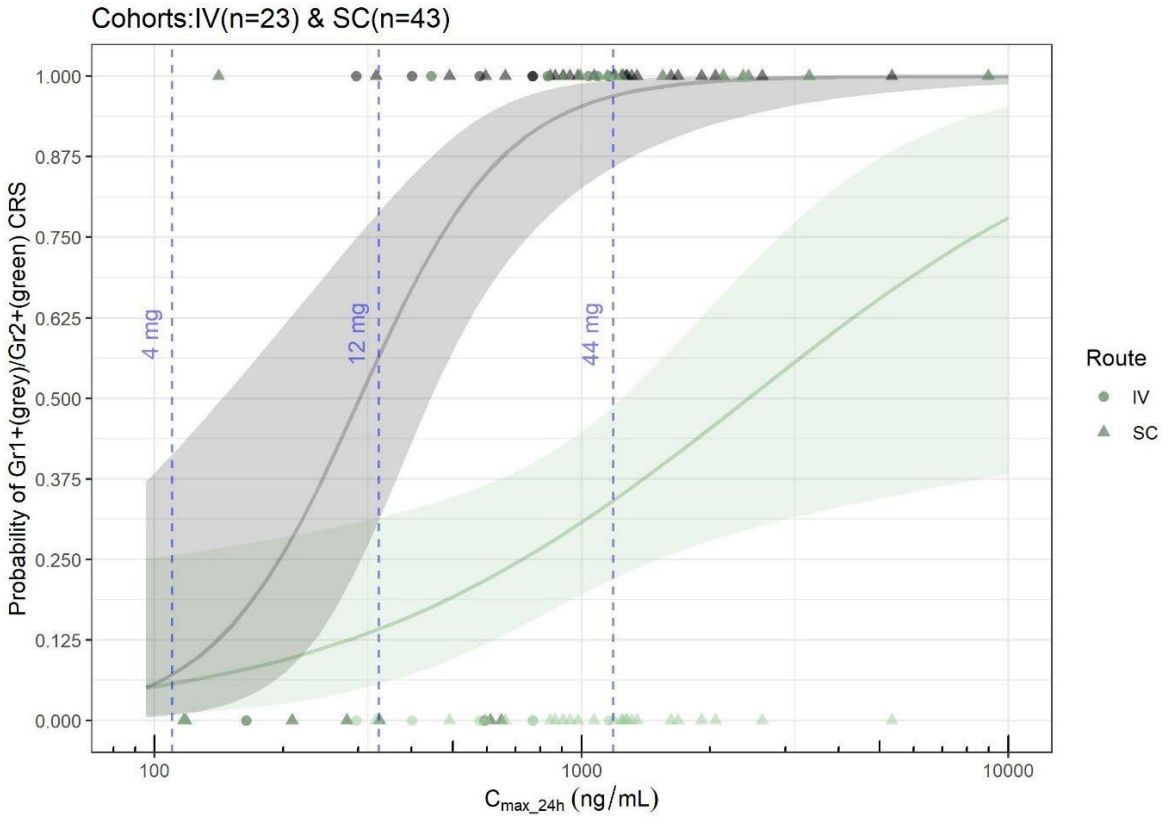
4.3.1. Justification for the 2 Step-up Priming Doses Regimen

fu the SC coho1is from Study C1071001, only 2 out of 50 pa.iiicipants experienced CRS after the second dose and no CRS events were observed after the third or later doses. The rate of Grade 1 and 2 CRS events in paiiicipants receiving dose levels 600 µg/kg (which is the body weight dosing equivalent of 44 mg) is 62.5% and 37.5%, respectively, according to ASTCT grading. The maximum severity of CRS was consistently observed after the first dose including pa1iicipants in the priming coho1is who received a higher dose on C1D8 indicating that CRS is associated mostly with the initial exposure (ie, the first dose). A logistic regression analysis that included data from both IV (n =23) and SC coho1is (n = 43) from Study C1071001 shows an association between eh-anatamab Cmax within 24 hours post first dose (Cmax-24h) and probability of CRS of All Grade and Grade 2 and higher (according to ASTCT criteria, Figure 1)

Priming dose approaches a.i·e commonly applied for T cell engager bispecific modalities to initially sensitize the immune system at lower doses to reduce rate and grade of CRS.[31-34]

Across the elranatamab program, multiple priming dose regimens are being investigated to determine optimal dosing strategies for the mitigation of CRS events early in elranatamab treatment. The Phase 2 Study C1071003 and Phase 3 Study C1071005 have implemented a priming dosing regimen that includes premedications as well as 2 step-up priming doses of 12 mg on C1D1 and 32 mg on C1D4 to reduce the rates of CRS observed with doses ≥ 600 µg/kg (body weight dosing equivalent of 44 mg) administered early in the treatment regimen. The current study will evaluate a priming dosing regimen that includes premedications as well as 2 step-up priming doses of 4 mg on C1D1 and 20 mg on C1D4 before increasing elranatamab dose to 76 mg on C1D8. The logistic regression analysis indicates that the predicted probability of Grade 2 or higher CRS after a starting dose of 4 mg on Cycle 1 Day 1 is 6% (95% CI: 1% to 26%) compared to a predicted probability of 34% (95% CI: 22% to 49%) associated with a regimen that uses a single priming dose of 44 mg on C1 D1 before increasing to full elranatamab dose of 76 mg on C1 D8, which is the RP2D implemented in the ongoing dose expansion cohort in Study C1071001. The model predicted rates of All Grade CRS at a starting dose of 4 mg and 44 mg initial priming doses are 7% (95% CI: 1%% to 41%%) and 97% (95% CI: 86% to 99%). Overall, the analysis predicts that a 4 mg initial priming dose will significantly reduce the rate of All Grade and Grade 2 and higher CRS associated with elranatamab treatment compared to a regimen using an initial single priming dose of 44 mg on C1D1.

Figure 1. Logistic Regression Analysis of Elranatamab Concentration at 24 hours Versus Probability of all Grade and Grade 2 CRS



4.3.2. Justification for Evaluation of Higher Elranatamab Doses

An MTD was not achieved in C1071001, and the safety and efficacy for doses greater than 76 mg has not been established. Increasing the dose of elranatamab may allow for a longer dosing interval and a lower frequency of administration while maintaining the overall exposure (ie, AUC) of total eh-anatamab between 152 mg Q2W similar to 76 mg QW.

Based on the results of the quantitative systems phru.macology simulations, higher eh-anatamab doses with longer dosing intervals (ie, Q2W, Q4W and- are expected to be adequate to maintain the response given the reduced disease burden in these paiiicipants. The higher eh-anatamab dose levels explored in Pru.i 2A/Pru.i 2B, specifically Pru.i 2A Dose level 2 of 152 mg Q2W/Q4W which is the tai·get dose level for Pa1i 2A/2B, provide a similru.·overall dose intensity (AUC) to 76 mg QW/Q2W. Dose level 1 (116 mg) represents~ 50% increases from 76 m • Dose level 2 152 m re resents~ 30% increase from 116 m CCI [redacted]

The dosing regimens to be evaluated in Pait 2AIB, Pru.i 2C and Pait 1 after 6 cycles and after 12 cycles are expected to finiher saturate the sBCMA sink and result in higher unbound eh-anatamab exposure across the dosing interval. Therefore, these regimens could derive, maintain and/or finiher deepen clinical responses. In addition, less frequent dosing might provide additional patient convenience and improve compliance.

CCI [redacted]

4.3.3. Definition of DLT (Part 2A and Part 2C)

Severity of AEs will be graded according to NCI CTCAE version 5.0. The severity of CRS and ICANS will be assessed according to the modified grading described by ASTCT. The DLT observation period will be 28 days staiting from the first 116 or 152 mg dose.

A pru.iicipant is classified as DLT-evaluable if they meet either criterion:

- Experiences a DLT during the DLT observation period,
- In the absence of a DLT, receives the planned number of doses at the planned dose level of the study inte1vention and receives scheduled safety assessments during the DLT obse1vation period.

If a pa1iicipant does not meet these criteria, he/she may be replaced.

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

As described in Table 5, any of the following AEs observed within the DLT observation period and considered related to study intervention will be classified as DLTs. Participants experiencing a DLT may resume dosing only if adequate recovery is achieved within the allowed time window and if permitted for the specific toxicity (see Sections 6.5.1 and 6.5.1.2).

Table 5. Hematological and Non-hematological Dose-limiting Toxicities

Hematological
• Grade 4 neutropenia lasting >5 days.
• Febrile neutropenia (defined as an 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 1 hour). If fever is determined to be a symptom of CRS confirmed by clinical course and cytokine levels, and resolves in a manner consistent with CRS, this would no longer be considered a DLT, and the participant may resume treatment.
• Grade ≥3 neutropenia with infection.
• Grade 4 thrombocytopenia: o For participants with baseline platelets ≥50,000/mm^3, any platelet count <25,000/mm^3 is a DLT o For participants with baseline platelets ≥25,000/mm^3 and <50,000/mm^3, any platelet count < 10,000/mm^3 is a DLT, while platelet counts < 25,000 and ≥10,000 are a DLT only if associated with Grade ≥2 bleeding or requiring platelet transfusion.
• Grade 3 thrombocytopenia with Grade ≥2 bleeding.
Non-hematological
• Grade ≥4 AEs.
• Grade 3 CRS, except those CRS events 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 3 AEs, with the exception of: o AEs attributed to a CRS event (ie, Grade 3 transaminitis) o Grade 3 nausea, vomiting and diarrhea that improve to Grade ≤ 2 within 72 hours after maximal medical management has been initiated o Grade 3 fatigue lasting <1 week o Grade 3 AEs that recover to baseline or Grade 1 within 5 days
• Confirmed DILI meeting Hy's law criteria (See Appendix 6)

Table 5. Hematological and Non-hematological Dose-limiting Toxicities

• Grade 3-4 laboratory abnonnalities with the exception of: o Grade 3-4 laboratory abnonnalities that are not associated with clinical sequelae and improve to Grade 2 with appropriate management or supplementation within 72 hours of their onset.
• Other clinically important or persistent AEs (eg, AEs responsible for significant dose delay or dose reduction) may also be considered a DLT following review by the investigators and the sponsor. DLTs need to represent a clinically significant shift from baseline.
• Grade 3 ISR•

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

4.3.4. Definition of RP2D for Part 2B and Part 1 From C7

The RP2D for eh-anatamab to be fmther evaluated in Pait 2B and Pait 1 after 6 cycles is the dose chosen based on Part 2A (Dose level 1 and Dose level 2). Dose level 2, 152 mg, is the MAD. The RP2D decision will be determined based on the totality of available data from Pait 2A and will include safety, efficacy, PK, and pha1macodynamics data. This will be a joint decision to be detennined by the investigators and the sponsor in dose level review meetings. Refer to Section 4.1 for more infonnation on the cmTent RP2D fmther investigated in Pait 2A DL2, Pait 2B and Pait 1.

CCI [redacted]

4.4. End of Study Definition

The study will be completed when all paiticipants have been followed for OS for at least 2 years from the date of enrollment.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate paiticipants ai·e enrolled. The following eligibility criteria ai·e designed to select pa1ticipants for whom pa1ticipation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a paiticulai·paiticipant is suitable for this protocol.

Prospective approval of protocol deviations to recmitment and enrollment criteria, also known as protocol waivers or exemptions, is not pe1mitted.

5.1. Inclusion Criteria

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

1. **Age and Sex:** Participants age ≥18 years (or the minimum country specific age of consent if >18).

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

- **Type of Participant and Disease Characteristics:**

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

3. Prior diagnosis of MM as defined according to IMWG criteria.[1]

4. Measurable disease based on IMWG criteria as defined by at least 1 of the following:

   a. Serum M-protein ≥0.5 g/dL by SPEP;

   b. Urinary M-protein excretion ≥200 mg/24 hours by UPEP;

   c. Serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

5. Refractory to at least 1 IMiD.

6. Refractory to at least 1 PI.

7. Refractory to at least 1 anti-CD38 antibody.

8. Relapsed or refractory to last anti-MM regimen.

Note: Refractory is defined as having disease progression while on therapy or within 60 days of last dose in any line, or no response to therapy.

9. ECOG performance status ≤1.

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

11. Adequate hepatic function characterized by the following:

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

b. AST ≤2.5 x ULN; and

c. ALT ≤2.5 x ULN

12. Adequate renal function defined according to local institutional standard method: eGFR ≥ 30 mL/min/1.73 m2 using CKD-EPI 2021 equation [2] or estimated creatinine clearance ≥ 30 mL/min using Cockcroft Gault formula. If both formulae are calculated, the higher of the 2 values may be used. A 24-hour urine collection for creatinine clearance may also be used in equivocal cases where amyloidosis is suspected.

13. Adequate BM function characterized by the following:

    a. ANC ≥1.0 × 10^9/L (use of G-CSF is permitted if completed at least 7 days prior to planned start of dosing);

    b. Platelets ≥25 × 10^9/L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and

    c. Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 14 days prior to planned start of dosing).

14. Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L).

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

Informed Consent:

16. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Smoldering MM.
2. Active plasma cell leukemia.
3. POEMS syndrome.
4. Amyloidosis.

5. Waldenström's macroglobulinemia

6. Known active CNS involvement or clinical signs of myelomatous meningeal involvement

7. Stem cell transplant within 12 weeks prior to enrollment or active GVHD.

8. Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:

    a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);

    b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);

    c. Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);

    d. Prolonged QT syndrome (or QTcF >470 msec at screening).

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

10. History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy.

11. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.

12. Active HBV, HCV, COVID-19/SARS-CoV-2, HIV, or AIDS-related illness, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.

    COVID-19/SARS-CoV-2: While SARS-CoV-2 testing is not mandated for entry into this study, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV-2 infection within 14 days prior to enrollment, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, they are excluded.

    HBV:

    - This criterion excludes participants with a positive HBsAg (ie, either acute or chronic active hepatitis).

- However, participants with HBV antibody positivity indicating immunity, either due to vaccination or prior natural infection, are eligible.

- Patients with positive anti-HBcAb but negative HBsAg and negative anti-HBsAb profile are eligible if HBV DNA is not detected.

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

14. Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ or Stage 0/1 malignancy with minimal risk of recurrence per investigator.

15. Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

16. Previous treatment with anti-BCMA bispecific antibody or CAR-T cell therapy.

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

Prior/Concurrent Clinical Study Experience:

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

19. A participant may be eligible even if they are in the follow-up phase of an investigational study as long as they meet the criteria for time elapsed from previous administration of investigational product. Cases must be discussed with sponsor's medical monitor to judge eligibility.

Other Exclusions:

20. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is using an appropriate method of contraception for the individual participant

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. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in the SoA (including long term follow-up visit/contacts covering the required contraception period [through 5 months post last dose of study intervention for WOCBP [Appendix 4]]), 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, considering that their risk for pregnancy may have changed since the last visit. Contraception check is only required for WOCBP.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant. If a participant is confirmed to be pregnant, study intervention should be discontinued.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number as for the initial screening.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to elranatamab.

6.1. Study Intervention(s) Administered

Intervention Name	Diluent	Eh-anatamab
Part 1, Part 2A, Pa1·t 2B, and Part 2C (group of pa11icipants receiving a specific treatment or no treatment)	Pait 1 and Part 2	All enrolled
Tvoe	Diluent	Biologic: BITE
Dose Formulation	Solution for SC injection	Solution for SC injection
Unit Dose Strength(s)	Diluent solution for Injection in a 6 mLvial	40 mg/mL with an extractable volume of 1.9 mL (76 mg per vial)
Dosa2e Level(s)	Suooorts 4 mg Dosage Level	See table below
Route of Administration	SC	SC
Use	Exoerimental	Exoerimental
IMPorNIMP	NIMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided in a cation containing I vial. Each vial and ca1ton will be open labeled as required per countiy reauirement.	Study intervention will be provided in a carton containing I vial. Each vial and cation will be open labeled as required per countiy requirement.
Current/Former Name(s) or Alias(es)	Diluent	Eh-anatamab!PF-06863135

Arm title	**Arm Type**	**Description**	**Associated Intervention Labels**
Pait 1	Experimental	Participants will receive eh-anatamab 4 mg on ClDI and 20 mg on ClD4 (2 priming doses) and then 76 mg QW for 6 cycles. Thereafter, pa1ticipants with PR or better response persisting for c:::2 months on QW will receive 76 mg Q2W and/or 116 m. or 152 m. 4W from C7 and onwat·ds. [redacted]	76 mg Full Dose

Arm title	Arm Type	Description	Associated Intervention Labels
Pa1t2A	Experimental	Participants will receive eh-anatamab 4 mg on ClDI and 20 mg on ClD4 (2 priming doses) and then 76 mg QW for I cycle. Thereafter, pa1ticipants will receive: - **Dose level 1:** 116 mg Q2W for C2 to C6. From C7 onwards, pruticipants with PR or better response for at least 2 cycles will receive I I6 mg Q4W. - **Dose level 2:** 152 mg Q2W for C2 to C6. From C7 onwards, pruticipants with PR or better response persisting for :C:: 2 months will receive 152 mg Q4W. CCI [redacted]	>76 mg Full Dose Longer Dosing Interval (Dose detennination)
Pa1t2B	Experimental	Participants will receive eh-anatamab 4 mg on ClDl and 20 mg on ClD4 (2 priming doses) and then 76 mg QW for **1** cycle. Thereafter, pruticipants will receive 116 or 152 mg Q2W for C2 to C6. From C7 onwards, pa1ticipants with PR or better response persisting for :C:: 2 months will receive 116 m or 152 m0 4W. CCI [redacted]	> 76 mg Full Dose Longer Dosing Interval (Dose expansion)
Pa1t2C	Experimental	CCI [redacted]	[redacted]

See Section 6.8 for required premedications for CRS.

6.1.1. Elranatamab

Qualified and trained investigator site personnel will administer eh-anatamab to pa1iicipants by SC injection. Ideally, each injection may be up to 2 mL in volume; however, if the maximum volume allowed per institution's policy is lower than 2 mL, the number of injections may be increased to accommodate this difference in volume and ensure the con-ect dose is delivered. If more than one injection is needed, these injections should be

administered within 2-3 minutes from each other. See Appendix 9 for details on administration of multiple injections to the abdomen. Elranatamab should be administered to the abdomen, with preference given to the lower quadrants when possible.

A minimum of 2 days should be maintained between the 2 step-up priming doses (C1D1 and C1D4), a minimum of 3 days should be maintained between C1D4 and the first full dose (C1D8); a minimum of 6 days should be maintained between doses thereafter.

The windows for the different administration schedules are -1/+3 days for C1D4, C1D8 and then ± 3 days for QW and Q2W and ± 6 days for Q4W or CCI Study staff should refer to the IP Manual for specific instructions on the handling, preparation and administration volumes of study intervention.

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

If the dose interval is changed, cycles will remain the same length (ie, 28-day cycles).

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

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

5. Study interventions should be stored in their original containers.

6. See the IP manual for storage conditions of the study intervention.

7. 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.

8. 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 biotherapy agents.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label study. No randomization or blinding mechanisms will be used; however, the specific study intervention dispensed to the participant will be assigned using an IRT.

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

The study will start with enrolling 30 participants in Part 1. Part 2 enrollment will start based on a joint agreement between the sponsor and the investigators after the review of the available data, including CRS incidence and severity.

Allocation to dose level will be decided by the sponsor based on the participant's eligibility and availability of open slots. Study intervention and allocation of participants will be assigned using IRT. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Following full assessment and determination that the participant meets all eligibility criteria, the investigator or designee will enroll the participant.

For Part 2A and Part 2C, no participant shall sign the informed consent document until the investigator or designee has received the confirmation of the participant's screening in writing from the sponsor or delegate.

Study intervention will be dispensed at the study visits summarized in the SoA. The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Participants 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 CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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

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

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

6.5. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule.

The recommended dose modification guidelines for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV-2 infection can be found in Appendix 8.

In the event of significant toxicity, dosing may be modified in any cycle as described in Table 6. All dose modifications should be based on the worst preceding toxicity and must be recorded on the CRF.

6.5.1. Elranatamab

6.5.1.1. Redosing Criteria

During a Cycle: Re-treatment following interruption for treatment-related toxicity and for peripheral neuropathy (any causality) within a cycle should follow the dose modification tables and guidance below.

At the Start of a Cycle: Dosing at the start of any new cycle should not occur until all of the following parameters have been met:

- ANC $\geq 1.0 \times 10^9$/L
- Platelets count $\geq 25 \times 10^9$/L
- Recovery of treatment-related non-hematologic toxicities to baseline or Grade ≤1 severity
- For any dosing day (at start of a cycle or during a cycle), no ongoing CRS or ICANS of any grade
- Recovery of treatment-emergent peripheral neuropathy to Grade ≤ 1 severity
- Recovery of any lung infection or other serious infection to baseline

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

The dose modifications for elranatamab-related toxicities and for peripheral neuropathy (any causality) are presented in Table 6. All dose modifications should be based on the worst preceding toxicity and must be recorded on the CRF.

Table 6. Dose Modifications for Elranatamab-Related Toxicity and for Peripheral Sensory or Motor Neuropathy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic (excluding peripheral neuropathy – see below)	Continue treatment.[a]	Continue treatment. Alternatively, per investigator discretion, withhold treatment until toxicity is Grade ≤1, then resume.[a]	Withhold treatment until toxicity is Grade ≤1 or has returned to baseline, then resume treatment.[a,b]	Permanently discontinue.[a,b]
Hematologic[c,d]	Continue treatment.	Continue treatment.	Withhold treatment until toxicity is Grade ≤2 or has returned to baseline, then resume treatment.[d]	Withhold treatment until toxicity is Grade ≤2 or returns to baseline.[d]
Peripheral sensory or motor neuropathy (any causality) See Section 8.3.8 for recommended work-up.	Continue treatment. Continue to monitor the participant for signs of worsening neuropathy [e]	For new or worsening Grade 2 peripheral neuropathy withhold treatment until resolution to Grade ≤1, then resume treatment. Continue to monitor the participant for signs of worsening neuropathy.[e] If Grade ≥2 neuropathy reoccurs, permanently discontinue elranatamab.	First occurrence: withhold treatment until neurologic toxicity symptoms improve to Grade ≤1. Recurrent: permanently discontinue elranatamab.	Permanently discontinue elranatamab

a Both elranatamab priming doses must be administered before the full elranatamab dose. If C1D4 dose cannot be administered on the planned date, elranatamab treatment may restart at the planned 20 mg C1D4 dose upon meeting the re-treatment criteria. If the 20 mg dose is tolerable, elranatamab should then be increased to the full 76 mg dose 1 week later. If after C1D4, a participant experiences a treatment-related adverse event that leads to a dose interruption or delay (ie, dose held on C1D8), elranatamab treatment may restart at the same dose (20 mg) upon meeting the re-treatment criteria (Section 6.5.1). If the 20 mg dose was tolerable, the elranatamab dose should be increased to 76 mg. In case of ongoing CRS or ICANS of any grade on any dosing day, dosing will be held until CRS or ICANS resolution.

b Grade 3 or 4 nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require dose modification or permanent discontinuation.

c Excludes lymphopenia which is expected based on the elranatamab mechanism of action.

d For thrombocytopenia: dosing can continue if platelets ≥25 × 10^9/L.

e Consider additional diagnostic work-up (see Section 8.3.8).

Note: Cycles will not be extended to allow make-up for missed doses.

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

Missed doses will not be made up and cycles will not be extended to allow for missed doses.

C1D1 will be based on Day 1 of elranatamab dosing. After C1D1,

- for QW regimen, if elranatamab cannot be administered on the planned day including the protocol defined window (±3 days), it should be skipped until the next planned dose (ie, if Day 15 cannot be administered within ±3 days of planned dose, the dose should be skipped until Day 22).
- for Q2W regimen, if elranatamab cannot be administered on the planned day including the protocol defined window (± 3 days), it should be skipped until the next planned dose (ie, if Day 15 cannot be administered within ± 3 days of planned dose, the dose should be skipped until Day 1 of the next cycle).
- For Q4W CCI [redacted], if elranatamab cannot be administered on the planned day including the protocol defined window (± 6 days), it should be skipped until Day 1 of the next cycle.

Participants must receive both elranatamab priming doses before receiving the elranatamab 76 mg dose. If C1D4 cannot be administered within the protocol defined window, elranatamab treatment may restart at the planned C1D4 dose upon meeting the re-treatment criteria. Upon re-treatment, if the C1D4 dose was tolerable, the elranatamab dose should be increased to the 76 mg dose 1 week later, after which QW dosing with the 76 mg dose should continue. If elranatamab treatment is interrupted for >2 weeks within the first cycle between the 20 mg priming dose and the first full dose (76 mg), the participant should be retreated with 20 mg elranatamab. If well-tolerated, the elranatamab dose can be escalated to 76 mg 1 week later.

For Part 2, participants should receive 2 doses of 76 mg before further dose escalation. After dose escalation, if the 116 mg or 152 mg dose is not tolerated due to elranatamab-related grade 3 and higher toxicity, after consultation with the Sponsor, the participant may return to the 76 mg QW dosing regimen for 6 cycles followed by Q2W if PR or better is persisting for ≥ 2 months on QW.

For Part 1, if the RP2D (116 mg or 152 mg dose) Q4W is not tolerated after C7 and beyond due to elranatamab-related Grade 3 and higher toxicity, after consultation with the Sponsor, the participant may return to the 76 mg dose Q2W. Less frequent dosing may be required to manage adverse events.

If re-treatment criteria are not met within 4 weeks (8 weeks if participants are on Q4W or PPD [redacted] of treatment interruption/delay, study intervention should be permanently discontinued, unless the benefit/risk assessment per the investigator suggests otherwise, in agreement with the sponsor. In the event of a treatment interruption/delay lasting >4 weeks (>8 weeks if on Q4W CCI [redacted] for reasons other than treatment-related toxicity (eg, elective surgery), treatment resumption will be decided in consultation with the sponsor.

6.5.1.3. Dose Reductions

Dose reduction of elranatamab below 76 mg is not permitted; dose delay is the primary method for managing elranatamab-related toxicities. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

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

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

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

6.7. Treatment of Overdose

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

The sponsor does not recommend specific treatment for an overdose.

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

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 90 days after the overdose of elranatamab.

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

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

5. Obtain a blood sample for PK analysis within 28 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

6.8. Concomitant Therapy

6.8.1. Premedications Required for Cytokine Release Syndrome

Part 1 and Part 2

For both the 2 step-up priming doses (4 and 20 mg) and first full dose (76 mg), administer these medications approximately 60 min (± 15 min) prior to elranatamab dose:

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

*Different but comparable doses due to local strength variations per local prescribing information are permissible.

Similar premedications for doses at other time points including the first 116 mg and 152 mg doses may be given according to the investigator's discretion.

See Appendix 10 for management of CRS and ICANS.[35,36]

6.8.2. Permitted Concomitant Medications/Therapies

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

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

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

See Appendix 12 for management of CRS and ICANS.

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

Cytokines have been shown to result in modest and temporary inhibition of major CYP enzymes (eg, CYP3A4 and CYP2C9). Therefore, treatment with elranatamab can result in modest and temporal increase in the exposure of concomitant medications that are substrates for these enzymes. Caution should be used upon concomitant use of sensitive substrates of CYP enzymes with narrow therapeutic index (eg, CYP3A4: alfentanil, cyclosporine,

dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus; CYP2C9: phenytoin, warfarin) especially during the initial treatment cycle. If the use of warfarin is clinically necessary, caution and additional INR monitoring is recommended during the initial treatment cycle.

The administration of drugs known to cause peripheral neuropathy should be carefully considered, and if possible, avoided by the investigator. Effective treatment and prophylaxis for infections should be prioritized.

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

Palliative radiotherapy to specific sites of disease in the event of increased localized pain will be permitted if considered medically necessary by the treating physician. Progressive disease should be ruled out. The appropriate interval of time between radiotherapy and study intervention has not been determined.

6.8.3. Prohibited During the Study

No additional anticancer therapy will be permitted while participants are receiving study intervention.

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

Administration of live attenuated vaccines is prohibited during study treatment, and for 90 days after the last dose of study treatment. Annual inactivated influenza vaccines are allowed.

6.8.4. 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.

6.8.5. Transfusion Support

During study intervention, primary prophylactic use of transfusion support for anemia and/or thrombocytopenia is allowed, as indicated by the current ASCO and AABB guidelines.[37,38]

6.8.6. Hematopoietic Growth Factors

Prophylactic use of G-CSF is restricted within 7 days of first elranatamab dose by eligibility. During study intervention, primary prophylactic use of G-CSF is not permitted during Cycle 1 and 2 of Part 2A and Part 2C, but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines.[39]

Use of erythropoietin growth factors is allowed as needed to treat anemia.

6.8.7. Infection Prophylaxis

The administration of bacterial, fungal and/or viral prophylaxis in accordance with NCCN, ESMO, IMWG and/or local institutional guidelines in participants at increased risk of infection is strongly encouraged. Refer to Appendix 15 for anti-infectious prophylaxis and monitoring recommendation.

Monitor immunoglobulin levels for the occurrence of hypogammaglobulinemia/immune-paresis. Administration of immunoglobulin for IgG level <400 mg/dL (excluding the M-spike in participants with IgG myeloma) is strongly recommended. In participants with IgG myeloma, evaluation of uninvolved immunoglobulins (IgA and IgM) can also be used to determine immune paresis and the need for immunoglobulin replacement. Participants are required to receive a prophylaxis against HSV/VZV and PJP infections during the course of the study (See Appendix 15).

6.8.8. COVID-19

All COVID-19 vaccines are permitted. COVID-19 vaccines received prior to study enrollment and during study participation should be collected in the CRF. The timing of vaccine administration relative to study intervention is at the discretion of the investigator although, if possible, it is best to avoid vaccine administration within 48 hours before or after the first and second doses of study intervention and to avoid the DLT observation period, if applicable. Discussions between the investigator and the sponsor regarding individual cases may occur if further clarification is required.

Participants with MM are at increased risk of severe disease and complications from COVID-19 infections.[40] Participants should be regularly educated on the continuing risk and symptoms of COVID-19 infection, best practices to reduce the risk of infection including mask usage, and the importance of regular testing including at home.

Participants are to be tested by PCR or antigen test for SARS-CoV-2 exposure before any elranatamab dosing (at any cycle) and upon suspected signs or symptoms of COVID-19 infection (eg, new or worsening fever, cough, sore throat, shortness of breath or fatigue). Frequent reflex testing is encouraged. A positive SARS-CoV-2 test result should be immediately reported to the study investigator and documented.

Participants who develop COVID-19 infection while on study should be treated in accordance with their treating healthcare provider's usual standard of care, local and/or regional guidelines, considering all treatments available to study participants, including

PAXLOVID™ and remdesivir. In accordance with standard of care practice, it is expected that initiation of treatment will start as soon as possible and ideally within 24 hours following a positive SARS-CoV-2 test.

For participants with SARS-CoV-2 infection, study intervention should be delayed for at least 14 days.

Recommendations from the American Society of Hematology and American Society for Transplantation and Cellular Therapy (ASH-ASTCT COVID-19 Vaccination for Hematopoietic Cell Transplant and CAR T Cell Recipients: Frequently Asked Questions), the European Society for Blood and Marrow Transplantation (Coronavirus Disease COVID-19: EBMT Recommendations), and Management of patients with multiple myeloma and COVID-19 in the post pandemic era: A consensus paper from the European Myeloma Network (EMN) should be followed [41-43].

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- 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 permanently discontinued, the participant will remain in the study to be evaluated for safety, disease assessments, subsequent anticancer therapies, and 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 review of concomitant treatments, contraception check, vital signs, and assessment for resolution of any treatment related AEs (see SoA for all activities).

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

Survival Long Term Follow-Up:

If the participant has not discontinued from study procedures, post-treatment study follow-up, and/or future collection of additional information, long term follow-up will continue as outlined in the SoA until the end of study (Section 4.4).

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

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

7.1.1. Potential Cases of Acute Kidney Injury

Abnormal values in SCr concurrent with presence or absence of increase in urea that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger confirmatory assessment of SCr as soon as practically

feasible, preferably within 48 hours from awareness. Confirmation that SCr relative to the participant's own baseline measurement is ≥0.3 mg/dL (or ≥26.5 μmol/L) should trigger immediate, supportive measures taken to correct apparent acute kidney injury and clinical evaluation—including detailed history, physical assessment, laboratory tests. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury (>50% decrease in eGFR compared to participant's baseline eGFR), with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study may include:

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

8.1. Efficacy Assessments

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

Disease assessments are to be conducted per SoA 28-day (±1 wk) interval whether dose given or not (ie, the 28-day interval [±1 wk] from C1D1 should be maintained regardless of dose delays/interruptions).

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

8.1.1. Laboratory Assessment for Evaluation of Disease Response

The following laboratory assessments will be performed locally for evaluation of disease response according to IMWG criteria. Assessments are to be conducted at the time points specified in the SoA. Assessments will include:

- SPEP for the measurement of all serum M proteins.
- Serum quantitative immunoglobulins (IgG, IgM, IgA, IgD, IgE) assessment is required for all participants at the time points specified in the SoA. In cases where SPEP is found to be unreliable (eg, IgA, IgD myeloma) for M-protein assessment, quantitative immunoglobulin measurements can be used for disease assessment. If used, quantitative immunoglobulin assessment must be used exclusively for a participant (ie, quantitative immunoglobulin and SPEP cannot be used interchangeably for disease assessment of the same participant). IgD or IgE are only required if the heavy chain component of the disease is known to be D or E.
- SIFE for definitive identification of specific M proteins (including IgG, IgA, IgM, and kappa and lambda light chains). SIFE will be required at baseline, when SPEP shows no measurable protein, at suspected CR/sCR and at suspected PD (clinical or biochemical).

- 24-hour UPEP for the measurement of urine M proteins. If any scheduled 24-hour UPEP is missed or is non-evaluable, a second attempt for collection of an evaluable specimen should be scheduled within 7 days of the missed assessment. For participants without measurable disease in the urine at baseline, UPEP is only required at suspected VGPR or CR/sCR, and at suspected PD (clinical or biochemical).

- 24-hour UIFE for definitive identification of specific M proteins (including IgG, IgA, IgM, and kappa and lambda light chains). UIFE will be required at baseline, when UPEP shows no measurable protein, at suspected CR/sCR and at suspected PD (clinical or biochemical).

- Involved and uninvolved serum FLC analysis, are required at screening, C1D1 and when both serum and urine M-components are deemed non-measurable (including at suspected CR). Serum free kappa, free lambda and free kappa/lambda ratio will be collected. Participants with measurable disease by SPEP or UPEP cannot have response assessed by serum FLC. Except for sCR, serum FLC levels should only be used for response assessment when both the serum and urine M component levels are deemed not measurable or uninterpretable. Serum FLC cannot replace UPEP/UIFE in any situation where urine M component is measurable at baseline.

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

On days of elranatamab administration, all samples will be collected prior to dosing.

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

PD must be confirmed (unless due to EMD). When PD (clinical or biochemical) is suspected, applicable tests (eg, SPEP, SIFE, UPEP, UIFE, serum FLC tests) should be repeated for confirmation prior to initiation of new anticancer therapy. To confirm PD, 2 discrete samples are required, and testing cannot be based upon the splitting of a single sample.

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

when the isotype is different. This may represent oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.

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

Imaging will be completed for evaluation of disease response according to IMWG criteria at the time points specified in the SoA. For paiiicipants with only skin involvement, skin lesions should be measmed with a mler at time points specified in the SoA.

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

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

Measurement of lesion size will be determined by the SPD.

Radiologic progression observed within the first month following the first dose of elranatamab will not be considered progressive disease.

Imaging obtained per the participant's standard of care prior to study enrollment and signing of consent do not need to be repeated and are acceptable to be used as baseline evaluation, if, (1) obtained within 42 days before start of study intervention, (2) the same technique can be used to follow identified lesions throughout the study for a given participant, and (3) appropriate documentation is available in the participant's source notes indicating that these assessments were performed as standard of care.

All participant's files and radiologic images must be available for source verification.

8.1.4. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's MM, including date of initial diagnosis, current stage Table 7), relevant disease characteristics, and prior treatments including systemic therapy, radiation, and/or stem cell transplant will be recorded on the CRF. Best response and date of disease progression (as applicable) for each prior treatment regimen will be recorded.

Table 7. Staging Systems for Multiple Myeloma

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta-2 microglobulin < 3.5 mg/L, Serum albumin ≥ 3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH[a] and Serum LDH < the upper limit of normal
II	Not ISS stage I or III	Not R-ISS stage I or III

Table 7. Staging Systems for Multiple Myeloma

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
III	Sernm beta-2 microglobulin 2:: 5.5 mg/L	ISS stage III and either: - high-risk chromosomal abnormalities by FISHb or -Sernm LDH > the upper limit of normal

a. Standard risk chromosomal abnonnalities by FISH= no high-risk chromosomal abno1mality.
b. High risk chromosomal abnonnalities by FISH= Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Source: Palumbo et al, 2015.(45]
Note: IfFISH results not available, karyotyping results can be used.

CCI

CCI [redacted]

8.2. Safety Assessments

Planned time points for all safety assessments are provided in SoA. Unscheduled clinical laborato1y measurements may be obtained at any time during the study to assess any perceived safety issues.

Data collected at screening that are used for inclusion/exclusion criteria, such as laborato1y data, ECGs and demographic data collected at screening will be repo1ied on the CRF.

8.2.1. Participant Demographics and Other Baseline Characteristics

Demographic data and medical histo1y will be collected at screening by the investigator or qualified designee, including relevant medical and surgical histo1y, and cmTent illnesses.

8.2.2. Physical Examinations

Physical examinations will be perfo1med at time points specified in the SoA. All physical examination data (not including neurological examinations, see below) collected during the course of the study will be considered source data only and will not be required to be repo1ied on the CRF. At screening, a comprehensive physical examination should be conducted including, general appearance, head, skin, neck, eyes, ears, nose, throat, mouth, lungs, heaii, abdomen, lymph nodes, extremities, musculoskeletal, and a thorough neurologic examination (see below). For subsequent visits, physical examinations may be tai·geted as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Neurological exaininations including assessment of mental state, motor function, senso1y function, gait, station, deep tendon reflexes, cranial nerve function and coordination will be peifonned at times specified in the SoA. All neurological examinations will be reported on the CRF.

All physical examinations, including neurological exaininations, occuning on dosing days must be perfo1med prior to eh-anatamab administration. Any treatment-emergent abnonnal physical/neurological examination findings will be recorded as AEs.

Screening weight and height will be repo1ied on the CRF.

Baseline encephalopathy assessment will be performed using the ICE tool (Lee et al 2019[48]), (Appendix 12) at ClDl. The ICE tool will also be used as pali of assessing each suspected !CANS event.

Physical exaination findings collected during the study will be considered source data and will not be required to be reported, unless othe1wise noted. Any untoward physical examination findings that are identified during the active collection period and meet the

definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.3. Vital Signs

Vital signs (temperature, HR, BP and O_2 saturation) should be collected per institutional standards at time points specified in the SoA prior to blood collection (all study parts). Pre-dose vital signs collected on C1D1, C1D4, C1D8, C1D15, C1D22 and C2D1 (for Part 2 only) should be reported in the CRF. If performed, abnormal vital signs associated with AEs (eg, CRS or an infection) should be reported in the CRF.

Vital signs should be monitored at least every 4 hours (±30 minutes) during the first 48 hours after first dose of study intervention and 24 hours after second dose of study intervention. For participants in Part 2, vital signs should be monitored at least every 4 hours (±30 min) during 24 hours after dosing on C2D1 (the latter may not be required for Part 2B and Part 2C depending on whether CRS is observed after C2D1 dose in Part 2A). In Part 1, an optional day of hospitalization may be considered for the first RP2D dosing (116 mg or 152 mg) Q4W depending on CRS profile observed in Part 2A and Part 2B. All these vital signs data should be reported in the CRF.

All vital sign measurements occurring on dosing days must be performed prior to elranatamab administration (and prior to premedications, as applicable) and blood collection. Abnormal vital sign results identified after the first dose of elranatamab and during the active collection period (as defined in Section 8.3.1) constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy or require changes in elranatamab dosing.

8.2.4. Electrocardiograms

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

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

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

baseline **and** is ≥450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

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

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

8.2.5. Echocardiograms/Multigated Acquisition Scans

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

8.2.6. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

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

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

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

All safety laboratory tests will be performed locally.

8.2.7. Pregnancy Testing

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

8.2.8. ECOG Performance Status

ECOG PS (Table 8) will be assessed at Screening.

Table 8. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

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

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

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

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

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

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

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

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

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 permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Electronic Data Collection Tool.

Investigators are not obligated to actively seek information on AEs or SAEs after the active collection period. However, if the investigator learns of any SAE, including a death, at any time after the active collection period, and the investigator considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Electronic Data Collection Tool.

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 Electronic Data Collection Tool immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for 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 or 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 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

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

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until pregnancy completion (or until pregnancy termination).

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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

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

8.3.5.3. Occupational Exposure

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

8.3.6. Cardiovascular and Death Events

Please refer to Appendix 7 for ECG findings of clinical significance and to Appendix 3 for reporting of deaths.

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

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the Electronic Data Collection Tool.

8.3.8.1. Cytokine release Syndrome

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

The severity of CRS will be assessed according to the ASTCT consensus criteria. See Appendix 12.

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

8.3.8.2. Immune Effector Cell-Associated Neurotoxicity Syndrome

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”.[48] It has been observed following administration of some CAR T-cells and BsAbs, and can occur independently of CRS.

The severity of ICANS will be graded according to the ASTCT consensus criteria. See Appendix 12, Section 10.12.

Additional management for Grade ≥3 CRS and ICANS is described in Section 9.4.1

8.3.8.3. 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.[49] Recently, peripheral neuropathy has been described following administration of BCMA-directed bispecific T-cell engagers.[30]

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

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

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

8.3.8.4. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

Safety Event	Recorded on the CRF	Reported Via the Electronic Data Collection Tool to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

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

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

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

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

Medication errors should be reported to Pfizer Safety within 24 hours on via the Electronic Data Collection Tool only when associated with an SAE

8.4. Pharmacokinetics

All participants will have blood samples collected for PK assessments of elranatamab serum concentrations at the time points specified in the SoA. In the event of suspected CRS, unexpected or serious AE, or AE leading to discontinuation of study intervention, additional PK samples should be collected if not already scheduled. The actual date/time of sample collection should be documented in the CRF. For each time point, blood samples of approximately 5 mL, to provide a minimum of 2 mL serum, will be collected for measurement of serum concentrations of elranatamab. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of PK sample collection will be recorded in the CRF.

The actual times may change, but the number of samples will remain the same. All effort should be made to obtain the samples at the exact nominal time relative to dosing (see SoA). Collection of samples up to and including 48 hours after dose administration that are obtained within 10% of the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the CRF. For predose PK

samples, collection should occur prior to administration of elranatamab (and prior to premedications if applicable) on that day.

Samples will be used to evaluate the PK of elranatamab. Each senun sample will be divided into 2 aliquots, to provide a minimum of 1 mL sernm for each aliquot. Samples collected for analyses of elranatamab sernm concentration may also be used to evaluate safety or efficacy aspects related to concerns arisin durin or after the stud and/or evaluation of the bioanalytical method, CCI

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

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

Refer to the lab manual for detailed collection, processing and shipping procedures.

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8.7. Immunogenicity Assessments

Blood samples of approximately 5 mL, to provide a minimum of 2 mL sennn, will be collected for detennination of ADA and NAb into appropriately labeled tubes at times specified in the SoA. Instmctions for the collection and handling of biological samples will be provided in the laborato1y manual. The actual date and time (24 hour clock time) of each sample will be recorded.

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

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Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples detennined to be positive for ADA may be fmiher chai·acterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sainple 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 detennination as to whether sample integrity has been compromised.

As pa1i of understanding the immunogenicity of the investigational product, samples may be used for evaluation of the bioanalytical method and/or additional characterization of an observed immuno enici , res onse. CCI [redacted]

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters ai·e not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summaiy and statistical analyses of the data collected in this study is outlined here and fmiher detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the prima1y endpoint definitions or their analyses will also be reflected in a protocol ainendment.

9.1. Statistical Hypotheses

The primary endpoint of this study is Grade ≥2 CRS rate for Part 1 & Part 2. No hypothesis for statistical significance will be tested. Instead, a Bayesian design will be used to estimate the true Grade ≥2 CRS rate in Part 1 and 2. Details are described in Section 9.5.

9.1.1. Estimands

9.1.1.1. Primary Estimand

The primary estimand is the treatment effect of elranatamab with a dosing regimen that includes 2 step-up priming doses with premedication on the rate of Grade ≥2 CRS as assessed by ASTCT criteria. It is defined by the following attributes:

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least one dose of study intervention elranatamab.
- Variable: Incidence of Grade ≥2 CRS as assessed by ASTCT criteria during C1.

  The intercurrent event is treatment discontinuation due to any reason, and is addressed by the treatment condition of interest attribute. All data collected after an intercurrent event of treatment discontinuation will be excluded
- Population-level summary: The median and its corresponding 2-sided 90% credible interval of Grade ≥2 CRS rate in the analysis population based on the posterior distribution.

9.1.1.2. Secondary Estimand

The secondary estimand is DLT rate estimated based on data from DLT-evaluable participants in Part 2A and Part 2C during the DLT observation period. It is defined by the following attributes:

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment and either experience DLT(s) during the DLT observation period or complete the DLT observation period without DLT. Participants without DLTs who receive less than the planned doses of the study intervention are not evaluable for DLTs.
- Variable: Occurrence of DLTs during the DLT observation period.
- Treatment condition: At least 1 dose of study intervention of elranatamab.
- Population-level summary measure: DLT rate defined as the number of DLT-evaluable participants with DLTs in the DLT observation period divided by the number of DLT-evaluable participants.

9.2. Analysis Sets

For pmposes of analysis, the following analysis sets are defined for Pait 1 and Pait 2, respectively.

Partici ant Anal sis Set	Descri tion
Safety Analysis Set	All emolled paiticipants who receive at least 1 dose of study inteivention.
DLT Evaluable Set	All emolled paiticipants in Pait 2A and Pait 2C who received the planned 2 doses of 116 mg or 152 mg of study inteivention dming the DLT obseivation pedod or who received at least 1 dose of 116 mg or 152 mg of study inteivention and expeiience DLT(s) dming the DLT obseivation eriod.
PK Analysis Set	The PK analysis set will include all paiticipants in the safety analysis set who have at least 1 postdose concentration measmement. The PK pai·ameter analysis set will include all paiticipants in the safety analysis set who have at least 1 of the PK pai·ameters of interest for eh·anatamab.
CCI [redacted]	[redacted]
Immunogenicity Analysis Set	[redacted] le tested for ADA.
CCI [redacted]	[redacted]

Note: "Emolled" means a paiticipant's, or his or her legally auth01ized representative's, agreement to paiticipate in a clinical study following completion of the infoimed consent process and was assigned to treatment. Potential paiticipants who ai·e screened for the pmpose of deteimining eligibility for the study, but do not pa1ticipate in the study, are not considered emolled, unless otheiwise specified by the protocol.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses ai·e peifonned and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a sUilllnaiy of the planned statistical analyses of the primaiy and secondaiy endpoints.

9.3.1. General Considerations

Unless otherwise specified, all analyses will be performed for each part (Part 1, Part 2) separately and for Part 1 and Part 2 combined. All efficacy analyses and safety analyses will be performed using the Safety Analysis Set.

No formal statistical testing will be conducted on this study. In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category. Time to event variables will be summarized using Kaplan-Meier estimates (product-limit estimates) together with a summary of associated statistics including the median time with 2-sided 95% CIs. Probabilities of an event at particular time points may be estimated with corresponding 2-sided 95% CIs.

9.3.2. Primary Endpoint/Estimand/Analysis

Grade ≥2 CRS rate during C1

The primary endpoint for Part 1 & Part 2 combined is Grade ≥2 CRS rate during C1, defined as the proportion of participants in the Safety Analysis Set experiencing Grade ≥2 CRS as assessed by ASTCT criteria.

The median and its corresponding 2-sided 90% credible interval based on the posterior distribution of Grade ≥2 CRS rate will be calculated. In addition, point estimates of Grade ≥2 CRS rate will be calculated along with the 2-sided 90% CIs using the Clopper-Pearson method (exact CI for a binomial proportion).

9.3.3. Secondary Endpoints/Estimands/Analyses

9.3.3.1. Secondary Safety Endpoint

Incidence of DLTs (Part 2A and Part 2C only)

The number and proportion of participants experiencing DLTs during the DLT observation period will be summarized and listed by dose level. Analyses of DLT will be performed on DLT Evaluable Analysis Set (as defined in Section 9.2).

Overall Safety Profile and Tolerability

AEs as characterized by type, frequency, severity, timing, seriousness, and relationship to elranatamab (Part 1 and Part 2). Laboratory abnormalities as characterized by type, frequency, severity and timing.

AEs (except CRS and ICANS) will be graded by the investigator according to NCI CTCAE v5.0 and coded using MedDRA. CRS and ICANS will be assessed according to the ASTCT criteria (See Appendix 13) and coded using MedDRA. AEs will be presented with

and without regard to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described.

Additional summaries will be provided for AEs that are observed with higher frequency and for AESIs identified in Section 8.3.8.

Clinical laboratory data will be classified by grade according to NCI CTCAE v5.0 and will be analyzed using summary statistics. The worst on-treatment grades during the treatment period will be summarized. Shifts in toxicity grading from baseline to highest grade during the on-treatment period will be displayed. Results for laboratory tests that are not part of NCI CTCAE will be presented as below, within, or above normal limits. Only participants with post-baseline laboratory values will be included in these analyses. Further details of analyses for all the laboratory parameters will be provided in the SAP.

9.3.3.2. Secondary Efficacy Endpoints

Objective Response Rate

ORR is defined as the proportion of participants in the Safety Analysis Set with an objective response per IMWG response criteria as determined by investigator.

Complete Response Rate

CRR is defined as the proportion of participants in the Safety Analysis Set with a BOR of confirmed sCR/CR per IMWG response criteria as determined by investigator.

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

Duration of Response

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

DOR will be censored on the date of the last adequate disease assessment for participants who do not have an event (PD or death due to any cause), on the date of the last adequate disease assessment before the new anti-cancer therapy for participants who start a new anti-cancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments.

DOR will be summarized using Kaplan Meier method and displayed graphically. Median DOR and 2-sided 95% CI (based on the Brookmeyer-Crowley method) will be provided.

Duration of Complete Response

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

DOCR will be censored on the date of the last adequate disease assessment for participants who do not have an event (PD or death due to any cause), on the date of the last adequate disease assessment before the new anti-cancer therapy for participants who start a new anti-cancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments.

DOCR will be summarized using Kaplan Meier method and displayed graphically. Median DOCR and 2 sided 95% CI will be provided.

Progression-free Survival

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

PFS will be censored as follows:

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

PFS will be summarized using Kaplan Meier method and displayed graphically. Median PFS and 2-sided 95% CI will be provided.

Overall Survival

OS is defined as the time from the date of first dose until death due to any cause. Survival status is expected to be collected irrespective of study intervention discontinuation or

paiticipant's request to discontinue study procedures. All paiticipants who have not withdrawn consent for fmther paiticipation in the study should be followed for survival until the end of the study. OS for paiticipants not known to have died are censored on the date of last known alive.

OS will be summarized using Kaplan Meier method and displayed graphically. Median OS and 2-sided 95% CI will be provided.

Time to Response

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

TTR will be summarized using mean, standai·d deviation, minimum, median, and maximum.

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9.3.3.3. Pharmacokinetic Analyses

PK data analyses will include descriptive smnmai·y statistics of the predose and postdose sernm concentrations of eh-anatamab by cohort, study visit and time point. In addition, the PK data from this study may be pooled with other studies to develop a population PK model. The coITelation between eh-anatainab Cmax-24 after the first step-up dose (ie, 4 mg) and the probability of All Grade and Grade 2 and higher CRS will be evaluated; other relevant PK meti·ics may be explored. The results of these analyses coITelating eh-anatamab exposure to probability of CRS will be repo1ted in the clinical study repo1t or a sepai·ate modeling repo1t. The coITelations between eh-anatamab exposure parameters and phaimacodynainic biomarker including cytokine data, efficacy and/or other safety outcomes will also be explored. The results of these modeling analyses may be repo1ted separately from the clinical study repo1t.

9.3.3.4. Immunogenicity Analyses

For illllllunogenicity data, the percentage of participants with at least one positive, post dose ADA will be smnmarized. Listings and Sllllllnaiy tabulations of the ADA data at baseline and post-first dose will be generated. Samples testing ADA positive will also be analyzed for the presence of NAb, and results will be similai·ly Sllllllnai·ized. For paiticipants with positive ADA or NAb, the magnitude (titer), time of onset, and duration of ADA or NAb response will also be described. The potential impact of immunogenicity on PK and clinical response

including phannacodynamic markers, safety/tolerability and efficacy will be explored, if wairnnted by the data.

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9.3.5. Other Safety Analyses

All safety analyses will be perfo1med on the Safety Analysis Set.

AEs, ECGs and safety laborato1y data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of paiiicipants. Any clinical laborato1y, ECG and PR abnonnalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical fonnat and summarized descriptively, where appropriate.

Medical histo1y and physical exainination and neurological examination infonnation, as applicable, collected during the course of the study will be considered source data and will not be required to be repo1ied, unless othe1wise noted. However, any untoward findings identified on physical and/or neurological exaininations 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 ai·e used for inclusion/exclusion criteria, such as laborato1y data, ECGs, and vital signs, will be considered source data, and will not be required to be repo1ied, unless othe1wise noted. Demographic data collected at screening will be repolied.

9.3.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG pai·aineters QT interval, heaii rate, QTcF interval, PR interval, and QRS complex will be smmnai·ized by treatment and time.

The number (%) of pa1ticipants 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	c::450-480	>480-500	>500
Increase from baseline		30-60	>60

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

9.3.5.2. Adverse Events

AEs (except CRS and ICANS) will be graded by the investigator according to NCI CTCAE version 5.0 and coded using Med.ORA. CRS and ICANS will be assessed according to ASTCT criteria (See Appendix 12) and coded using Med.ORA. AEs will be characterized by type, frequency, severity, timing, seriousness, and relationship to ehanatamab. AEs will be presented with and without regai·d to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity Grades 1 through 5, will be described. Additional summaries will be provided for AEs that ai·e observed with higher frequency and for AESis identified in Section 8.3.8, including CRS and ICANS.

9.3.5.3. Laboratory Test Abnormalities

Clinical laborato1y data will be classified by grade according to NCI CTCAE version 5.0 and will be analyzed using summaiy statistics. The worst on-treatment grades during the treatment period will be summarized. Shifts in toxicity grading from baseline to highest grade during the on-treatment period will be displayed. Results for laborato1y tests that ai·e not pa1t of NCI CTCAE will be presented as below, within, or above n01mal liinits. Only paiticipants with post-baseline laborato1y values will be included in these analyses. Fmther details of analyses for all the laborato1y pai·ameters will be provided in the SAP.

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9.4. Interim Analyses

9.4.1. Interim Safety Assessments

futerim safety assessments will be perfonned on this study and will be perfo1med on Pait 1 and 2 combined.

An internal safety review team will review cumulative safety data during the study conduct (see Section 10.1.5.1). In addition, the incidence of the following events will each be monitored by the Sponsor throughout the study. The review results and decisions will be documented in the study TMF.

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

If the number of participants observed to have such identified events exceeds a prespecified threshold, the study will be placed on a temporary enrollment hold by the sponsor. During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. Participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the investigator in consultation with the sponsor. In the event that any criteria for the temporary enrollment hold are met, written notification documenting the reason for the temporary hold and/or termination will be provided by the sponsor to the investigators, the EC/IRBs, the regulatory authorities, and any CRO(s) used in the study.

The criteria for placing the study on temporary hold for the following safety reasons are based on Bayesian posterior probabilities. Using a non-informative Beta (0.5, 0.5) prior distribution, if the number of participants observed to have Grade 3 or 4 CRS results in a $\geq$ 0.80 posterior probability that the true Grade 3 or 4 CRS rate exceeds 20%, the study will be put on a temporary hold. Separate but similar criteria will be used for participants with Grade 3-4 ICANS and treatment-related Grade 4 non-hematologic events (excluding CRS and ICANS). Table 9 summarizes the minimum number of participants with such identified events that would meet the above criteria.

Table 9. Minimum Number of Participants With Identified Events That Would Prompt Temporary Enrollment Hold (CRS, ICANS, Non-hematologic treatment-related AEs)

Number of Evaluable Participants	10-13	14-18	19-22	23-26	27-30	31-35	36-39
Minimum number of participants with Grade 3-4 CRS events that would lead to a temporary enrollment hold*	4	5	6	7	8	9	10

Table 9. Minimum Number of Participants With Identified Events That Would Prompt Temporary Enrollment Hold (CRS, ICANS, Non-hematologic treatment-related AEs)

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

Prior distribution: Beta (0.5,0.5)
Criteria for 40 or more evaluable participants will be calculated such that the study will be put on temporary hold if the posterior probability that the true event rate exceeds 20% is greater than or equal to 0.80.
Evaluable participants are defined as those who have received at least 1 dose of study treatment having an identified event or those without such an event who have been followed for at least 28 days from first dose.
* The study will be put on temporary hold as soon as the minimum number of evaluable participants with the identified AEs has reached the threshold (eg, if there are 4 participants experiencing the identified AE out of the first 6 evaluable participants, the study will be put on hold). A minimum of 4 events are required to trigger a temporary hold.

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

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

Table 10 summarizes the minimum number of evaluable participants with such identified events that would meet the above criteria.

Table 10. Minimum Number of Participants With Identified Treatment-Related Events That Would Prompt Temporary Enrollment Hold (GBS/GB-like AEs, Peripheral Neuropathy/IR Neurologic AEs)

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

Prior distribution: Beta (0.5,0.5)

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

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

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

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

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

9.4.2. Interim Analysis for Futility

An interim analysis for futility will be performed on the 30 participants enrolled and treated in Part 1 to assess the safety of elranatamab in terms of CRS rate using a dose regimen with 2 step-up priming doses. The primary endpoint of Grade ≥2 CRS rate during C1 will be evaluated at this analysis using a futility boundary based on the predictive probability assuming a Beta (0.7, 1.3) prior. More specifically, the study may stop for futility if the predictive probability of observing 20 or fewer participants with Grade ≥2 CRS events in 76 participants at the primary analysis based on the data observed at the interim analysis is less than 10%. With 30 participants at the interim analysis, if there are 11 or more participants with Grade ≥2 CRS events, further accrual may be stopped for the study. Otherwise, the study will proceed as planned to the primary analysis as described in Section 9.3.2.

The interim futility analysis will be conducted once the 30 participants in Part 1 either complete C1 of study intervention or discontinued the study intervention prior to C1. The exact futility boundary will be updated prior to the time of the analysis based on the actual number of participants enrolled and treated.

The interim analysis may also be performed at other time points for the purpose of safety assessment and/or supporting clinical development. The exact futility boundary will be updated prior to the time of the analysis based on the actual number of participants enrolled and treated. Table 11 summarizes the futility boundary in terms of number of participants with Grade ≥2 CRS events at the interim analysis.

Table 11. Futility Boundary (Number of Participants with Grade ≥2 CRS Events) at the Interim Analysis

Number of participants at the interim analysis	15-17	18-21	22-24	25-27	28-31	32-35	36-38	39-42
Minimum # of participants with Grade ≥2 CRS events at the interim analysis to stop the study for futility	7	8	9	10	11	12	13	14

The internal core study team will review the interim futility analysis results and document all decisions in the study TMF. The analysis details will be documented and approved in the SAP.

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve approximately 76 participants enrolled and treated in both Part 1 and Part 2. This sample size is based on the primary endpoint of rate of Grade ≥2 CRS as assessed by ASTCT criteria during Cycle 1 (Section 9.3.2). Approximately 30 participants will be enrolled and treated in Part 1, approximately 8 to 16 participants will be enrolled in Part 2A for DLT evaluation, approximately 22 participants will be enrolled to have at least 15 participants treated for 2 cycles in Part 2B and approximately 8 participants will be enrolled and treated in Part 2C.

The actual number of participants in each part may change depending on the tolerability assessment in Part 2A. If Dose level 1 in Part 2A is deemed intolerable, the study will complete the enrollment in Part 1 only for a total of approximately 76 participants.

9.5.1. Primary Endpoint

A Bayesian dual-criterion design [3] will be used to estimate the primary endpoint of the true Grade ≥2 CRS rate during C1. With this design, the following criteria are defined:

- Bayesian statistical significance: Substantial evidence that the true Grade ≥2 CRS rate exceeds a pre-specified value. For this study, Bayesian statistical significance will be achieved if the posterior probability of the true Grade ≥2 CRS rate exceeding 35% is <10%;

- Clinical relevance: The maximum number Grade ≥2 CRS events threshold that could justify further clinical development. For this study, it is defined as the median of the posterior distribution of the true Grade ≥2 CRS rate is ≤ 27%.

The analysis will use a Beta-binomial model (binomial sampling for number of Grade ≥2 CRS events and a beta prior distribution). A minimally informative beta prior distribution of the true Grade ≥2 CRS rate will be used. It is assumed a priori that the true mean Grade ≥2 CRS rate is 35%, so the prior distribution will be Beta (0.7, 1.3). Using this prior and based on the dual criteria defined above, approximately 76 participants will be enrolled and treated and a maximum of 20 participants with Grade ≥2 CRS events is allowed to meet the dual criteria in 76 participants. If exactly 20 participants in 76 participants experience Grade ≥2 CRS events, the observed Grade ≥2 CRS rate is 26.3% with median 26.3% and 90% credible interval of (18.7%, 35.0%) based on the posterior distribution.

The primary analysis will be conducted once all participants have completed Cycle 1 of study intervention or have otherwise discontinued the study intervention.

Table 12 presents the operating characteristics of this 2-stage design, ie, the probability of early trial termination at the interim futility analysis and the probability of observing the critical number of Grade ≥2 CRS (ie ≤ 20 participants with Grade ≥2 CRS events in 76 participants) at the primary analysis if the true Grade ≥2 CRS rate is 20%, 21%, 22%, 23%, 27% and 35%, respectively. For example, if the true Grade ≥2 CRS rate = 22%, the probability of stopping the study due to futility at the interim analysis is 0.048, and the probability of observing ≤ 20 participants with Grade ≥2 CRS rate at the primary analysis is 0.835.

Table 12. Operating Characteristics of Bayesian 2-Stage Dual-Criterion Design for Grade ≥2 CRS rate

True Grade ≥2 CRS Rate	Prob of Exceeding Futility Boundary at the Interim (R1/N1 ≥11/30)	Prob of GO Decision at the Primary Analysis* (R/N ≤ 20/76 and R1/N1 <11/30)	Prob of No-GO Decision at the Primary Analysis* (R/N > 20/76 and R1/N1 <11/30)
20%	0.026	0.919	0.055
21%	0.036	0.882	0.082
22%	0.048	0.835	0.116
23%	0.064	0.779	0.157
27%	0.161	0.488	0.351
35%	0.492	0.065	0.443

* The study does not meet futility criteria at the interim analysis and continues to the primary analysis.
CRS = cytokine release syndrome;
R1 = Number of participants with Grade ≥2 CRS events required at the interim futility analysis to stop the study for futility;
N1 = Number of participants at the interim analysis;
R = Number of participants with Grade ≥2 CRS events required to meet the dual criteria at the primary analysis;
N = Number of participants at the primary analysis.

At the time of the primary analysis, the critical number of participants with Grade ≥2 CRS events to be observed will be updated based on the actual number of participants enrolled and treated.

An interim analysis for non-binding futility will be conducted on the 30 participants enrolled and treated in Part 1 of the study. Details are described in Section 9.4.2.

9.5.2. Part 2A and Part 2C

In Part 2A and 2C, approximately 8 participants at each dose level will be enrolled and treated to ensure at least 6 DLT evaluable participants (as defined in Section 9.2) to be evaluated. If any participant is deemed non-evaluable for DLT, additional participants may be enrolled to ensure there are a sufficient number of evaluable participants in Part 2A.

A BLRM will be utilized for dose determination in Part 2A as well as dose opening in Part 2C. The dosing decision and estimation of the RP2D of elranatamab will be guided by the estimation of the posterior probability of DLT in the DLT observation period. Other evidence such as safety data beyond DLT window, clinical activity, PK, and PD data will also be evaluated in determining RP2D. After each dosing cohort of participants completes the DLT observation period, the posterior distribution for the risk of DLT for each dose level will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals.

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

Dosing decisions are guided by the EWOC principle.[50] A dose level may only be used for the next dosing cohort of participants if the risk of excessive toxicity ([0.33, 1]) at that dose level is less than 25%.

Table 13 shows some hypothetical dose escalation data scenarios and the corresponding recommendations for the next dose. For example, in Scenario 1, if 1 participant experiences a DLT out of 6 DLT-evaluable participants at 116 mg Q2W dose level, the recommendation is to escalate to the next dose level (152 mg Q2W) with probability of overdosing of 0.083 at 152 mg dose level. In Scenario 3, if 3 participants experience DLTs out of 6 DLT-evaluable participants at 116 mg Q2W dose level, the dose level is deemed too toxic, and the dose finding process will stop with no RP2D identified.

For Part 2C, the dose level to be explored (116 mg QW or 152 mg QW) depends on the toxicity profile observed in Part 2A. For example, if there is 0 DLT in 6 DLT-evaluable participants at both Dose level 1 and Dose level 2 in Part 2A, respectively, then 152 mg QW may be evaluated in Part 2C. However, if there is 1 DLT observed in 6 DLT-evaluable participants at both Dose level 1 and Dose level 2 in Part 2A, respectively, then 116 mg QW may be evaluated in Part 2C.

Table 13. Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose

Scenarios	Elranatamab Dose Evaluated (mg; SC)	D/N	Elranatamab Next Dose (mg; SC)	Pr(TT) at Next Dose	Pr(OD) at Next Dose
1	116 Q2W	1/6	152 Q2W	0.362	0.083
2	116 Q2W	2/6	116 Q2W	0.461	0.161
3	116 Q2W	3/6	N/A	N/A	N/A
4	152 Q2W 116 Q2W	1/6 0/6	152 Q2W	0.199	0.010
5	152 Q2W 116 Q2W	1/6 1/6	152 Q2W	0.408	0.048
6	152 Q2W 116 Q2W	2/6 1/6	152 Q2W	0.555	0.147
7	152 Q2W 116 Q2W	3/6 1/6	116 Q2W	0.582	0.167

Table 13. Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose

Scenarios	Elranatamab Dose Evaluated (mg; SC)	D/N	Elranatamab Next Dose (mg; SC)	Pr(TT) at Next Dose	Pr(OD) at Next Dose
8	152 Q2W 116 Q2W	0/6 0/6	152 QW	0.283	0.058
9	152 Q2W 116 Q2W	1/6 1/6	116 QW	0.519	0.188

Abbreviations: D=number of participants with DLT, N=number of DLT-evaluable participants; mg=milligrams; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; QW=once weekly; Q2W=once every two weeks; SC=subcutaneous.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their 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 (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or their 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 or their legally authorized representative must be informed that their 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 or their legally authorized representative.

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

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

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

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

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

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

10.1.4. Data Protection

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

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

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

An internal safety review team will monitor safety and tolerability on an ongoing basis, and the internal core study team will review and evaluate the safety data including Grade ≥ 2 CRS incidence at the interim futility analysis.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in 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/CTIS

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

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available

18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data and its origin can be found in the Study Monitoring Plan which is maintained by the sponsor.

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

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

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

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant’s first visit..

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to)

regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

10.1.10. Publication Policy

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

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

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, “publication”) before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the

investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.11. Sponsor’s Qualified Medical Personnel

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

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

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

10.2. Appendix 2: Clinical Laboratory Assessments

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 14. Protocol Required Safety Laboratory Assessments (locally performed)

Hematology	Chemistry	Other
• Hemoglobin • Platelet count • WBC count • Plasma cell count Absolute: • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes • Plasma cells Database should be constructed to allow capture of WBC differential counts as percent and absolute values but only 1 or the other should be used by the site to collect data. Results will be reported as absolute values after conversion and graded according to the CTCAE criteria	• BUN (or blood urea) • Creatinine • Glucose (non-fasting) • Total Calcium • Sodium • Potassium • Chloride • Magnesium • Phosphorus or Phosphates • AST, ALT[c] • Total bilirubin • Alkaline phosphatase • Albumin • Chloride • Total CO_2 (bicarbonate) • Total Protein • Lactate dehydrogenase (LDH)[a] • Uric acid[a] • Serum beta-2 microglobulin[a,d]	• CMV by quantitative PCR • PT/INR • For female participants of childbearing potential Pregnancy test (β-hCG) [b] • HBV tests (HBsAg and HBcAb, HBsAb) [e]HCV Ab[e] • SARS-CoV-2 testing[f]

a. At baseline (minimum) and as clinically indicated.
b. For female participants of childbearing potential only. Serum test is required at screening; for other time points, urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC.
c. For Hy's law potential cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.
d. Required for multiple myeloma staging.
e. To be performed at screening or as clinically indicated per PI assessment throughout study period. In the case of apparent ongoing HBV or HCV infection, reflex serum DNA or RNA viral load testing, respectively, will be performed if required by local regulation.
f. From protocol amendment 4, PCR or antigen test are required predose on Day 1 (CXD1) and upon suspected exposure to SARS-CoV-2 and at signs or symptoms of COVID-19 infection.

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

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occunence in a patient or clinical study pa1ticipant, 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 abnonnal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnonnal laborato1y test results (hematology, clinical chemistiy, or minalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measmements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnonnal laborato1y 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/smgical intervention; • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant dmg treatment, or other therapy. • Exacerbation of a chronic or intennittent preexisting condition, including either an increase in :frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administi·ation, even though it may have been present before the strut of the study. • Signs, symptoms, or the clinical sequelae of a suspected dmg-dmg interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study inte1vention or a conc01nitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-haiming intent. Such overdoses should be repo1ted regai·dless of sequelae.

Events	Meeting the AE Definition
•	Any clinically significant abnonnal laborato1y findings or other abnonnal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiiicipant'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 paiiicipant's condition.
•	Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
•	Situations in which an untowai·d medical occunence 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 sta1i 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 repolied as AEs.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed below:
a. **Results in death**
b. **Is life-threatening** The te1m "life-threatening" in the definition of "serious" refers to an event in which the paiticipant was at risk of death at the time of the event. It does not refer to an event that hypothetically inight have caused death if it were more severe.
c. **Requires inpatient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the paiiicipant has been detained (usually involving at least an overnight stay) at the hospital or emergency wai·d for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect.

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

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

g. Other situations:

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

leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Severity section).

10.3.3. Recording/Reporting and FollowUp of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for repo1iing SAEs on the CT SAE Repo1i Fo1m to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Repo1i Fo1m for repo1iing of SAE information is not the same as the AE page of the CRF. When the same data are collected, the fonns must be completed in a consistent manner. AEs should be recorded using concise medical tenninology and the same AE te1m should be used on both the CRF and the CT SAE Repo1i Fo1m for repo1iing of SAE infonnation.

Safety Event	Recorded on the CRF	Reported Via the Electronic Data Collection Tool or on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with exposure during pregnancy or breastfeeding **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are repo1ied (whether or not there is an associated SAE)* All instances ofEDB are repo1ied (whether or not there is an associated SAE). **
Environmental or occupational exposure to the product under study to a non-paiiicipant (not involving EDP or EDB).	None. Exposure to a study non-pa1iicipant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be repo1ied.***

* **EDP** (with or without an associated AE or SAE): any pregnancy infonnation is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is repo1ted to Pfizer Safety using the CT SAE Repo1t Form.

** **EDB** is repo1ted to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Fo1m.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laborato1y repo1is, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE info1mation in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the paiiicipant's medical records to Pfizer Safety in lieu of completion of the Electronic Data Collection Tool/CT SAE Repo1i Fonn/AE or SAE CRF page.
- There may be instances when copies of medical records for ce1iain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the paiticipant 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 info1mation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Severity

The investigator will make an assessment of severity for each AE repo1ied during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE system). An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	Clinical Description of Severity
1	MILDAE
2	MODERATEAE
3	SEVEREAE
4	LIFE-THREATENING; urgent intervention indicated
5	DEATH RELATED TO AE

The severity of CRS and ICANS will be graded according to ASTCT criteria.[48] See Appendix 12.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occmTence of each AE or SAE. The investigator will use clinical judgment to detennine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arglllllents to suggest a causal relationship, rather than a relationship cannot be mled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product infonnation, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **!!!!!.ll** doclllllent in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occmTed and the investigator has minimal infonnation 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 infonnation and send an SAE follow-up repo1i with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulato1y reporting requirements.
- If the investigator does not know whether or not the study inte1vention caused the event, then the event will be handled as "related to study inte1vention" for repo1iing pmposes, as defined by the sponsor. In addition, if the investigator dete1mines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and repo1i such an assessment in the dedicated section of the Electronic Data Collection Tool or CT SAE Repo1i Fo1m and in accordance with the SAE repo1iing requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perfo1m or atTange 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 folly as possible. This may include additional laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated info1mation will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the infonnation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primaiy mechanism for repo1ting 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) to repo1t the event within 24 hours. • The site will enter the SAE into the electronic data collection tool (ie eSAE) or paper fonn (as applicable) as soon as the data ai·e available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the enby of new data or changes to existing data. • If a site receives a repo1t of a new SAE from a study paiticipant or receives updated data on a previously repo1ted SAE after the electi·onic data collection tool has been taken off-line, then the site can repo1t this info1mation on a paper SAE fonn (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile trnnsmission of the CT SAE Repo1i Fo1m is the preferred method to transmit this infonnation to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Repo1i Form sent by overnight mail or couner service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Repo1i Fo1m pages within the designated repo1iing time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

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

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

10.4.3. Woman of Childbearing and Non-Childbearing Potential

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

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

Women in the following categories are <u>not</u> 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 of age and not using hormonal contraception or HRT.

  - A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

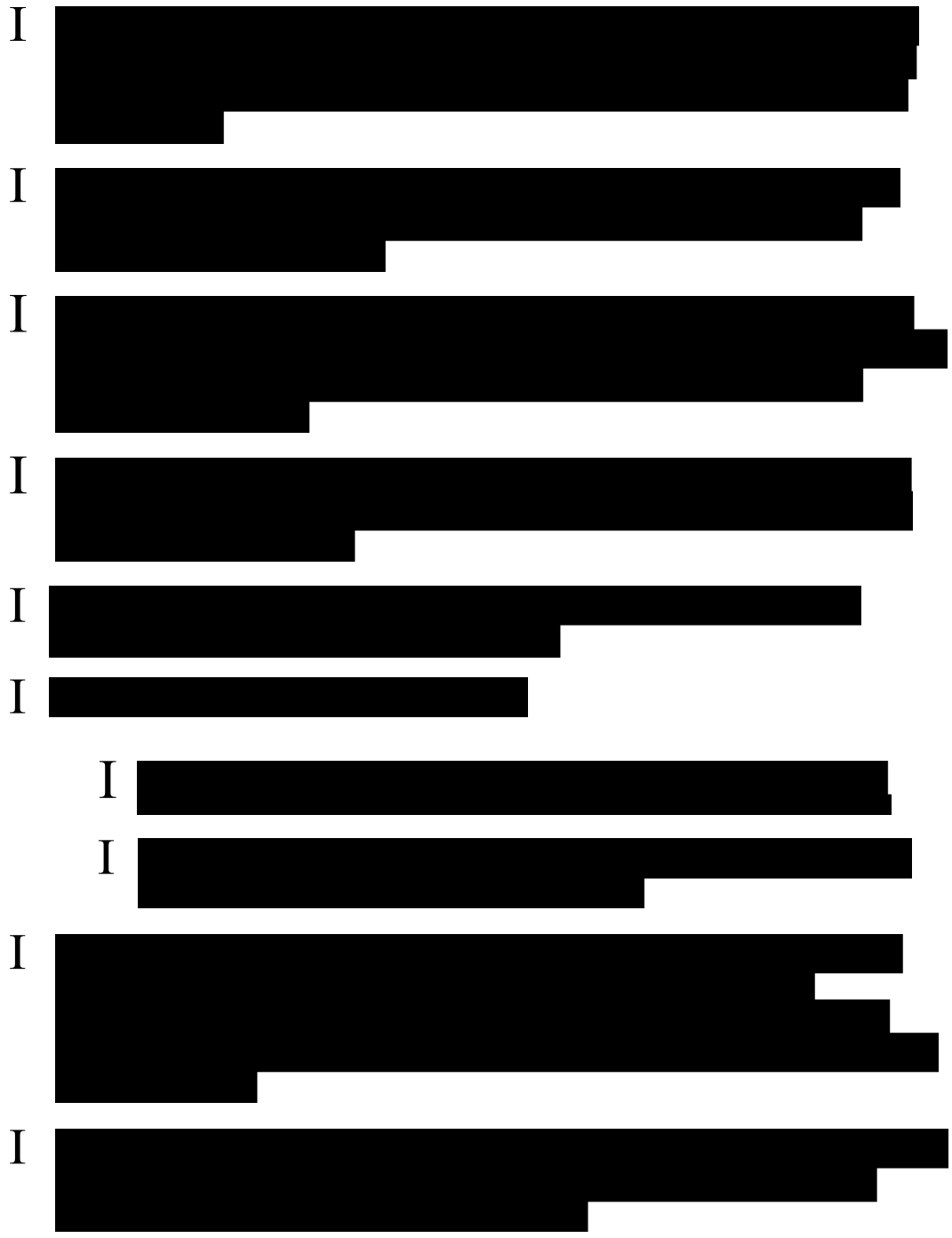
   - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis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

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*;
    - Intravaginal + barrier*;
    - Transdermal + barrier*;
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*;
    - Injectable + barrier*.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

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

CCI



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 “adaptors” 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 Hy's law cases, 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, or 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, 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 AE
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by60 ms 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 sho1i intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious AE

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• Newonset left bundle branch block (QRS complex>120 ms).
• Newonset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free paiiicipants in sinus rhythm, with documented periods of asystole3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free paiiicipants with atrial fibrillation and bradycardia with **1** or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventriculai·response rate: rapid＝rate >120 bpm.
• Sustained supraventricular tachycai·dia (rate>120 bpm) ("sustained"＝sho1i duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventriculai·rhythm (heali rate <40 born). accelerated idioventriculai·rhvthm *(HR* >40 born to <100 born) and

monomo1phic/polymo1phic ventricular tachycardia (HR>100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heali block.

ECG Findings That Qualify as SAE

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyaiThythmias (>30 seconds' dmation).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cai·dioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any aiThythmia classified as an adverse expenence.

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Eligibility

While SARS-CoV-2 testing is not mandated for entry into this study, local clinical practice standards for testing should be followed. A participant should be excluded if they have a positive test result for SARS-CoV-2 infection within 14 days prior to enrollment, is known to have asymptomatic infection, or is suspected of having SARS-CoV-2. Participants with active infections are excluded from study participation as per exclusion criterion 12 When the infection resolves, the participant may be considered for re-screening. Also See Section 6.8.8.

10.8.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the SoA 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 possibly an accompanying informant) and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

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

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

10.8.3. Alternative Facilities for Safety Assessments

10.8.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

See Section 10.2.

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

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

10.8.3.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.8.4. Study Intervention

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

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

- For symptomatic participants with active SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.

- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV-2-related symptoms should have recovered to ≤Grade 1 for a minimum of 72 hours.

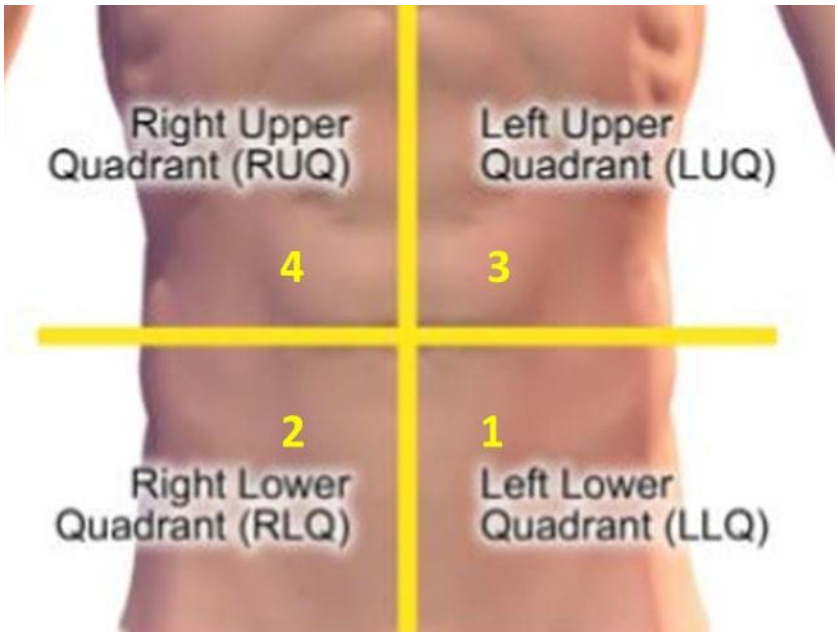
- Continue to consider potential drug-drug interactions as described in Section 6.8 for any concomitant medication administered for treatment of SARS-CoV-2 infection

10.8.5. Adverse Events and Serious Adverse Events

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

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

10.9. Appendix 9: Subcutaneous Injection Site Locations



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

Administer the required number of injections in the following order:

1. Lower left quadrant;
2. Lower right quadrant
3. Upper left quadrant
4. Upper right quadrant

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

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

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

10.10. Appendix 10: IMWG Response Criteria for Multiple Myeloma

Paiiicipants must have measurable disease at emollment (study ent:Iy) as defined by:

- Sernm M-protein ::::o.5 g/dL (5 g/L);
- Urine M-protein ::::200 mg/24 hours;
- Sernm FLC assay: involved sennn FLC level ::::10 mg/dL, provided serum FLC ratio is abnonnal.

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

All response assessments will be entered on the CRF.

All response categories require 2 consecutive assessments made any time before sta1iing new therapy. To confiim response or PD, 2 discrete samples ai·e required and testing cannot be based upon the splitting of a single sainple.

Table 15. IMWG MRD Criteria

Response	**IMWG MRD Criteria** (requires a CR as defined below)
[redacted]	[redacted]
Flow MRD-negative	• CR as defined below plus: • Absence of phenotypically aberrant clonal plasma cells by NGF on BMA using the EuroFlow standard procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of **1** in 10^5 nucleated cells
Sequencing MRD-negative	• CR as defined below plus: • Absence of clonal plasma cells by NGS on BMA in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing ofBMA using the LymphoSIGHT platfo1m (or validated e uivalent method with a minimum sensitivi of **1** in 10^5 nucleated cells
Imaging plus MRD-negative	• CR as defined below plus: • 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 suITOundin° nonnal tissue

Table 16. Modified IMWG Response Criteria

Response[a]	Modified IMWG Criteria
Stringent Complete Response (sCR)	CR as defined below plus: • Normal serum FLC ratio and absence of clonal cells in BMB/BMA [b] by immunohistochemistry or immunofluorescence (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ participants, respectively, after counting ≥100 plasma cells).[b,c] • If the only measurable disease is by serum FLC levels, sCR is defined as normal serum FLC ratio of 0.26 to 1.65 plus absence of clonal cells in BMB/BMA [b] by immunohistochemistry or immunofluorescence (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ participants, respectively, after counting ≥100 plasma cells).[b,c]
Complete Response (CR)	• Negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and <5% plasma cells in BMA.[b,d] • If the only measurable disease is by serum FLC levels, CR is defined as normal serum FLC ratio of 0.26 to 1.65, plus criteria listed above.[b,d]
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis. OR • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h. • If the only measurable disease is by serum FLC levels, VGPR is defined as a ≥90% decrease in the difference between involved and uninvolved serum FLC levels. • In addition to these criteria, if present at baseline, a >90% reduction compared with baseline in the size (SPD) of soft tissue plasmacytomas[d]
Partial Response (PR)	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h. • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved serum FLC levels is required in place of the M-protein criteria. • In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[d]
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 these, if present

Table 16. Modified IMWG Response Criteria

Response•	Modified IMWG Criteria
	at baseline, a50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.d
No Change/Stable Disease (SD)	• Not meeting criteria for sCR, CR, VGPR, PR, MR or PD.
Progressive Disease (PD)b,e.f	Any one or more of the following criteria: • Increase of c::25% from lowest confomed response value in any 1 or more of the following:e,f Semm M-component (the absolute increase must be 0.5 g/d.L); Semm M-protein increase c::1 g/d.L, if the lowest M component was c::5 g/d.L; Urine M-protein (the absolute increase must be c::200 mg/24 h). In paiiicipants without measurable semm and urine M-protein levels, the difference between involved and uninvolved semm FLC levels (absolute increase must be>10mg/d.L); In patients without measurable semm and mine M- rotein levels and without measurable involved semm FLC levels, CCI - percentage inespective of baseline status (absolute increase must bd 0%) • Appearance of a new lesion(s), 50% increase from nadir in SPD of >1 lesion, o50% increase in the longest diaineter of a previous lesion>1 cm in short axis.d • 50% increase in circulating plasma cells (minimum of200 cells per µL) if this is the only measure of disease

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

CCI [redacted]

c Presence/absence of clonal cells is based upon the *Kl>.,* ratio. An abno1mal *Kl>.,* ratio by IHC or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnonnal ratio reflecting presence of an abno1mal clone is *Kl>.,*of>4:1 or <l :2.

d Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or dedicated CT scans where applicable. Measurement of tumor size will be dete1mined by the SPD.

e PD confumation requires 2 consecutive assessments made at any time prior to the institution of any new anticancer therapy. If alternate therapy is sta1ted before confinning PD, any additional testing during subsequent therapy can be used to confinn PD. Pa1ticipants will be considered to have PD if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for

Table 16. Modified IMWG Response Criteria

Response[a]	Modified IMWG Criteria

participants who had a measurable serum or urine M- protein (M-spike) at baseline, PD cannot be defined by increases in serum FLC alone.

f For PD, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

ADDITIONAL NOTES:

- If participants do not have measurable disease at baseline they can only be assessed for CR or PD.
- Except for sCR, serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable or uninterpretable .
- In cases where SPEP is found to be unreliable (eg, IgA,IgD myelomas) for M-protein assessment, quantitative immunoglobulin measurements are preferred for disease assessment; the same percentage changes apply as for serum M-protein. If used, quantitative immunoglobulin assessment must be used exclusively for a participant (ie, quantitative immunoglobulin and SPEP cannot be used interchangeably for disease assessment of the same participant).

Source: Adapted from Kumar et al, 2016.[51]

10.11. Appendix 11: Prior Lines of Therapy

The following guidelines (adapted from [52]) are to be used to quantitate the number of prior lines of anti-MM therapy a participant has received.

Line of Therapy
A line of therapy consists of at least 1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (eg, 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by SCT consolidation, and lenalidomide maintenance is considered 1 line).

New line of Therapy
A treatment is considered a new line of therapy if any of the following conditions are met:

- **Start of a new line of treatment after discontinuation of a previous line**. If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. A regimen is considered to have been discontinued if all the drugs in that given regimen have been stopped. A regimen is not considered to have been discontinued if some of the drugs of the regimen, but not all, have been discontinued.

  The reasons for discontinuation, addition, substitution, or SCT do not influence how lines are counted. It is recognized that reasons for change may include end of planned therapy, toxicity, progression, lack of response, inadequate response, etc.

- **The unplanned addition or substitution of 1 or more drugs in an existing regimen.** Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.

- **SCT.** In patients undergoing >1 SCT, except in the case of a planned tandem SCT with a predefined interval (such as 3 months), each SCT (autologous or allogeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different.

  A planned tandem SCT is an exception and is considered 1 line. Planned induction and/or consolidation, maintenance with any SCT (frontline, relapse, autologous or allogeneic) is considered 1 line.

Interruptions and dose modifications

- If a regimen is interrupted or discontinued for any reason and the same drug or combination is restarted without any other intervening regimen, then it should be counted as a single line.

- However, if a regimen is interrupted or discontinued for any reason, and then restarted at a later time point but 1 or more other regimens were administered in

between, or the regimen is modified through the addition of 1 or more agents, then it should be counted as 2 lines.

- Modification of the dosing of the same regimen should not be considered a new line of therapy.

10.12. Appendix 12: CRS and ICANS Grading, Mitigation, and Management

10.12.1. Cytokine release syndrome

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

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

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

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

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

CRS grading will follow ASTCT criteria (Table 17). For CRS management, published treatment guidelines are recommended[35,36], but they may be modified as needed by the responsible investigator according to the best practices at their institute. In case of Grade 2 or higher CRS event, the medical monitor may be contacted for further guidance.

Table 17. ASTCT CRS Grading

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

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

a Fever: Temp ≥38°C and not attributable to any other cause. In participants who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

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

c Low-flow nasal cannula or facemask is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula or facemask is defined as oxygen delivered at >6 L/min. This is modified from original ASTCT criteria to differentiate between low-flow and high-flow facemask.

Source: (Lee et al, 2019)[48]

10.12.1.1. CRS management guidelines by ASTCT Severity Grading[35,36]

Participants will be hospitalized for at least 2 days after the first dose (C1D1) and at least 1 day after the second dose (C1D4) for safety surveillance.

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

Grade 1 CRS:

Fever

- Acetaminophen/paracetamol and hypothermia blanket for the treatment of fever.
- NSAIDs such as ibuprofen can be used as second treatment option for fever if not contraindicated.
- Assess for infection using blood and urine cultures, and chest radiography.
- Empiric broad-spectrum antibiotics and filgrastim if neutropenic.
- Maintenance IV fluids for hydration.
- Symptomatic management of constitutional symptoms or organ toxicity.

- Consider tocilizumab 8 mg/kg (maximum dose 800 mg) IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever.

Grade 2 CRS:

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

Hypotension

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

Hypoxia

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

Grade 3 CRS:

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

Hypotension

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

Grade 4 CRS:

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

Hypotension

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

Hypoxia

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

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

Although less commonly seen than CRS, ICANS has been observed with some T-cell directed therapies and may manifest as aphasia, delirium, encephalopathy, lethargy, difficulty concentrating, agitation, tremor, seizures, and cerebral edema. If ICANS is observed in relation to elranatamab, the ASTCT criteria (Table 18 and Table 19) will be used for grading and published guidelines are recommended for management. These treatment guidelines may be modified as needed by the responsible investigator according to the best practices at their institute.

Table 18. 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 19. ASTCT ICANS Grading

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

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

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

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

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

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

Source: (Lee et al, 2019) [48]

10.12.2.1. ICANS Management Guidelines Per ASTCT[35,36]

ICANS Grade 1:

- Vigilant supportive care; aspiration precautions; IV hydration.
- Withhold oral intake of food, medicines, and fluids; assess swallowing.
- Convert all oral medications and/or nutrition to IV if swallowing is impaired.
- Avoid medications that cause CNS depression.
- Neurology consultation.
- If suspected, evaluate for elevated ICP with fundoscopic exam for papilledema and lumbar puncture for CSF opening pressure.
- MRI of the brain with and without contrast; CT scan of the brain can be performed if MRI is not feasible.

- Daily 30 min EEG until symptoms resolve.
- Consider anti-IL-6 therapy with tocilizumab 8 mg/kg (maximum 800 mg) IV or siltuximab 11 mg/kg IV in case of concurrent CRS.

ICANS Grade 2:

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

ICANS Grade 3:

- Supportive care and neurological work-up as indicated for Grade 1 ICANS.
- ICU transfer is recommended.
- If EEG shows non-convulsive status epilepticus:
    - Assess airway, breathing, and circulation; check blood glucose.
    - Lorazepam 0.5 mg IV, with additional 0.5 mg IV every 5 min, as needed, up to a total of 2 mg to control electrographical seizures.
    - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
    - If seizures persist, transfer to ICU and treat with phenobarbital loading dose of 60 mg IV.
    - Recommended maintenance therapy after resolution of non-convulsive status epilepticus are as follows:
        - lorazepam 0.5 mg IV every 8 hours for three doses;
        - levetiracetam 1,000 mg IV every 12 hours; duration of therapy per investigator/treating physician’s discretion;
        - phenobarbital 30 mg IV every 12 hours; duration of therapy per investigator/treating physician’s discretion.
    - Lacosamide may also be considered for treatment of seizures should the seizures persist. Lacosamide should not be used in participants with concurrent CRS in order to avoid arrhythmias and hypotension.
- For convulsive status epilepticus:
    - Assess airway, breathing, and circulation; check blood glucose.
    - Transfer to ICU.

- Lorazepam 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures.
- Levetiracetam 500 mg IV bolus, as well as maintenance doses.
- If seizures persist, add phenobarbital at a loading dose of 15 mg/kg IV.
- Maintenance doses after resolution of convulsive status epilepticus:
    - lorazepam 0.5 mg IV every 8 hours for three doses;
    - levetiracetam 1,000 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion;
    - phenobarbital 1-3 mg/kg IV every 12 hours; duration of therapy per investigator/treating physician's discretion.
- Lacosamide may also be considered for treatment of seizures should the seizures persist. Lacosamide should not be used in participants with concurrent CRS in order to avoid arrhythmias and hypotension.
- Continuous EEG monitoring should be performed, if seizures are refractory to treatment.

- High-dose methylprednisolone IV 1 g/day for focal/local edema.
- Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 1 ICANS and if not administered previously.
- Corticosteroids as outlined for Grade 2 ICANS if symptoms worsen despite anti-IL-6 therapy, or for ICANS without concurrent CRS; continue corticosteroids until improvement to Grade 1 ICANS and then taper.

ICANS Grade 4:

- Supportive care and neurological work-up as outlined for Grade 1 ICANS.
- ICU monitoring; consider mechanical ventilation for airway protection.
- Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 ICANS.
- High-dose corticosteroids continued until improvement to Grade 1 ICANS and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
- For convulsive status epilepticus, treat as described for Grade 3 ICANS.
- MRI of the spine should be obtained for focal motor weakness.
- To manage elevated ICP:
- Elevate head of the participant's bed to an angle of 30 degrees.
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 hrs.
- Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below):
    - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hrs while monitoring metabolic profile and serum osmolality every 6 hrs, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40.
    - Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50-75 ml/hour while monitoring electrolytes every 4 hrs, and withhold infusion if serum Na levels reach ≥155 mEq/l.
    - For participants with imminent herniation: initial 30 ml of 23.4% hypertonic saline; repeat after 15 min, if needed.
- If patient has Ommaya reservoir, drain CSF to target opening pressure of <20 mmHg
- Consider neurosurgery consultation for ventriculoperitoneal shunt in participants with cerebral edema, and IV anesthetics for burst-suppression pattern on EEG.
- Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension.

10.13. Appendix 13: Concomitant Medications That May Result in DDI

Treatment with efranatamab has a potential for resulting in modest and transient increase in the exposure of concomitant medications that are substrates for major CYP enzymes (eg, CYP3A4 and CYP2C9). Caution should be used upon concomitant use of sensitive substrntes of CYP enzymes with naiTow therapeutic index, listed in the table, especially during the initial treatment cycle. If the use of waifarin is clinically necessaiy, caution and additional INR monitoring is recommended during the initial treatment cycle.

The Pfizer study teain is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgement on the ongoing paiticipation of any paiticipant with prohibited medication use during the study.

This list of diugs prohibited for potential DDI concerns with the IMP may be revised dming the course of the study with written notification from sponsor, to include or exclude specific diugs or diug categories for vai·ious reasons (eg, emerging DDI results for the IMP, availability of new information in literatme on the DDI potential of other diugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Drug Category	Drugs
CYP3A4 Substrate	alfentanil cyclosporine dihydroergotamine ergotamine fentanyl pimozide quinidine sirolimus tacrolimus
CYP2C9 Substrate	Phenytoin warfarin

Investigators should consult the product prescribing infonnation for any other medication used dming the study for infonnation regarding medication that is prohibited for concomitant use.

10.14. Appendix 14: Country specific requirements

10.14.1. Japan

Japan Regulato1y Requirements

For Section 8.2.6. Clinical Safety Laborato1y Assessments, the following additional laborato1y HBV monitoring during study treatment should be followed as a precaution:

- For paiiicipants with a positive HBsAb and positive HBcAb test but with a negative HBV DNA test at screening, HB viral load should be monitored for re-activation eve1y 12 weeks. If HBV relapse is observed, the event should be collected in the AE section of the CRF, but the test data will not be required to be repo11ed on the CRF. Paiiicipants with an HBsAb positive test who have been vaccinated with HBV ai·e exempt from the testing of HB viral load.

- Administration of study inte1vention will be intem.1pted for a paiticipant with an HBV viral load positive test at any time during the study. Staiiing nucleoside antagonist administration immediately should be considered in parallel with consultation with a hepatologist in accordance with the Japan Society ofHepatology (JSH) Guidelines for the management of Hepatitis B Vims infection.

CCI

[redacted]

[redacted]

Premedications

The sponsor lists each of the study inte1ventions in the following table because safety infonnation for these study inte1ventions must be repo11ed to the Japan regulato1y authorities and investigator(s)/IRB/EC of the investigator site(s) in Japan in accordance with the Japanese regulato1y requirements. The investigator in Japan provides the sponsor with the safety infonnation necessaiy for safety repo11ing to the Japan regulato1y authorities.

Intervention Name	Acetaminoohen	Diohenhydramine	Dexamethasone
Tvoe	Drng	Drng	Drng
Dose Formulation	Tablet	Tablet or Solution for iniection	Tablet or Solution for iniection
Unit Dose Stremz:th(s)	650 mg (or equivalent)	25 mg (or equivalent)	20 mg (or equivalent)

Route of Administration	PO	PO or IV	PO or IV
IMP or NIMP	NIMP/AxMP	NIMP/AxMP	NIMP/AxMP
Sourcing	Provided locally by the trial site.	Provided locally by the trial site.	Provided locally by the trial site.
SRSD	Ireland SmPC for Paracetamol/Diphenhydramine Hydrochloride	Ireland SmPC for Paracetamol/Diphenhydramine Hydrochloride	EU SmPC for Neofordex

10.14.2. United States

The informed consent cannot be provided by a legally authorized representative in the US. Only participants who are capable of giving informed consent by themselves are eligible to participate in the study.

10.15. Appendix 15: Anti-infectious Prophylaxis and Monitoring

Participants should receive antimicrobial prophylaxis as detailed below.

Risk factors	Prophylaxis/ Treatment/ Testing/ Monitoring	Start	Stop	Required/ Recommended
HSV/VZV	Acyclovir or alternative	Antiviral prophylaxis within 1 week after starting treatment is required to prevent herpes zoster reactivation	Continue for 3 months following the end of treatment Continue for 3 months following the end of treatment	Required
CMV	CMV testing by PCR is required at screening. On study testing should be performed either monthly or every 1 to 3 cycles depending on risk factors and baseline CMV viral load Valganciclovir 900 mg PO BID Alternative (ganciclovir IV foscarnet IV) or other approved agents.	Initiation of antiviral treatment is recommended for participants with CMV copy number ≥1000/mL, or per local standard of care (other risk factors including the rise in CMV copy number should be considered). Treatment is required for symptomatic participants irrespective of viral load.	Continue therapy until two consecutive measurements at least 14 days apart show viral load < 1000/mL and resolution of symptoms (if present)	Required
Pneumocystis jirovecii Pneumonia (PJP)	PJP prophylaxis is required for all participants for at least 6 months Trimethoprim-sulfamethoxazole DS 1 tablet PO daily, three times per week Alternatives: Pentamidine (or alternative), or Dapsone – 100 mg PO daily or 50 mg PO BID, or Atovaquone – 1500 mg PO daily	Day 1 of first dose of elranatamab	Suggested duration: until CD4 count ≥200 cells/μL based on 2 consecutive measurements at least 14 days apart (whichever is longer). Prophylaxis may be extended at the discretion of the investigator as clinically indicated.	Required
SARS-CoV-2	Starting with protocol amendment 4, PCR or antigen test are required predose on Day 1 (CXD1), upon suspected exposure to SARS-CoV-2 and at signs or symptoms of	Initiate treatment (eg PAXLOVID™, remdesivir) as soon as possible, ideally within 24 hours following a positive SARS-CoV-2 test	For participants with SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms or positive test result.	Required

	COVID-19 infection (eg, new or worsening fever, cough, sore throat, shortness of breath or fatigue).		In addition, the participant should be afebrile for 72 hours, and COVID-19 - related symptoms should have recovered to ≤Grade 1 for a minimum of 72 hours	
Hypogamma-globulinemia/ Immunoglo-bulin replacement : intravenous immunoglo-bulin (IVIG) or subcutaneous immunoglo-bulin (SCIG)	Monitor immunoglobulin levels for the occurrence of hypogammaglobuli-nemia/ immune paresis	Administration of immunoglobulin for IgG level < 400 mg/dL is strongly recommended (excluding M-spike in participants with IgG myeloma). In participants with IgG myeloma, evaluation of uninvolved immunoglobulins [IgA, IgM] can also be used to determine immune-paresis and the requirement for immunoglobulin replacement.)	Until resolution of hypogammaglobuline mia	Recommended
Bacterial infection	Fluoroquinolones (levofloxacin - 500 mg PO or IV daily, or equivalent) Suggested alternative for participants with allergy to quinolones: Cefpodoxime - 200 mg PO twice a day	For all participants at high risk of infections during course of treatment (eg history of pneumonia, Grade 4 neutropenia), an initial 3-month prophylactic course of fluoroquinolones is recommended	Stop after 3-months of initial prophylaxis if ANC ≥1000/µL	Recommended
			After initial 3-month treatment, administer for 14 days for ANC <1000/µL Prophylaxis may be extended at the discretion of the investigator as clinically indicated	

Fungal Infection	Fluconazole - 400 mg daily (or equivalent)	For participants with prolonged neutropenia (eg, ANC <500/µL for >7 days)	At neutropenia resolution (for example, ANC ≥500/µL). Prophylaxis may be extended at the discretion of the investigator as clinically indicated.	Recommended
	Consider switch to posaconazole or equivalent	Prolonged ANC <500/µL >3 weeks	Until neutropenia resolution (ANC ≥500/µl)	
Other viral infections	While on study treatment, as clinically indicated, in patients with suspected infection, consider testing for other potential viruses such as adenovirus and EBV.	For participants with positive test, initiate treatment/supportive care as per local standard of care and hold study interventions	Until resolution of signs and symptoms or per local standard of care	Recommended
Neutropenia/ G-CSF Prophylaxis[a]	Prophylactic or therapeutic administration of G-CSF in participants with severe neutropenia or serious neutropenic complications is strongly recommended consistent with the ASCO guidelines[53] to decrease the risk of neutropenia specifically in participants with baseline extensive BM involvement and/or low neutrophil counts.	For participants with ANC <1000/µL	Until resolution of neutropenia	Recommended

a. Eligibility restricts use of G-CSF within 7 days prior to start of study intervention. Note that primary prophylactic use of G-CSF is not permitted during Cycle 1 and 2 of Part 2A and Part 2C, but may be used to treat treatment emergent neutropenia [54-58].

10.16. Appendix 16: Protocol Amendment History

The protocol amendment sUIIllnaiy of changes table for the cmTent amendment is located directly before the TOC. The protocol amendment sUIIllnaiy of changes tables for past amendment(s) can be found below:

Amendment 3 (22 Nov 2022)

Overall Rationale for the Amendment:

The primary rationale for this amendment is to add a Part 3 CCI [redacted] and to include a detailed guidance for infection prophylaxis. Additional coITections or revisions were made to clai·ify or more completely define processes.

Section # and Name	Description of Change	Brief Rationale	Substantial (YIN)
Section 1.1, Synopsis, Overall Design; Section 1.2 Schema; Section 4.1, Overall Desi	Updated schematic study design and overall desi__ b, addin Pait 3. CCI [redacted]	To reflect study design change in multiple sections	Y
Section 1.1, Synopsis; number of paiticipants, Statistical methods, Section 3, Objectives, Endpoints, And Estimands; Section 9, Statistical Considerations (9.1, 9.2 Analysis sets; 9.3, 9.4, 9.5, Sample Size Detennination (Pait 1, 2 and3	Updated statistical section related to Pait 3, coITection of the DLT evaluable set for emolled paiticipants in Pait 2A and Pait 2C (Section 9.2)	To reflect statistical changes in multiple sections regarding the addition of Pait 3 and to clarify the definition of the DLT evaluable set	Y
Section 1.1, Synopsis, Section 5.2 criteria	Modified the EC #12: "Paiticipants with positive anti-HBcAb but negative HBsAg and negative anti-HBsAb profile ai·e eligible if HBV DNA is not detected." Also added "COVID-19" and "or AIDS-related illness" and "While SARS-CoV-2 testing is not mandated for entiy into this study, testing should follow local clinical practice standai·ds. If a paiticipant has a positive test result for SARS-CoV-2 infection within 14	To clarify eligibility criteria for HBV, COVID-19 and AIDS related illness at baseline	Y

Section # and Name	Description of Change	Brief Rationale	Substantial (YIN)
	days prior to enrolhnent, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, the paiticipant is excluded.		
Section **1.1,** Synopsis, Section 5.2 Exclusion criteria #13 and #18-20	Modified the EC #13: CCI [redacted] Added ECs #18-20 to the Synopsis. Modified the EC #20: "Investigator site staff or Pfizer employees directly involved in the conduct of the study and their family members, site staff othe1wise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their respective fainily members." To align with new rotocol tem late	To ensure pa1ticipants are excluded in Pait 3 CCI [redacted] To align with Section 5.2	y
Section 1.3 Schedule of Activities (Pait **1,** 2 and Part 3)	Added CMV assessment by quantitative PCR. For pa1ticipants ah-eady enrolled and treated under Pait **1** and Pait 2, a CMV testing should be perfo1med as a baseline reference for CMV status at the next scheduled dosing visit and repeated either monthly or eve1y **1** to 3 cycles depending on risk factors and baseline CMV viral load as clinically indicated. Removed CMV testing at C2 for Pait 2 and removed CMV testing at C2-C6 and C7+ for Pali **1** (to align Paits **1,** 2 and 3 with the note in each SoA)	ToaddCMV testing at screenmg or prior to first administration of study diug for safety monitoring and at different timepoints as clinically indicated (Pait **1,** 2 and 3) and ensure that pa1ticipants ah-eady enrolled will getaCMV testin during	y

Section # and Name	Description of Change	Brief Rationale	Substantial (YIN)
		their next scheduled visit, as clinically indicated (Pait **1** and Pait 2.	
Section 6.8.7, Prophylaxis for Infections	Reference to Appendix 15 for anti-infectious prophylaxis and monitoring. Revised guidance for the use of IV irmnunoglobulins and **h** o amma lobulinernia.	Added required treatment as per Dear Investigator Letter dated 08 **Jul** 2022.	y
Section 6.8.8 COVID-19	Creation of a new section, alignment with BCMA program, Revised guidance for COVID-19 testing and treatment for paiticipants with COVID-19 positive tests.	Clai·ification for investigators as perPACL dated 25 May 2022.	y
Section 10.15 Appendix 15-Anti infectious Prophylaxis and Monitoring	Added anti infectious prophylaxis/ hypogammaglobulinernia/neutrnpenia guidance	Provide guidance to investigative sites as per Dear Investigator Letter dated 08 **Jul** 2022.	y
Section 6.8.2 Concomitant Therapy	Added guidance for administration of mugs known to cause peripheral neuropathy, added: "Effective treatment and prophylaxis for infections should be prioritized"	Avoid conflict with di11gs recormnended in anti-infectious prophylaxis and monitoring guidance A endix 15 .	y
Section 2.3.1-Benefit/Risk assessment	Added infections as a potential risk of clinical si ificance for ekanatainab, CCI [redacted]	Suppo1ted by clinical data from ekanatamab and other therapies with sirnilai· proposed	y

Section # and Name	Description of Change	Brief Rationale	Substantial (YIN)
		mechanism of action [redacted]	
Section 2.3.**1**- Benefit/Risk assessment	Added that "effective ti·eatment and prophylaxis for infections should be prioritized" in the risk section for peripheral nemopathy	To avoid conflict with chugs recommended in anti-infectious prophylaxis guidance (A endix 15	y
Study title and brief title, Section **1.1**, Synopsis,	Updated the title and brief title [redacted]	The addition of Part 3 allows for evaluation of the safety and efficacy of [redacted] EORTC is not needed	y
Schedule 1.3 Schedule of Activities -Part 3- Hospitalization (Paii **1** and Paii 3)	Added SoA table for Pait 3, added a potential hospitalization for the first RP2D elranatamab dose at C7D**1** (116 or 152 mg) Q4W	To reflect study design change on SoA specific to Pait 3 and allow potential hospitalization for safety management at RP2DQ4Win Pait **1** and Paii 3	y

Section # and Name	Description of Change	Brief Rationale	Substantial (YIN)
CCI			y
CCI			y
Section 6.5 Dose Modification	When 20 mg eh-anatamab priming dose is repeated after treatment intenuption for >2 weeks, escalation to 76 m should occur **1** week later	Align with SoA cycles	y
Section 6.5.1 Dose Modification	For Q2W regimen, the window between consecutive <losings is changed to (-1/+6 days)	Align with SoA cycles and respect a minimumof6 days between doses	y

Section # and Name	Description of Change	Brief Rationale	Substantial (YIN)
Section 6.5.1.2	Removed 'recommended' from description of dose modification for eh-anatamab-related toxicities	The dose modifications for eh-anatamab are required per protocol	y
Section 6.8.1 Premedications Required for Cytokine Release Syndrome- Part 3	Addition of Pali 3 pre-medication for CRS	To clarify the use of dexamethasone CCI [redacted]	y
Section 6.8.3.1 Prohibited medication during study	New section added to include prohibited medication with dexamethasone	To clarify prohibited medication with dexamethasone and added live attenuated vaccine period of prohibition	y
CCI [redacted]	[redacted]	[redacted]	[redacted]
Schedule 1.3 Schedule of Activities (Pait 1, 2 and 3) and Section 8.2.3 Vital signs	To request vital signs collection in CRF for the periods of scheduled hospitalizations and if abnonnal and associated with AEs (eg, CRS or an infection	Align with program-level updates	N
Section 1.3 Schedule of Activities (Paits 1 and 2); disease assessment - Notes for SPEP, SIFE, FLC, UPEP, UIFE, Sennn quantitative immunoglobulins, rmagmg	Clarified that disease assessment, SPEP, SIFE, FLC, UPEP, UIFE, Sennn quantitative immunoglobulins, imaging are conducted eve1y 28 days from ClDl, Clarification that once all EMD has resolved/disappeai·ed, imaging can be conducted annually (or earlier if clinically indicated) and at sus ected PD	Align with program-level updates	N

Section # and Name	Description of Change	Brief Rationale	Substantial (YIN)
Section 1.3 Schedule of Activities (Pait **1,** 2, 3) Appendix 10: IMWG Response Criteria for Multiple Myeloma	Added semm FLC to be used for response assessment only when senun and urine M protein are non-measurable or uninte1pretable, except for sCR	Distinguish performing FLC analysis from using FLC results for response assessment	N
Schedule 1.3 Schedule of Activities (Pait 1, 2 and 3) - Clinical Procedures/Assessments	Clarified that during the treatment period, all assessments must be done within 72 hours prior to dosing, except for disease assessments which are to be done eve1y 28 days from ClDl	Align with program-level updates	N
CCI	[redacted]	[redacted]	
Section 1.3 Schedule of Activities (Pait 2, 3)-Neurolo ic exain	Added that sta1ting C2D1 up to end of C6, neurological exain is to be erfo1med biweekl	Align with Q2W dosing of eh-anatamab	**N**
Section 2.2-Background info1mation- Table 4	Added as more clinical data become available	Align with program-level u dates.	**N**
Section 6.8.3-Prohibited during the study	Added that administration of live attenuated vaccines is prohibited during study treatment, and for 90 days after the last dose of study treatment. Annual inactivated influenza vaccines ai·e allowed.	Align with program-level updates	**N**
Section 7.**1.1** Potential Cases of Kidney fujmy	Guidance added for actions in cases of acute kidney injmy.	Align with program-level u dates.	**N**
Section 8.1.3 -hnaging assessments	Added that "radiologic progression observed within the first month following the first dose of eh-anatainab will not be considered progressive disease and that imaging is acce table to be used as baseline	Align with program-level updates and to align with imaging section in SOA.	**N**

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
	evaluation, if can be obtained within 42 days before start of study intervention. Added that bone lesions and any soft tissue plasmacytoma documented at baseline must undergo serial monitoring. Paramedullary disease or plasmacytomas associated with bone are not considered EMD.		
Section 10.2. Appendix 2: Clinical Laboratory Assessments- Table 17	Addition of CMV by quantitative PCR	Align with new guidance Anti-infectious Prophylaxis (Appendix 15)	N
Section 10.14 Japan Tocilizumab	Added additional information for tocilizumab	Satisfies safety reporting requirements in Japan	N
Section 10.14 United States	Added US-specific requirements that LAR are not allowed for informed consent process	To address US IRB request as per PACL dated 03 August 2022.	N
Global	Minor administrative, editorial, typographical, new bibliographic references, abbreviations list or formatting changes.	Updated for grammatical correctness, consistency, references, and/or clarity.	N

Amendment 2 (10-June-2022)

Overall Rationale for the Amendment:

Changes are mainly to align study procedures and statistical analysis across ongoing clinical studies conducted with elranatamab, to revise eligibility criteria to improve participant recruitment, to allow participants enrolled in Part 1 to switch to a Q4W regimen and to correct or clarify inconsistencies identified in the previous version of the C1071009 protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
1.2 Schema (Study Design)	Rules for transitioning from Part 2A to Part 2C revised	Clarify the criteria for opening Part 2C	Y
1.2 Schema (Study Design), synopsis, 3 Objectives, Endpoints, and Estimands, 4.1 Overall Design, 4.3.3 Definition of DLT, 9.5.2 Part 2A and Part 2C	Revised DLT observation period definition to 28 days starting on the first dose of 116 or 152 mg.	Clarify the DLT period to ensure that it includes the time period after initiation of the higher dose of elranatamab	Y
1.2 Schema (Study Design), Synopsis, 1.3. Part 1 Schedule of Assessments, 2.1 Study Rationale, 2.3.1 Risk Assessment, 2.3.2 Benefit Assessment, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design, 4.3.2 Justification for Evaluation of Higher Elranatamab Doses, 4.3.4 Definition of RP2D for Part 2B and Part 1 from C7, 6.1 Study Intervention(s) Administered, 6.5.2 Dose	Participants enrolled in Part 1 should be switched to the RP2D identified in Part 2A (116 mg or 152 mg) administered Q4W after 6 cycles if PR or better is persisting for ≥ 2 months.	Gain additional elranatamab monotherapy data using higher dose and longer dosing interval.	Y

Section # and Name	Description of Change	Brief Rationale	Substantial
Modifications for Ehanatamab-Related Toxicity and Peripheral Neuro ath .			
1.3 Schedule of Activities	Clarifications on requirements for laborato1y disease assessments (serum, urine and CCI and una m	Provide clarity to investigative sites and hannonize across ongoing eh-anatamab studies	y
	Increased window for vital signs measurements during hospitalization period	Provide flexibility to the sites	y
	CCI [redacted]	[redacted]	[redacted]
Section 1.3 SOA and 8.1.3 hnaging Assessments	Clarified EMD defmition and revised frequency of unagmg.	Revised to better align with Standard of Care and to provide clarity to the sites.	y
2.2.3.2 Clinical Overview	Updated data from C1071001 study and added data from C1071003 stud	Updated to reflect cunent available clinical data on eh-anatamab	y
Both Section 2.2.3.2 Ehanatamab Clinical Overview and Benefit/Risk Assessment	Updated clinical data from ongoing Phase **1** (C1071001) and Phase 2 (C1071003) studies to align with the annual IB update.	Update sites on clinical experience with ehanatamab in the Study C1071009 target patient population	y
Section 4.1 Overall Design and Section 4.3.5 Dose Level in Pait 2C	Clarified the mies to open Pali2C	Clarify the process for opening Pait 2C	y
5.**1** Inclusion criteria: Criteria #13	Timeframe between transfusion suppo1t and G-CSF suppo1t and planned C1D1 was extended	• Ha1monize across elranatamab studies	y

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
		• Improve participant recruitment	
5.2 Exclusion criteria:	Added: • Waldenström's macroglobulinemia (#5) • Known active CNS involvement or clinical signs of myelomatous meningeal involvement (#6)	Revise target participant population and harmonize across elranatamab studies	Y
5.2 Exclusion criteria #14	Clarified text pertaining to active malignancy	Provide clarity to investigative sites and harmonize across ongoing elranatamab studies	Y
5.2 Exclusion criteria #16	Added BCMA CAR-T cell therapy	Revise target participant population	Y
6.5.2 Dose Modifications for Elranatamab-related Toxicity and for Peripheral Neuropathy	Added guidance in case the 116 mg or 152 mg is not tolerated	Guidance was missing in the previous version of the protocol	Y
Section 6.5.2, Dose Modifications for Elranatamab-Related Toxicity and associated table.	Added the procedure for restarting elranatamab treatment for participants who have a dose interruption >2 weeks within the 1st cycle.	Added to mitigate CRS risk and to align across the clinical elranatamab program.	Y
	Removed instructions for dose reductions.	To clarify dose modification guidance and to align across the clinical elranatamab program and standard approaches for management of TEAEs with an immuno-oncology agent.	Y
Section 6.5.3, Dose Reductions	Updated to indicate that dose reduction of	To clarify dose modification guidance and to align across the clinical elranatamab	Y

Section # and Name	Description of Change	Brief Rationale	Substantial
	eh-anatamab below 76 mg is no longer pennitted.	program and standard approaches for management ofTEAEs with an immuno-oncolo a ent.	
6.8 Concomitant Therapy	Added Section 6.8.7 Infection Prophylaxis	Guidance added to all ongoing studies in the eh-anatamab program. This guidance will reduce the risk of infection for study aitici ants.	y
8.**1.1** Laborato1y Assessment for Evaluation of Disease Response	Added sennn quantitative immunoglobulins and clarified timepoints for other parameters	Suppo1t monitoring of disease response for paiticipants with IgA/IgD MM and monitoring of hypogammaglobulinemia; Haimonize with ongoing eh-anatainab studies	y
8.3.8 Adverse Events of Special Interest	Peripheral neuropathy added as an AES!.	Peripheral neuropathy added as an AES! across all ongoing clinical studies in the prograin.	y
CCI [redacted]	[redacted]	[redacted]	[redacted]
9.4.1. Interim Safety Assessments	Revised criteria for placing enrollment on a tempora1y hold.	For haimonization with Study C1071003 using posterior probability of 0.8 instead of 0.9.	y
9.5.2 Sample Size Detennination	Added mies for DLT frequencies and characteristics for dose recommendations for Pait 2C	Clarify the criteria for opening Pait 2C	y
9.5.2 Pait 2A and Pait 2C	Clai·ified BLRM approach applies to Pait 2A and Pait 2C and revised mies for Part 2C	Clarify the process for opening Pait 2C	y
Appendix 2: Clinical	Added collection of plasma cell count, magnesium, and phosphorus or phosphates to	Changes made across all ongoing eh-anatamab studies to enhance safe monitorin	y

Section # and Name	Description of Change	Brief Rationale	Substantial
Laborato1y Assessments	list of required safety laborato1 assessments		
Appendix 8, section 10.8.1	Revised eligibility timeframe for paiiicipants with COVID-19 positive tests.	Clarification for investigators	y
Appendix 10 IMWG Response Criteria for Multiple M eloma	Criteria for IMWG response criteria revised	Changes made across all ongoing ekanatamab studies to allow BMA for assessing sCR.	y
Appendix 14, Section 10.14.2	Added info1mation on SRSD for tocilizumab and remedications	Added required text due to new Japan regulation.	y
1.2 Schema (Study Design), 3 Objectives, Endpoints and estimands, 4.1 Overall Design, Section 4.3.4 Definition of RP2D for Paii 2B; 9.5.2. Pali 2AandPaii2C	RemovedMTD	Clarify that RP2D will be identified as MTD may not be reached.	N
1.3 Schedule of Activities	Added the enrollment in IRTonClDl [redacted]	Provide clarity to the sites	N
Section 3 Objectives, Endpoints and Estimands	Changed naine of CCRR and DOCCR to CRR and DOCR, respectively [redacted]	Haimonize with ongoing ekanatainab studies to remove the tenn 'Cumulative' and provide a better clai·ity.	N

Section # and Name	Description of Change	Brief Rationale	Substantial
5.1 Inclusion criteria: Criteria #12	Recommended fonnula for assessing eGFR was u dated	Alignment with cmTent best practices for assessing renal function	N
5.2 Exclusion criteria: Criteria #12	Clarified text pertaining to SARS-CoV2 infection.	Provide clarity to investigative sites	N
6.1.1 Administration	Revised windows	Haimonize across ongoing eh-anatainab studies	N
6.3.1 Allocation to Study Intervention	Revised to clai-ify the process for pa1ticipant slot assignment for Pali 2A and Pait 2C	To reflect the cohort management plan that applies for Pait 2A and Pait 2C	N
Section 6.7, Treatment of Overdose No. 2	Modified monitoring requirements for AEs/SAEs.	Aligned with safety repo1ting period.	N
6.8.1 Premedications Required for Cytokine Release S drome	Premedication can be administered on the day of a dose higher than 76 mg is administered.	To align with the change in DLT observation period.	N
6.8.2 Pennitted Concoinitant Medications/The rap1es	Revised guidance on palliative radiotherapy to more clearly state that this is allowed when considered medically necessaiy provided that disease progression has been rnled out	Guidance revised for all ongoing studies in the eh-anatainab program to ensme that investigators understand when palliative radiotherapy is pe1missible.	N
6.8.2 Pennitted Concoinitant Medications/The rap1es	Added guidance on testing and treatment for pa1ticipants who may be exposed to COVID-19 or may develop a COVID-19 infection	Guidance added as MM patients ai·e at increased risk of severe disease and complications from COVID-19 infection.	N
CCI [redacted]	[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale	Substantial
8.1.4 Disease Characteristics and Treatment Histo1y	FISH and/or kaiyotyping can be perfo1med	Allow flexibility to the sites, haimonize across ongoing eh-anatainab studies	N
CCI	[redacted]	[redacted]	[redacted]
8.2.3 Vital signs	Increased window for vital signs measurements during hos italization eriod	Provide flexibility to the sites	N
8.2.6 Clinical Safety Laborato1y Assessments	Added guidance to review laborato1y repo1is prior to dosing	To ensure sites are checking that paiticipants ai·e meeting dosing criteria	N
8.3.1 Time Period and Frequency for Collecting AE and SAE Info1mation	Clai·ified end of AE and SAE collection period	Updated to ensure consistencies throughout protocol	N
8.4 Phaimacokinetics	Clai·ified that predose samples should be collected prior to premedications if an.	Haimonize across ongoing eh-anatainab studies	N
8.4 Phaimacokinetics	Removal of the date and time of the last dose prior to PK sample collection for each sample	To reflect the data cmTently collected in the eCRF	N
CCI	[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
CCI [redacted]	[redacted]	[redacted]	[redacted]
9.1.1.1 Primaiy Estimand	Clai·ified intercurrent event handlin	Clarify primaiy analysis	N
9.1.1.2 Secondaiy Estimand	Removed intercurrent event	Clarify secondaiy analysis	N
9.1.1.2 Secondaiy Estimand	Definition ofDLT evaluable pa1ticipant clai·ified	Updated to provide better clarity to the site.	N
9.2 Analysis Sets	Clai·ified DLT Evaluable Set	Specify that this applies to Pait 2A and Pait 2C	N
9.3.3.2 Secondaiy Efficacy Endpoints	Changed naine of CCRR and DOCCR to CRR and DOCR, respectively	Haimonize with ongoing eh-anatainab studies to remove the tenn 'Cumulative' and provide a better clai·ity.	N
	Revised CCI [redacted]	[redacted]	[redacted]
9.3.5.1 Electrocai·diogra m Anal sis	Revised threshold for QTcF Assessment	Haimonize with ongoing eh-anatainab studies	N
10.1.3 Info1med Consent Process	Added Legally authorized re resentative	Reflect current version of the Info1med Consent Document	N
Appendix 11	Added guidelines on prior lines of therapy	Haimonization with C1071003 and C1071005 stud rotocols	N
Appendix 13	Added guidelines on concomitant medications that ma result in DDI	Haimonization with C1071003 and C1071005 stud rotocols	N
Appendix 14	Sponsor will provide tocilizumab to investigative sites in Ja an	To satisfy local requirement	N
Multiple sections	Co1Tection of inconsistencies and	Improve clai·ity of protocol for investi ator sites	N

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
	typographical errors identified in Protocol Amendment 1		

Amendment 1 (09-June-2022)

Overall Rationale for the Amendment: As per regulatory requirements (US FDA), updates are included to describe peripheral neuropathy (including GBS) as an important potential risk of elranatamab and measures to mitigate the risk including (a) addition of various new safety monitoring measures; (b) modification to participant selection (exclusion) for those potentially at higher risk; (c) addition of dose modification rules for peripheral neuropathy; (d) addition of recommended work-up for peripheral neuropathy; and (e) addition of considerations regarding concomitant medications. In addition, the criteria for placing the study on temporary hold (specifically related to neuropathy or other IR neurological AEs) have been defined.

In addition, the safety reporting period after last dose of study intervention has been increased to 90 days in order to capture all potential AEs, including late onset immune-related neurologic AEs. The contraception use after the last dose of study intervention has also been extended from 28 days to 90 days (as required by some HAs for another elranatamab study and to align across the elranatamab clinical program).

Furthermore, the 2 step-up priming doses regimen have been reduced to 4 mg on C1D1 and 20 mg on C1D4 to assess whether lowering initial doses will further mitigate the risk of Grade 2 or higher CRS during the first week of treatment with elranatamab.

In addition, before starting the Dose Determination Part for full doses higher than 76 mg (formerly Part 1A), data on this new step-up priming dose regimen will be first collected along with the 76 mg full dose regimen. Now, the former Part 2 of the study has become Part 1 of the study.

Some eligibility criteria have been revised including the exclusion of participants previously treated with BCMA targeted therapy which is now restricted to participants previously treated with anti-BCMA bispecific antibody.

Time points for disease response assessment have been clarified and staging systems for multiple myeloma have been explicitly defined.

Discrepancies identified in the initial Final Approved Protocol have been corrected.

Section# and Name	Description of Change	Brief Rationale
Synopsis, Section 1.3 (Schedule of Activities), Section 2.2.3.2.1 (Summaiy of Clinical Safety: Study C1071001), Section 2.3.1 (Risk Assessment), Section 5.2 (Exclusion criteria), Section 6.5.1 (Redosing criteria), Section 6.5.2 (Dose Modifications for Ekanatamab-Related Toxicity and for Peripheral Neuropathy), Section 6.8.2 (Pe1mitted Concomitant Medicationsffherapies), Section 8.2.2 (Physical exaininations), Section 8.2.9 (Peripheral neuropathy), Section 9.4.1 (Interim Safety Assessments) and Section 11 (References)	Added text describing peripheral neuropathy in paiiicipants in the C1071001 Phase 1 study and measures to mitigate this risk including additional neurological examinations, exclusion of paiiicipants who may be at higher risk for peripheral neuropathy, new redosing criteria, new dose modification guidance and new stopping mles for peripheral neuropathy.	Per regulato1y requirements (US FDA) because of the new important risk of peripheral neuropathy.
Synopsis, Section 1.3 (Schedule of Activities), Section 3 (Objectives, End_oints_and Estimands), CCI Section 9.2 (Analysis sets) and CCI	CCI	
Section 1.3 (Schedule of Activities), Section 8.2.6 (Clinical Safety Laborato1y Assessments), Section 8.3.1 (Time Period and Frequency for Collecting AE and SAE info1mation)	The safety reporting period after last dose of study intervention has been increased from 28 days to 90 days.	In order to capture all potential AEs, including late onset immune-related neurologic AEs.
Section 1.3 (Schedule of Activities), Section 5.3.1 (Contraception), Section 8.3.5.1 Ex osure Durin	Contraception use has been extended from 28 days to 90 days after the last dose of	Required by some HAs for another study and aligned across the ekanatamab clinical program.

Section # and Name	Description of Change	Brief Rationale
pregnancy), Section 10.4. (Contraceptive and Barrier Guidance)	study intervention. Pregnancy data collected until pregnancy completion or termination.	
Synopsis, Section 1.2 Schema, Section 2.3.1 (Risk Assessment), Section 2.3.2 (Benefit Assessment), Section 4.1 (Overall Design), Section 4.3.1 (Justification for the 2 Step-up Priming Doses Regimen), Section 6.1 (Study Intervention(s) Administered), Section 6.5.3 (Dose Reductions), Section 6.5.2 (Dose Modifications for Elranatamab-Related Toxicity and for Peripheral Neuropathy) and Section 6.8.1 (Premedications Required for Cytokine Release Syndrome)	Step-up priming doses reduced from 12 mg to 4 mg on C1D1 and from 32 mg to 20 mg on C1D4.	To assess whether lowering initial doses will further mitigate the risk of Grade 2 or higher CRS during the first week of treatment with elranatamab.
Synopsis, Section 1.2 (Schema), Section 1.3 (Schedule of Activities), Section 2.1 (Study Rationale), Section 2.3.1 (Risk Assessment), Section 2.3.2 (Benefit Assessment), Section 3 (Objectives, Endpoints and Estimands), Section 4 (Study design), Section 6.1 (Study Intervention Administered), Section 6.3.1 (Allocation to Study Intervention), Section 6.5.3 (Dose Reductions), Section 6.8.6 (Hematopoietic Growth Factor), Section 8.2.3 (Vital	Part 2 of the initial approved protocol becoming Part 1 and futility analysis to be conducted after enrollment in Part 1 is completed.	To assess the revised step-up priming dose regimen along with the 76 mg Full dose regimen before starting the Dose Determination Part with full doses higher than 76 mg.

Section# and Name	Description of Change	Brief Rationale
Signs), Section 9.1.1.2 (Seconda1y Estimand), Section 9.3.3.1 (Seconda1y Safety Endpoints), Section 9.4.2 (Interim Analysis for Futility), Section 9.5 (Sample Size Detennination)		
Section 1.3 Schedule of Activities and Section 8.2.4 Electrocardiograms	Added that ECG can be peiff 1med as clinically indicated.	As per US FDA request to ensure participant's safety.
Synopsis	Added inclusion criterion on sennn calcium and extended the timeframe for transfusion and use of G-CSF from 7 to 28 days.	To align across the eh-anatamab clinical program. Hypercalcemia is an important complication of Multiple Myeloma, which should be coITected prior to study participation. Exclusion of transfusions and growth factors within 28 days is necessa1y to ensure nonnal organ function.
Synopsis	Revision of exclusion criterion on BCMA targeted therapy.	To improve paiiicipant recrnitment with a less restrictive criterion.
Synopsis	Added that active infection must be resolved at least 14 days prior to emolhnent	To clai·ify exclusion criterion related to infections and to align across the eh-anatamab clinical program.
Section 1.3 (Schedule of Activities)	Revision of time points for imaging, added hepatitis B and C testing at screening, hematology only to be done at C1D4.	To align across the eh-anatamab clinical program.
CCI [redacted]	[redacted]	[redacted]

Section# and Name	Description of Change	Brief Rationale
Section 2.2.3.2 (First-in-Human Study of Eh-anatamab (C1071001))	Revision of background info1mation based on a new cut-off date of 15 April 2021.	To align with the revised fuvestigator Brochure.
CCI [redacted]	[redacted]	[redacted]
Section 4.3.3 (Definition of DLT)	Use of G-CSF, allergic reaction and anaphylactic reaction are no longer defined as DLT. Confomed DILi defined as DLT and other changes for Grade 3 non-hematologic AEs.	To align across the eh-anatamab clinical program.
Section 5.1 (fuclusion criteria)	Added inclusion criterion on sennn calcium and extended the timeframe for transfusion and use of G-CSF from 7 to 28 days.	To align across the eh-anatamab clinical program. Hypercalcemia is an important complication of Multiple Myeloma, which should be co1Tected prior to study participation. Exclusion of transfusions and growth factors within 28 days is necessa1y to ensure nonnal organ function.
Section 5.2 (Exclusion criteria)	Revision of exclusion criterion on BCMA targeted therapy.	To improve paiiicipant recrnitment with a less restrictive criterion.
Section 5.2 (Exclusion criteria)	Guidance added for COVID-19/SARS-CoV2 infection.	To clai·ify the expectations in te1ms of SARS-CoV2 testing.
Section 5.2 (Exclusion criteria)	Added that active infection must be resolved at least 14 days prior to emolhnent	To clai·ify exclusion criterion related to infections and to align across the eh-anatamab clinical program.
Section 6.1.1 (Administration)	Guidance added for the minimum of days	To align across the eh-anatamab clinical program.

Section # and Name	Description of Change	Brief Rationale
	between elranatamab doses.	
Section 6.6	Added guidance for treatment access at the end of the study participation.	To align across the elranatamab clinical program.
Section 6.8.1 Permitted Concomitant Medications/Therapies	Clarified that oral contraceptives are metabolized by CYP enzymes and thus cytokines released during elranatamab treatment may cause drug-drug interaction with hormonal oral contraceptives and may accentuate the associated side effects	As per US FDA request to protect participant's safety.
Section 7.1 (Discontinuation of Study Intervention)	Clarifications on Follow-up Visit and Survival Long Term Follow-up	To be consistent with the Schedule of Activities and to align across the elranatamab clinical program.
Section 1.3 (Schedule of Activities) and Section 8.1 (Efficacy Assessments)	Time points for Disease response assessments were clarified (every 28 days whether a dose is given or not).	To align across the elranatamab program and to make a distinction between elranatamab dosing and disease response assessment.
Section 8.1.1 (Laboratory Assessment for Evaluation of Disease Response)	Only M-protein will be collected.	To align across the elranatamab program.
Section 8.1.3 (Imaging Assessments)	Removal of 'target' lesions and addition of guidance for participants with only skin lesions.	To align across the elranatamab program.
Section 8.1.4 (Disease Characteristics and Treatment History)	Added Table on Staging Systems for Multiple Myeloma.	To more explicitly define staging system.

Section# and Name	Description of Change	Brief Rationale
Section 1.3 (Schedule of Activities) and Section 8.2.4 (Electrocardiograms)	ECG to be perfonned prior to premedications administration if applicable.	To clarify time points.
Section 8.3.8 (Adverse Events of Special Interest)	Added clarifications on premedications and AESI management.	To align across the elranatamab clinical program.
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 10.2 (Appendix 2 Clinical Laborato1y Assessments)	Added beta-2 microglobulin for multiple myeloma staging, mic acid and hepatitis B and C testing.	To align across the elranatamab clinical program.
Section 10.4 (Appendix 4 Contraceptive and BaiTier Guidance)	Removed 'Injectable' for combined estrogen and progestogen contraception.	To comply with contraception guidance.
Section 10.9 (Appendix 9) Subcutaneous Injection Site Locations	Added that injection site location will be recorded in eCRF.	As per US FDA request to evaluate the impact of injection sites on elranatamab PK.
Section 10.10 (Appendix 10 IMWG Response Criteria for Multiple Myeloma	Complete Response criteria revised when the only measmable disease is by semm FLC levels.	To comply with the IMWG Response criteria for multiple myeloma.
Section 10.11 (Appendix 11 CRS and!CANS Grading, Mitigation and Management)	Added hospitalization and premedications requirements for CRS mitigation and management.	Upon request of some HAs for another clinical study with elranatamab; to align across the clinical program.

Section # and Name	Description of Change	Brief Rationale
Section 10.12 (Appendix 12 Country specific requirements)	Added guidance for Japan.	To monitor potential HBV infection during study treatment and to specify that there is no expectation to disclose genetic testing results to the study participants, at any time.
Section 11 (References)	Added references related to the peripheral neuropathy risk	To align with protocol section text.
Global	Inconsistencies in final approved protocol corrected, minor administrative changes.	To align protocol section text.

10.17. Appendix 17: Abbreviations

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

Abbreviation	Term
AABB	American Association of Blood Banks
ADA	antidrug antibodies
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen presenting cell
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ASH	American Society of Hematology
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
AV	atrioventricular
AxMP	Auxiliary medicinal product
β-hCG	beta-human chorionic gonadotropin
BCMA	B-cell maturation antigen
BICR	Blinded Independent Central Review
BID	twice daily
BITE	bi-specific T-cell engager
BLRM	Bayesian logistic regression model
BM	bone marrow
CCI	[redacted]
BMI	body mass index
CCI	[redacted]
BOR	best overall response
BP	blood pressure
bpm	beats per minute
BsAb	bispecific antibody
BUN	blood urea nitrogen
C	cycle
C#D#	cycle and day (eg, C1D1 = Cycle 1 Day 1)
CAR-T	chimeric antigen receptor T-cell therapy
CRR	complete response rate
CD#	cluster of differentiation and number (eg, CD3)
CCI	[redacted]
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences

Abbreviation	Term
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
C_{max}	maximum observed concentration
$C_{max-24h}$	maximum observed concentration within 24 hours postdose
CMC	Chemistry, Manufacturing, and Controls
CMV	cytomegalovirus
CNS	central nervous system
CO_2	carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	c-reactive protein
CRR	complete response rate
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial; computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTMS	clinical trial management system
C_{trough}	trough concentration
CXDX	Cycle X Day X
CYP	cytochrome P450
D	day
DCR	disease control rate
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DL	dose level
DLRM	dose level review meeting
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOCR	duration of complete response
CCI	[redacted]
DOR	duration of response
DU	dispensable unit

Abbreviation	Term
DVT	deep vein thrombosis
EBMT	European Society for Blood and MaiTow Trans lantation
EBV	Epstein-Barr virus
EC	ethics committee; exclusion criteria
ECC	emergency contact card
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EEG	electroencephalographic
eGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EMD	extramedullary disease
EMG	electromyography
EMN	Emopean Myeloma Network
CCI	[redacted]
EOS	end of study
EOT	end of treatment
eSAE	electrnnic data collection tool for serious adverse event
EU	Emo ean Union
EudraCT	Emopean Union Dmg Regulating Authorities Clinical Trials (Emo ean Clinical Trials Database
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration (United States
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ h bridization
FLC	free li ht chain
FSH	follicle-stimulating hormone
FU	follow-u p
GBS	Guillain-Barre syndrome
G-CSF	granulocyte colony stimulatin factor
GCP	Good Clinical Practice
DNA	genomic DNA
GGT	gamma-glutamyl transferase

Abbreviation	Term
GI	gastrointestinal
GLP	good laboratory practice
GVHD	graft versus host disease
HA	Health Authority
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio; heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HSV	herpes simplex virus
IA	interim analysis
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICD	informed consent document
ICE	immune effector cell-associated encephalopathy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP	intracranial pressure
ICU	intensive care unit
ID	identification
IFN	interferon-gamma
Ig	immunoglobulin
IgG2	immunoglobulin G2
IHC	immunohistochemistry
IL	interleukin
IMiD	immunomodulatory imide drug
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IQR	interquartile range
IR	Immune-related
irAE	immune-related adverse events
IRB	Institutional Review Board
IRC	internal review committee

Abbreviation	Term
IRR	infusion related reaction
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ISR	injection site reaction
ISS	International Staging System
IV	intravenous
IVIG	intravenous immunoglobulins
IWR	interactive Web-based response
J-PI	Japan prescribing information
LBBB	left bundle branch block
LD	low dose
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LTFU	long term follow-up
LVEF	left ventricular ejection fraction
mAB	monoclonal antibody
mDOR	Median duration of response
MABEL	minimal anticipated biological effect level
MAD	maximum administered dose
MAP	meta-analytic-predictive
MD	multiple dose
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHC	major histocompatibility complex
MM	multiple myeloma
mmHg	millimeters of mercury
mos	months
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition
MY20	myeloma quality of life questionnaire
N or n	number
N/A	not applicable
NAb	neutralizing antibodies
NCI	National Cancer Institute
NCV	Nerve conducting velocity
NDMM	Newly Diagnosed Multiple Myeloma
NE	not evaluable
NGF	Next generation flow

Abbreviation	Term
NGS	next generation sequencing
NIMP	non-investigational medicinal product
NKF	National Kidney Foundation
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
OD	overdose
ORR	objective response rate
OS	overall survival
PACL	protocol administrative change letter
PCR	polymerase chain reaction
PD	pharmacodynamics(s); progressive disease
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	principal investigator; proteasome inhibitor
PJP	Pneumocystis Jiroveci Pneumonia
PK	pharmacokinetic(s)
PN	Peripheral neuropathy
POEMS	polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
PO	Per Os
PPP	pregnancy prevention program
PR	partial response
PR (interval)	Period, measured in milliseconds, that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization)
CCI	[redacted]
Pr(OD)	probability of overdosing
Pr(TT)	probability of target toxicity
PS	performance status
PT	prothrombin time; preferred term
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
QD	every day
QLQ-###	Quality of Life Questionnaire – Version or variant
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
Qual	qualitative

Abbreviation	Term
Q#W	every # week (eg Q2W = every 2 weeks)
R_{ac}	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RFS	relapse-free survival
R-ISS	Revised International Staging System
RNA	ribonucleic acid
ROW	rest of world
RP2D	recommended Phase 2 dose
RR	response rate; relapsed/refractory
RRMM	Relapsed or refractory multiple myeloma
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
CCI	[redacted]
SC	subcutaneous
SCIG	subcutaneous immunoglobulin
SCr	Serum Creatinine
sCR	stringent complete response
SD	stable disease
SF	superfamily
SIFE	serum protein immunofixation electrophoresis
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
CCI	[redacted]
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SPD	sum of the products of diameters
SPEP	serum protein electrophoresis
SRSD	single-reference safety document
SUSAR	suspected unexpected serious adverse reaction
SWOG	Southwest Oncology Group
$t_{1/2}$	terminal elimination half-life
TBD	to be determined
TBili	total bilirubin
TBR	tumor background ratio
TCR	t-cell receptor
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis

Abbreviation	Term
TNF	tumor necrosis factor
T_{max}	time to maximum concentration
TME	tumor microenvironment
TMF	trial master file
TNFr SF17	tumor necrosis factor receptor superfamily 17
TOC	table of contents
TT	target toxicity
TTP	time to progression
TTR	time to tumor response
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
USPI	United States Package Insert
Vd/F	apparent volume of distribution
VGPR	very good partial response
VZV	varicella zoster virus
WBC	white blood cell
WOC	withdrawal of consent
WOCBP	woman/women of childbearing potential

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