Title Page

MAGNETISMM-4

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

Study Intervention Number:	PF-06863135
Study Intervention Name:	Elranatamab
US IND Number:	153359
EudraCT Number:	2021-003885-11
ClinicalTrials.gov ID:	NCT05090566
Protocol Number:	C1071004
Phase:	1b/2
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: Umbrella Study of Elranatamab (PF-06863135) in Combination with Other Anti-Cancer Treatments in Participants with Multiple Myeloma

Document History

Document	Version Date	Applicable changes found in:(Refer to the applicable parts of this complex-protocol for the SoC)
Amendment 8	31 October 2023	Master, Sub-study A; Sub-study B, List of Studies
Amendment 7	28 July 2022	Master; Sub-study A; Sub-study B, List of Studies (revised master umbrella schematic and estimated number of participants in Sub-study A)
Amendment 6	02 Dec 2021	Master; Sub-study A; Sub-study B
Amendment 5	08 Nov 2021	Master (List of Abbreviations only); List of Studies (revised Sub-study B patient population and estimated number of participants); Sub-study B
Amendment 4	09 August 2021	Master (List of Abbreviations only); Sub-study B
Amendment 3	29 July 2021	Master; Sub-study A
Amendment 2	17 June 2021	Master; Revision and separation of Sub-study A
Amendment 1	14 February 2021	Master and Sub-study A as single document
Original protocol	11 December 2020	

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

Protocol Amendment Summary of Changes Table

Amendment 8 (31 October 2023)

Overall Rationale for the Amendment: Updated Dose Escalation Levels in Sub-study A and removed Dose Expansion part in Sub-study B.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Updated number of expected participants and list of sub-studies	Reduced number of overall participants and removed placeholder for planned Sub-studies C, D, and E	List of Sub-studies
Specified which anti-infectious prophylaxis agents are required vs recommended	Clarified anti-infectious prophylaxis guidance	Section 10.16 (Anti-Infectious Prophylaxis & Monitoring)
Non-Substantial Modifications		
Updated background information from other elranatamab clinical studies with high level summary	Most current information is contained in the elranatamab Investigator's Brochure	Section 2.2.3.2 (Clinical Overview)
Updated standard elranatamab administration text	Aligned with protocol SOP template	Section 6.1.1 (Administration)
Defined EMD	Clarified paramedullary disease or plasmacytomas associated with bone are not considered EMD	Section 8.1.3 (Imaging Assessments)
Updated timeframe of ECG collection during study conduct	Provided additional flexibility in conducting ECGs	Section 8.2.3 (Electrocardiograms)
Updated mandatory text	Aligned with protocol SOP template	Section 10.1 (Regulatory, Ethical, and Study Oversight Considerations)
Removed COVID-19/SARS-CoV-2 testing text.	COVID-19/SARS-CoV-2-specific text is provided in each sub-study	Section 10.9.1 (Eligibility)
Protocol Administrative Change Letter dated 16 November 2022 (vital signs data collection) not incorporated in this amendment	Program level decision that additional vital signs data collected during hospitalization does not need to be reported on the CRF as indicated in this PACL	Not Applicable
General editorial updates	Provided clarification, improved readability, and corrected grammatical errors	Throughout the protocol

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LIST OF TABLES

1. PROTOCOL SUMMARY

See the individual sub-study protocols for summaries.

1.1. Schedule of Activities

The individual SoA tables provide an overview of the protocol visits and procedures for each respective sub-study. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the sub-study protocols for detailed information on each assessment required for compliance with the protocol.

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

2. INTRODUCTION

Elranatamab (PF-06863135) is a heterodimeric humanized full-length bispecific IgG2 kappa mAb that is currently being investigated alone and in combination with other agents in adult patients with RRMM, as well as in adult patients with NDMM.

Study C1071004 is an umbrella protocol for the treatment of participants with MM. Elranatamab will be administered as the common therapy in combination with other anti-cancer agents.

Sub-studies (combinations of elranatamab with other anti-cancer therapies) will be included as sub-protocols to this master umbrella protocol. Each sub-study will be conducted independently. All sub-studies will begin as Phase 1 to determine the RP2D of the combination, and some sub-studies will include additional cohorts to further test the safety and efficacy of the combination.

2.1. Study Rationale

This study aims to evaluate the safety, efficacy, PK, and pharmacodynamics of combinations of elranatamab with other anti-cancer therapies in the treatment of participants with MM.

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 (Sung et al, 2021). 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 (American Cancer Society, 2021).

Despite recent advances in treatment, MM remains an incurable disease and almost all patients, even those who initially respond to treatment, are expected to relapse. Even for patients who receive ASCT, the median time to relapse is only 17.2 months (Jimenez-Zepeda

et al, 2015). Similarly, for patients who are treated with novel PI-based or IMiD-based combination regimens as frontline treatment, the median time to relapse is 16.4 months (Lopez et al, 2015).

MM patients typically receive many lines of treatment as their disease progresses and becomes 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, 2019) had received ≥ 5 lines of therapy and other trials have included populations receiving a median of 6 (min-max: 3-18) prior therapies (Mailankody et al, 2020) and a median of 5 (min-max: 3 to 18) prior therapies (Berdeja et al, 2020).

Outcomes in the RRMM population are quite poor; for example, patients with RRMM who respond poorly to PI-based or IMiD-based regimens showed a median OS of 13 months (95% CI: 11, 15) (Kumar et al, 2017). Newer and more effective therapies have substantially increased patient benefit; however, in this real-world setting (N=3449), the most recent 4-year survival is only 75% (Nandakumar et al, 2019). Results from trials in patient populations similar to the current protocol are summarized in Table 1. The lack of effective and durable therapeutic options highlights the unmet medical need in the RRMM patient population.

Table 1. Efficacy Results 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
Idecabtagene vicleucel	IMiD, PI, anti CD38 mAb	6 (3-6)	72% (72/100)[b]	11.0	ABECMA® 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 (Lonial et al, 2021)
Melphalan flufenamide + dexamethasone[a,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
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

Table 1. 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
Elotuzumab + lenalidomide + dexamethasone	IMiD, PI, melphalan	2 (1-4+)	78.5% (252/321)	Median number of (28-day) treatment cycles = 14	EMPLICITI® USPI, ELOQUENT-2 study (Bruzzese et al, 2022)
Ciltacabtagene autoleucel	IMiD, PI, anti-CD38 mAb	6	97.9% (95/97)	21.8 (21.8, NE)	CARVYKTI USPI

a Accelerated approval, ORR and mDOR are presented for belamaf dosage of 2.5 mg/kg
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 overall survival data (ie, lack of efficacy) in the ITT population of the Phase 3 OCEAN study (Oncopeptides, 2021).
(EMPLICITI (elotuzumab), 2019; BLENREP (belantamab mafodotin-blmf) USPI, 2020; POMALYST (pomalidomide capsule), 2020; ABECMA (idecabtagene vicleucel suspension) USPI, 2021; DARZALEX (daratumumab injection) USPI, 2021; KYPROLIS (carfilzomib injection) USPI, 2021; PEPAXTO (melphalan flufenamide injection) USPI, 2021; XPOVIO (selinexor tablet) USPI, 2021; CARVYKTI (ciltacabtagene autoleucel) suspension for intravenous infusion, 2022)

2.2.2. BCMA and CD3

BCMA is a transmembrane glycoprotein belonging to the TNFr superfamily. BCMA is normally expressed exclusively in lymphocytes of the B-cell lineage, including plasmablasts and differentiated plasma cells, where it is involved in the regulation of B-cell maturation. BCMA is widely expressed on malignant plasma cells collected from patients with MM whereas BCMA is detected in a very small proportion of normal BM mononuclear cells from healthy volunteers (Sanchez et al, 2012). Cleavage of cell surface BCMA by γ-secretase releases sBCMA (Laurent et al, 2015) which can act as a decoy for BCMA-directed antibodies. Inhibition of γ-secretase can reduce levels of sBCMA and increase activity of BCMA-directed therapies (Pont et al, 2019). sBCMA levels in serum are elevated in patients with MM and correlate with the proportion of MM cells in the BM microenvironment. sBCMA levels are independent of renal function, which permits its use as a biomarker in patients with renal insufficiency, and BCMA is detectable in the serum of patients with nonsecretory disease (Ghermezi et al, 2017). Moreover, patients in 2 studies with high baseline levels of sBCMA appeared to have poorer clinical outcomes (Sanchez et al, 2012; Ghermezi et al, 2017).

T-cells are potent immune cells capable of mediating adaptive immunity through the expression of TCRs, which are comprised of an alpha beta heterodimer responsible for antigen recognition and a transmembrane CD3 protein complex that mediates receptor signaling and triggering of T-cell activation (Smith-Garvin et al, 2009). TCRs recognize

specific protein fragments (ie, peptides) presented by MHC proteins on APCs, virally infected cells, and tumor cells. Triggering of CD3 signaling in a CD8+ T-cell synapsed with another cell presenting a target antigen can cause the T-cell to release perforin and granzyme B, resulting in cancer cell lysis and death. Cancer cells can avoid T-cell recognition and destruction by down modulating peptide/MHC presentation. One way to remove dependence on peptide/MHC presentation is through direct bridging of a cell-surface antigen on a target cell with the extracellular CD3 on T-cells, leading to T-cell signaling equivalent to that generated by MHC/TCR based engagement.

2.2.3. Elranatamab

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 one epitope of elranatamab to CD3-expressing T-cells and a second epitope to BCMA-expressing MM cells.

2.2.3.1. Nonclinical Studies of Elranatamab

In vitro, elranatamab has been shown to induce cytokine release by human T-cells and to redirect patient T-cells to lyse tumor cells from MM patients in a concentration-dependent manner. Elranatamab also showed robust anti-tumor activity in vivo following a single dose in 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 (Panowski et al, 2019; Karwacz et al, 2020). 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. Two 1-month GLP toxicology studies in cynomolgus monkeys using IV and SC routes of administration showed mechanism-based effects, including increased T-cell activation, increased serum cytokine concentrations and microscopic findings in the secondary lymphoid tissues. Other changes noted related to the primary pharmacology included transient decreases in circulating lymphocytes and reductions in serum globulins.

2.2.3.2. Clinical Overview

Elranatamab is being studied in adult participants with RRMM, as well as in adult participants with NDMM.

Based on Phase 1 (C1071001) and Phase 2 (C1071003) studies, elranatamab demonstrated clinically meaningful efficacy, manageable safety, and a positive benefit/risk profile for the treatment of participants with RRMM.

After 9 months of follow-up and a median (range) treatment duration of 4.37 (range: 0.03, 12.06) months, Study C1071003 met its primary endpoint demonstrating a statistically significant and clinically meaningful confirmed ORR assessed by BICR in BCMA-naïve (Cohort A) participants. The confirmed ORR by BICR was 61.0% (95% CI: 51.8, 69.6).

Elranatamab monotherapy demonstrated durable response in participants with a confirmed objective response assessed by BICR. In Cohort A, the median DOR (months) by BICR was not yet reached (95% CI: 12.0, NE), and among responders, the Kaplan-Meier probability of maintaining response at 9 months was 84.4% (95% CI: 72.7, 91.4).

For further information refer to the elranatamab IB and elranatamab (Elrexfio™) local prescribing information.

2.2.4. Background for Combination Partners

For background details on each of the combination partners including safety and efficacy data, please refer to Section 2.2 of the appropriate sub-study protocol.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of elranatamab and combination partner(s) may be found in the individual IBs or the Prescribing Information as applicable. The SRSD for elranatamab is the IB. Refer to each sub-study protocol for additional information.

2.3.1. Risk Assessment

The potential risks of clinical importance, the summary of data/rationale for risk, and the mitigation strategies for elranatamab and combination partners are presented in Section 2.3.1 of the sub-study protocols.

2.3.2. Benefit Assessment

Refer Section 2.3.2 of the individual sub-study protocols for benefit assessments.

2.3.3. Overall Benefit/Risk Conclusion

Refer to Section 2.3.3 of the individual sub-study protocols for the overall benefit/risk conclusion(s).

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Refer to Section 3 of the individual sub-study protocols for objectives, endpoints, and estimands for each sub-study.

4. STUDY DESIGN

4.1. Overall Design

Refer to Section 4.1 of each sub-study protocol for overall study design.

4.2. Scientific Rationale for Study Design

Based on preliminary data from the ongoing Phase 1 study (C1071001), elranatamab has the potential to provide clinical benefit to participants with MM (see Section 2.2.3.2). Based on

the rationale presented in Section 4.2 of each sub-protocol it is anticipated that efficacy may be improved by combining elranatamab with other anti-cancer therapies.

4.2.1. Participant Input Into Design

Refer to each sub-study protocol for participant input into design.

4.2.2. Diversity of Study Population in the United States

Reasonable attempts will be made to enroll participants with the distribution of characteristics in Table 2 to ensure the study population as a whole enrolled in the US is representative of the patient population who will use elranatamab in clinical practice.

Table 2. Demographic Breakdown of Multiple Myeloma in the US

Race	Proportion (%)
Black/African American	19
American Indian or Alaska Native	1
Asian	6
Native Hawaiian or other Pacific Islander	Not reported
White	72
Unknown	2
Ethnicity	
Hispanic or Latino(a) or of Spanish Origin	12
Not Hispanic or Latino(a) or of Spanish Origin	88
Sex	
Male	56
Female	44
Age (years)	
18-39	1
40-64	36
≥ 65	63

Source: SEER

4.2.3. Choice of Contraception/Barrier Requirements

Refer to Section 4.2.3 of the individual sub-study protocols for contraception guidelines.

4.2.4. Biomarkers

Refer to Section 4.2.4 of the individual sub-study protocols for details on biomarkers.

4.2.5. Collection of Retained Research Samples

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

4.3. Justification for Dose

Refer to Section 4.3 of each sub-study protocol.

4.3.1. Combination Partners

The doses of the combination partners will be at the respective single-agent RP2D or a suitable alternative dosing regimen as specified in Section 4.3.1 of the respective sub-study protocols.

4.4. End of Study Definition

End of study in all participating countries is defined for the entire study, which occurs once all sub-studies have met the below criteria:

For each sub-study, participants will be followed until death or for up to 2 years after the last participant first dose, whichever comes first.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

Refer to Section 5.1 of each sub-study protocol for inclusion criteria.

Participants are eligible to be included in the study only if all of the criteria listed in each of the sub-study protocols apply.

5.2. Exclusion Criteria

Refer to Section 5.2 of each sub-study protocol for exclusion criteria.

5.3. Lifestyle Considerations

Refer to Section 5.3 of each sub-study protocol.

5.3.1. Contraception

Refer to Section 5.3.1 of each sub-study protocol for contraception guidance.

5.4. Screen Failures

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

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

Refer to Section 6 of each sub-study protocol for descriptions of study interventions.

6.1. Study Intervention(s) Administered

Refer to Section 6.1 of each sub-study protocol for descriptions of study interventions administered.

6.1.1. Administration

Administration of elranatamab will be performed at the site by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study interventions at the site, participants will be observed as described in Section 6.1.1 of each sub-study protocol by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

Refer to Section 6.1.1 of each sub-study protocol for descriptions of study interventions administered.

6.2. Preparation, Handling, Storage and Accountability

Refer to Section 6.2 of each sub-study protocol for details regarding study intervention preparation, handling, dispensing, storage, and accountability.

6.2.1. Preparation and Dispensing

Refer to Section 6.2.1 of each sub-study protocol for details regarding study intervention preparation, handling, dispensing, storage, and accountability.

6.3. Measures to Minimize Bias: Randomization and Blinding

Refer to Section 6.3 of each sub-study protocol for details regarding measures to minimize bias.

6.3.1. Allocation to Study Intervention

This is an open-label study. No randomization or blinding mechanisms will be used. Based on regional or site-specific requirements or regulatory/IRB limitations, not all sub-studies of the trial may be open at all sites/regions. The sponsor may pause recruitment of sub-studies individually.

Allocation to sub-studies will be decided by the Investigator and reviewed by the Sponsor based on the participant's eligibility and availability of open slots.

6.4. Study Intervention Compliance

Refer to Section 6.4 of each sub-study protocol for details regarding study intervention compliance.

6.5. Dose Modification

Refer to Section 6.5 of each sub-study protocol for details regarding dose modifications.

- For retreatment criteria: Refer to each sub-study protocol.
- For guidance on dose interruptions/delays: Refer to each sub-study protocol.
- For details regarding dose reductions for study intervention: Refer to each sub-study protocol.
- For detailed dose modification tables: Refer to each sub-study protocol.

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

Refer to Section 6.6 of each sub-study protocol for details regarding study intervention access after the end of the study.

6.7. Treatment of Overdose

Refer to Section 6.7 of each sub-study protocol for details regarding treatment of overdose.

6.8. Concomitant Therapy

Refer to Section 6.8 of each sub-study protocol for details regarding concomitant therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Note: Results from the planned interim analyses (Section 9 in each sub-study protocol) may be used for sponsor decisions regarding termination of the study or for specific cohorts and/or investigator decisions regarding discontinuation of individual participants from study intervention or from the study.

7.1. Discontinuation of Study Intervention

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

- Objective disease progression;
- Lack of efficacy (eg, increase of disease burden not qualifying as PD according to IMWG criteria)
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy or breastfeeding;
- Medication error without associated adverse event
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Withdrawal by participant;
- Investigator decision;
- Study completed;
- 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 anti-cancer therapies and survival. Refer to each sub-study protocol SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.1.1. Follow-Up Visits (28/90 Days):

7.1.1.1. 28-35 Days Post-Dose

At least 28 calendar days, and no more than 35 calendar days after discontinuation of study intervention, participants will return to clinic for a safety follow-up visit, including review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related AEs (refer to each sub-study protocol 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.

7.1.1.2. 90 Days Post-Dose

The 90-day post-dose follow-up visit for AEs and contraception check may be performed via remote contact (eg, telephone). The investigator may complete these follow-up visits in clinic if any concerns are noted during the remote contact. This visit will coincide with the first long term follow up visit.

7.1.2. Long Term Follow-Up

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

Participants will be contacted by telephone every 12 weeks from the last dose of study drug to confirm survival status and collect information on any new anti-cancer therapies initiated/disease status. Date of disease progression recorded in the source notes will be collected. Public records may be used to find current contact information and/or to document date of death, if permitted by local law.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Withdrawal by participant;
- Lost to follow-up;
- Death;

- Study terminated by sponsor;
- Study completed.

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

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data (apart from the collection of publicly available information as described in Section 7.1.2) should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. 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 individual sub-study protocol SoAs. 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 individual sub-study protocol SoAs, 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 provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the in the individual sub-study protocol SoAs.

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

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

8.1. Efficacy Assessments

Disease response will be assessed according to IMWG response criteria (Appendix 11). All response categories (except stable disease) require 2 consecutive assessments (confirmation).

Disease assessments should continue up through the End of Treatment visit if the End of Treatment reason is PD. For participants that discontinue study intervention without disease progression and remain in follow-up, disease assessments should be conducted every 4 weeks until 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 (Appendix 11). Assessments are to be conducted at the time points specified in the individual sub-study SoAs. Assessments will include:

- SPEP for the measurement of serum proteins, including M proteins.
- SIFE for definitive identification of specific M proteins (including IgG, IgA, IgM, and kappa and lambda light chains). SIFE will be required at baseline, when SPEP shows no measurable protein, at suspected 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 not 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 required only 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, required only when both serum and urine M components are deemed non measurable (including at suspected CR). Serum free kappa, free lambda and free kappa/lambda ratio will be collected.

Note: For participants treated with daratumumab, isatuximab, or elotuzumab less than 114 days prior to baseline assessment, these drugs may interfere with SPEP and SIFE. Therefore, for these participants, serum FLC assay should be completed at screening, C0D1, and 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.

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.

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

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

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

8.1.2. Bone Marrow Sample Assessments for Evaluation of Disease Status

BM evaluations will be performed to follow disease status according to IMWG criteria (Appendix 11) at the time points specified in the individual sub-study SoAs.

In addition, screening BMA samples will be evaluated locally by FISH (and/or karyotyping if an adequate sample is obtainable) to report chromosomal abnormalities, including but not limited to those defining high-risk MM [eg, t(4;14), t(14;16), del(17/17p),] (Palumbo et al, 2015). In the case of an unevaluable BMA sample, the most recent cytogenetic results available should be reported.

If all criteria for CR are met except percent plasma cells in BM, then additional BMA/BMB should be performed every 3 months until CR is achieved, as long as other CR criteria are maintained.

BMA (required)/BMB (optional) samples will be collected as per the individual sub-study SoA to evaluate the percentage of plasma cells and in case of suspected sCR, to evaluate the presence/absence of clonal cells by immunohistochemistry, immunofluorescence (eg flow cytometry) analysis (see Appendix 11).

When BM plasma cell infiltration is assessed by both BMA and BMB, the highest value of plasma cell infiltration should be utilized for response evaluation. If BMB is performed at screening and has higher plasma cell % than BMA, then BMB should continue to be performed with BMA throughout the study.

When BMA/BMB samples are taken for response evaluation, samples for biomarker analysis will also be collected (see Section 8.6).

BMA obtained while a participant is in suspected or actual CR will be evaluated by a central lab for MRD using NGS (see Section 8.6.1).

All relevant reports must be available for source verification and for potential peer review.

8.1.3. Imaging Assessments (PET/CT, CT, MRI, or low-dose CT)

Imaging will be completed for evaluation of disease response according to IMWG criteria (Appendix 11) at the time points specified in the individual sub-study protocol SoAs. For participants with only skin involvement, skin lesions should be measured with a ruler at time points specified in the individual sub-study protocol SoAs.

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 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, 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 28 days before start of study intervention, (2) the same technique can be used to follow identified lesions throughout the study for a given participant, and (3) appropriate documentation is available in the participant's source notes indicating that these assessments were performed as standard of care.

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

8.1.4. Patient Reported Outcomes

Refer to Section 8.1.1 of each sub-study protocol for details regarding Patient Reported Outcomes.

8.1.5. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's MM, including date of initial diagnosis, current R-ISS stage, 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.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the individual sub-study protocol SoAs. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

8.2.1. Physical and Neurological Examinations

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

Neurological examinations will be performed at times specified in the individual sub-study protocol SoAs and will include assessment of mental state (including cognitive function), motor function, sensory function, gait, deep tendon reflexes, cranial nerve function, station, and coordination. All neurological examinations will be reported on the CRF.

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

Weight and height will be reported on the CRF. Height is to be recorded at screening only.

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

8.2.2. Vital Signs

Vital signs (HR, BP, temperature, and O_2 saturation) should be collected per institutional standards at time points specified in the individual sub-study protocol SoAs prior to blood collection. The only vital sign data collected on the CRF will be per the individual sub-study protocol SoAs. Any other vital sign data collected during the course of the study will be considered source data only and not reported on the CRF, any vital signs associated with AEs should be collected on the CRF.

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

Vital signs should be monitored every 4 hours (±30 min) during hospitalization for study intervention.

8.2.3. Electrocardiograms

Standard 12 lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the individual sub-study protocol SoAs 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 5 minutes in a supine position.

A triplicate ECG (3 serial ECGs) conducted within approximately 5 to 10 minutes total time will be performed at all time points, except screening (single ECG at screening), as specified in the individual sub-study protocol SoAs. ECG assessments will be performed prior to (or at least 2 hours after) PK sample collection and prior to administration of any study treatment (and premedication, when used). 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 promptly 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. 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 assessments should be skipped if CRS symptoms are ongoing.

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

8.2.4. Echocardiograms/Multigated Acquisition Scans

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

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 of the individual sub-study protocols for the list of clinical safety laboratory tests to be performed and the sub-study protocol SoAs for the timing and frequency. All protocol required laboratory assessments, as defined in Appendix 2 of each sub-study protocol, must be conducted in accordance with the laboratory manual and the sub-study protocol SoAs. 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 (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. See Appendix 15 for kidney injury safety monitoring.

All safety laboratory tests will be performed locally.

8.2.6. Pregnancy Testing

See Section 8.2.1 of the individual sub-study protocols.

8.2.7. ECOG Performance Status

ECOG PS (Table 3) will be assessed at the time points specified in the individual sub-study protocol SoAs.

Table 3. 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

8.2.8. Local Site Injection Tolerability Assessment

Any observed abnormality at the injection site will be judged by the investigator to determine whether a corresponding AE should be reported; otherwise details of these assessments will not be recorded on the CRF. When appropriate, at the discretion of the investigator, a participant with an ISR may be referred for a dermatological consultation and skin biopsy may be obtained for future examination of the ISR. If injection site reaction is noted, site tolerability assessments should continue until the symptoms resolve.

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 in this section, 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 study intervention.

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 CT SAE Report Form.

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for 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 in Section 7.3).

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities 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 for example ingestion, inhalation, or skin contact.

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

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected if EDP occurs 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, eg, ingestion, 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 Section 10.3.2 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

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

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

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 consensus grading from the ASTCT. See Appendix 12.

Premedication for CRS prophylaxis is required at the time points specified in the individual sub-study protocol SoAs. Refer to Section 6.8 of the individual sub-study protocols for premedication requirements.

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" (Lee et al, 2019). 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.

8.3.8.3. Peripheral Neuropathy

Peripheral neuropathy is a common complication of MM and its treatment. The etiology of peripheral neuropathy may be MM, 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 include paresthesias, numbness, burning

sensation and muscle weakness, which are generally mild, but in rare cases can be disabling or even life-threatening. Treatment-emergent peripheral neuropathy symptoms are usually symmetric, distal and progressive (Richardson et al, 2012). Recently, peripheral neuropathy has been described following administration of BCMA-directed bispecific T-cell engagers (Topp et al, 2020).

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

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

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

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

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

8.4. Pharmacokinetics

Refer to Section 8.4 of each sub-study protocol for details regarding sample collection and processing for combination partner PK.

8.4.1. Elranatamab

All participants will have blood samples collected for PK assessments of free and total elranatamab serum concentrations at the time points specified in the individual sub-study protocol SoAs. 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 free and total serum concentrations of elranatamab. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of PK sample collection as well as the date and time of the last dose prior to PK sample collection for each sample will be recorded in the CRF.

The actual times may change, but the number of samples will remain the same. All effort should be made to obtain the samples at the exact nominal time relative to dosing (see the SoA). Collection of samples that are obtained within 10% of the nominal time relative to dosing (eg, 2 hours and 24 minutes for the 24-hour postdose time point) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the CRF. For pre-dose PK samples, collection should occur prior to administration of pre-medications, and prior to elranatamab alone or elranatamab and any combination partner on that day.

Serum samples will be used to evaluate the PK of elranatamab. Each serum sample will be divided into 2 aliquots, to provide a minimum of 1 mL serum for each aliquot. Samples collected for analyses of free and total elranatamab serum concentration may also be used to

evaluate safety or efficacy aspects related to concerns arising during or after the study and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Samples collected for measurement of free and total elranatamab serum 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.

8.5. Genetics

8.5.1. Specified Genetics

Genetic assessments will be performed utilizing BMA, saliva, and blood samples as described in Section 8.5 and in the individual sub-study protocol SoAs.

Please refer to relevant subsections in Section 8.6.

8.5.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the individual sub-study protocol SoAs, as local regulations and IRBs/ECs allow.

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

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

8.6. Biomarkers

Refer to the individual sub-study protocols for any sub-study specific biomarker assessments.

All biomarker samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the biomarker sample handling procedures (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.

Note that to enable accurate assessment of biomarker endpoints, biomarker samples may be used for evaluation of bioanalytical methods.

All effort should be made to obtain the blood samples at the exact nominal time relative to dosing (see individual sub-study protocol SoAs). Collection of samples that are obtained within 10% of the nominal time relative to dosing (eg, 2 hours and 24 minutes for the 24-hour postdose time point) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the CRF. For pre-dose samples, collection should occur prior to administration of elranatamab alone or elranatamab and any combination partner on that day or to any premedication.

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

A BMA sample will be taken at the time points specified in the individual sub-study protocol SoAs. NGS of the pre-dose sample identifies rearranged immune receptors (eg, IgH, IgK, and IgL receptor gene sequences), as well as select translocation sequences. This unique immunoglobulin receptor repertoire defines the participant-specific dominant malignant plasma cell clone (the index clone) and is used as a reference that is compared to subsequent samples collected after initiation of treatment. BMA samples will be used to determine the MRD negativity rate with a threshold of CCI whenever a BMA/BMB sample is taken for disease response evaluation.

Screening Sample: A BMA sample collected at screening will be used for identification of the dominant (index) malignant clone. If the central laboratory is unable to identify the dominant (index) malignant clone with the screening sample, or if the participant does not have a BMA collected at screening, the site can submit an archival BMA sample. If an archival sample is not available, but the participant has a test result from a previous Adaptive Biotechnologies clonoSEQ® MRD assay performed at their Seattle, WA (US) laboratory that identified the index multiple myeloma clone, and the result is retrievable and useable in this study, the sponsor may give approval to use this result instead of submitting an alternative BMA sample.

If neither of these two options are available, the site can submit an alternative BMA sample collected at screening. Acceptable alternative or archival sample types include:

- Cells pellet/suspension from BMA, minimum 1 million cells, or
- 1 million frozen BMMCs dry cell pellet or cell suspension collected from fresh BMA, or
- BMA smear slides or touch prep slides, 3-5 slides total, or
- Re-cut slides from bone marrow clot tissue block, minimum 5 slides, 8 microns thick, or
- Re-cut scrolls from a bone marrow clot tissue block, minimum 8 scrolls, 5 microns thick, or
- Genomic DNA (gDNA) isolated from bone marrow aspirate

On-Treatment sample: A freshly collected BMA sample for MRD determination is required at various times during treatment (ie, after C0D1). If the central laboratory is unable to determine MRD status with the on-treatment sample that was submitted, the sponsor may request an alternative sample type from the same collection.

The BMA sample types for MRD tracking include any of the following (see the Laboratory Manual for specific sample requirements):

- Cell pellet/suspension from BMA, minimum 1 million cells, or
- 5-10 million frozen BMMCs dry cell pellet or cell suspension collected from fresh BMA.
- Genomic DNA (gDNA) isolated from bone marrow aspirate.

8.6.2. Bone Marrow Biopsy for Protein Profiling

A BMB may be collected at the times specified in the sub-study protocol SoAs. If BMB was not collected at screening for disease assessment, then a BMB sample is optional for all collections.

This sample will be used to assess the levels and/or distribution of a range of markers implicated in MM (eg, BCMA, immune cell populations).

8.6.3. Bone Marrow Aspirate for Molecular Profiling

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

RNA and DNA sequencing analysis will be performed and the data will be used to examine correlations between gene mutation status or gene expression signatures and clinical outcome. As samples will be collected while participants are on treatment and at EOT, these analyses may also define the pharmacodynamics of elranatamab and/or combination partner(s), or identify biomarkers that correlate with and potentially define mechanisms of resistance and relapse.

8.6.4. Serum Sample to Assess Circulating Proteins and/or Metabolite Analysis

A serum sample will be collected at time points specified in the individual sub-study protocol SoAs. This sample will be used for circulating protein analysis, M protein analysis (eg, mass spectrometry analysis to track residual disease) and/or metabolomic analysis. If CRS is suspected, an additional sample should be collected if not already scheduled.

8.6.5. Blood Sample to Assess sBCMA Levels

A plasma sample for sBCMA assessment will be collected at the times specified in the individual sub-study protocol SoAs. An additional plasma sample for sBCMA assessment should also be collected at the time of PD if a sample is not already scheduled to be taken. sBCMA levels will be measured in plasma at baseline and at various time points during study intervention, which may enable correlations between sBCMA levels and drug exposure and response. Instructions for sample collection, processing, storage and shipment will be provided in the laboratory manual.

8.6.6. Blood Sample for T-cell Receptor (TCR) Sequencing

A blood sample will be collected at time points specified in the individual sub-study protocol SoAs. This sample will be used to assess the clonality, diversity and pharmacodynamics of the peripheral blood TCR repertoire.

8.6.7. Blood Sample for Immune Cell Profiling

A blood sample will be collected at time points specified in the individual sub-study protocol SoAs. This sample will be used to examine the levels and distribution of blood cell populations by either by RNA sequencing analysis and/or by DNA sequencing and/or by specialized epigenetic phenotyping approaches.

8.6.8. Blood Sample for Circulating Free (cf) DNA

A blood sample will be collected at time points specified in the individual sub-study protocol SoAs. This sample will be used to examine cfDNA.

Collection of this sample is not applicable for participants at sites unable to process the sample per the laboratory manual.

8.6.9. Saliva Sample for Germline Comparator

A saliva sample will be collected from all participants pre-dose on C0D1 and will be used for exploratory targeted and/or whole exome/genome sequencing. These samples will be used as a germline comparator to identify somatic tumor DNA mutations and will not be used to generate free standing germline sequencing results.

8.7. Immunogenicity Assessments

8.7.1. Elranatamab

Blood samples of approximately 5 mL, to provide a minimum of 2 mL serum, will be collected for determination of ADA and NAb into appropriately labeled tubes at times specified in in the individual sub-study protocol SoAs. Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Participants having an unresolved AE that is possibly related to anti-elranatamab antibodies at their last assessment will be asked to return to the clinic for ADA and drug concentration

blood sampling at approximately 3-month intervals until the AE or its sequelae resolve or stabilize at a level acceptable to the investigator and sponsor.

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

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

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

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

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

See Section 9 of the individual sub-study protocols.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant 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

Refer to the individual sub-study protocols.

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 Study 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 Source Document Locator, 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.

The sponsor or designee will perform monitoring 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. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. 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.

10.1.11. 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.

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

10.1.12. Sponsor's Qualified Medical Personnel

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

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

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

10.2. Appendix 2: Clinical Laboratory Assessments

See Appendix 2 of each sub-study protocol.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of 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 term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect.

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

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

g. Other situations:

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

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

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

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported 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 reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). **

Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

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

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

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

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

Assessment of Severity

- The investigator will make an assessment of severity for each AE reported during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE v5.0 system). An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

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.

The severity of CRS and ICANS will be graded according to ASTCT criteria (Lee et al, 2019). See Section 10.12.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an**

assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Electronic Data Collection Tool or CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Paper CT SAE Report Form

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

See the individual sub-study protocols for male and female participant reproductive inclusion criteria, women of childbearing and non-childbearing potential, and contraception methods (Sections 10.4.1 through 10.4.4).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for specified genetic analysis (see Section 8.5.1) will be stored for up to 15 years or other period as per local requirements beyond the completion of this study (eg, CSR finalization).
    - Retained samples for banking will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
    - Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × 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. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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 May 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 by ≥60 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 short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious AE

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New onset left bundle branch block (QRS complex >120 ms).
• New onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).

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

ECG Findings That Qualify as SAE

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

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

10.8. Appendix 8: Country-Specific Requirements

See the individual sub-study protocols for any country-specific requirements.

10.9. Appendix 9: Alternative Measures During Public Emergencies

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

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

10.9.1. Eligibility

See the individual sub-study protocols for specific requirements.

10.9.2. Telehealth Visits

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

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

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

10.9.3. Alternative Facilities for Safety Assessments

10.9.3.1. 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. See the individual sub-study protocols for safety laboratory evaluations which may be performed at a local laboratory.

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.

10.9.3.2. Imaging

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

10.9.3.3. 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.

10.9.4. 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:

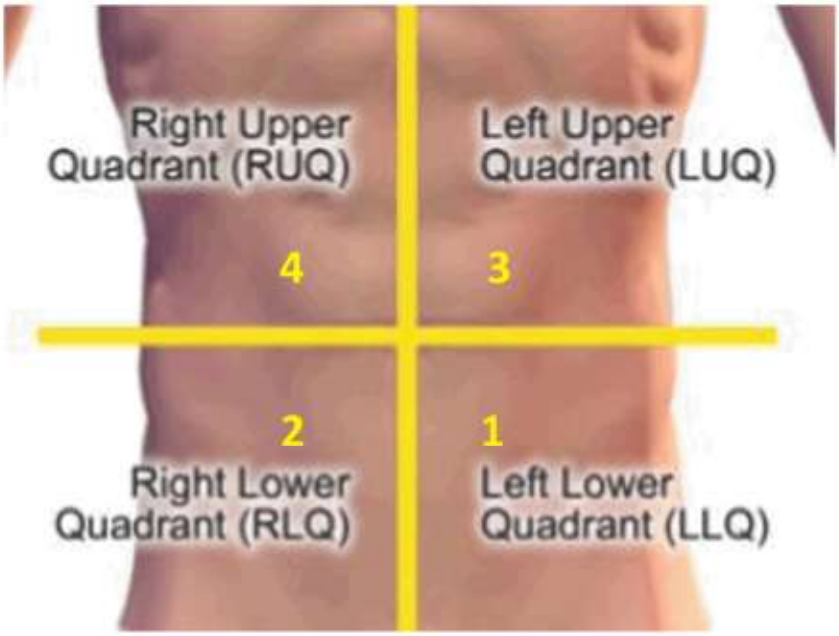
- For symptomatic participants with active SARS-CoV-2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV-2-related symptoms should have recovered to Grade $\leq$1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in the individual sub-study protocols for any concomitant medication administered for treatment of SARS-CoV-2 infection.

10.9.5. Adverse Events and Serious Adverse Events

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

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

10.10. Appendix 10: 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.

If more than 1 study intervention is administered SC, the 2 treatments should not be administered in the same quadrant whenever possible so that it will be easier to distinguish which drug caused any injection site reactions that may occur.

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 8.3 for AE reporting.

10.11. Appendix 11: IMWG Response Criteria for Multiple Myeloma

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

- Serum M protein ≥0.5 g/dL (5 g/L);
- Urine M protein ≥200 mg/24 hours;
- Serum FLC assay: involved FLC level ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65).

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

All response assessments will be entered on the CRF.

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

Response[a]	Modified IMWG Criteria
Sustained MRD-negative	• CR as defined below plus: • MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	• CR as defined below plus: • Absence of phenotypically aberrant clonal plasma cells by NGF on BMA using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
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 of BMA using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
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 surrounding normal tissue
Stringent Complete Response (sCR)	• CR as defined below plus: – Normal serum FLC ratio and absence of clonal cells in BMA/BMB by immunohistochemistry, immunofluorescence (eg, flow cytometry).[b,c] – If the only measurable disease is by serum FLC levels, sCR is defined as normal serum FLC ratio of 0.26 to 1.65 plus absence of clonal cells in BMA/BMB by immunohistochemistry, immunofluorescence (eg, flow cytometry)[b,c]

Response[a]	Modified IMWG Criteria
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 at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.[d]
No Change/Stable Disease (SD)	• Not meeting criteria for sCR, CR, VGPR, PR, MR or PD.
Progressive Disease (PD)[b,e,f]	Any 1 or more of the following criteria: • Increase of ≥25% from lowest confirmed response value in any 1 or more of the following:[e,f] • Serum M-component (the absolute increase must be ≥0.5 g/dL); • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; • Urine M-protein (the absolute increase must be ≥200 mg/24 h). • In participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved serum FLC levels (absolute increase must be >10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved serum FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%). • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis.[d] • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

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

Response[a]	Modified IMWG Criteria

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

c Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by IHC or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

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

e PD confirmation requires two consecutive assessments made at any time prior to the institution of any new anticancer therapy. If alternate therapy is started before confirming PD, any additional testing during subsequent therapy can be used to confirm PD. Participants will be considered to have PD if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for participants who had a measurable serum or urine M-protein (M-spike) at baseline, PD cannot be defined by increases in serum FLC alone.

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

ADDITIONAL NOTES:

- If participants do not have measurable disease at baseline they can only be assessed for at least a CR or PD.
- Serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable (including at suspected CR).
- 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)

10.12. Appendix 12: CRS and ICANS Grading, Mitigation

10.12.1. Cytokine release syndrome

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 (Lee et al, 2019)(Table 4). For CRS management, published treatment guidelines are recommended but they may be modified as needed by the responsible investigator according to the best practices at their institute (Neelapu et al, 2018; Neelapu, 2019).

Table 4. 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)

10.12.1.1. CRS management guidelines by ASTCT Severity Grading

(Neelapu et al, 2018; Neelapu, 2019)

For all participants during hospitalization for study intervention:

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

Grade 1 CRS:

Fever

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

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 hours; if refractory, increase to 20 mg IV every 6 hours.

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 (Lee et al, 2019). If ICANS is observed in relation to elranatamab, the ASTCT criteria will be used for grading and

published guidelines are recommended for management (Neelapu et al, 2018; Lee et al, 2019; Neelapu, 2019).These treatment guidelines may be modified as needed by the responsible investigator according to the best practices at their institute.

Table 5. 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 6. 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

Table 6. ASTCT ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4

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)

10.12.2.1. ICANS Management Guidelines Per ASTCT

(Neelapu et al, 2018; Neelapu, 2019)

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 3 doses;
    - levetiracetam 1000 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion;
    - phenobarbital 30 mg IV every 12 hours; duration of therapy per investigator/treating physician's discretion.
  - Lacosamide may also be considered for treatment of seizures should the seizures persist. Lacosamide should not be used in participants with concurrent CRS in order to avoid arrhythmias and hypotension.
- For convulsive status epilepticus:
  - Assess airway, breathing, and circulation; check blood glucose.
  - Transfer to ICU.
  - Lorazepam 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures.
  - Levetiracetam 500 mg IV bolus, as well as maintenance doses.
  - If seizures persist, add phenobarbital at a loading dose of 15 mg/kg IV.
  - Maintenance doses after resolution of convulsive status epilepticus:
    - lorazepam 0.5 mg IV every 8 hours for 3 doses;
    - levetiracetam 1000 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 $PaCO_2$ of 28–30 mmHg, but maintained for no longer than 24 hours.
  - Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below):
    - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40.
    - Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50-75 mL/hour while monitoring electrolytes every 4 h, 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: Multiple Myeloma Staging

Table 7. R-ISS Staging System for Multiple Myeloma

Stage	Revised-ISS (R-ISS)
I	ISS stage I and standard-risk chromosomal abnormalities by FISH[a] and Serum LDH < ULN
II	Not R-ISS stage I or III
III	ISS stage III and either High-risk chromosomal abnormalities by FISH[b] or Serum LDH > ULN

a. Standard risk chromosomal abnormalities by FISH = no high-risk chromosomal abnormality.
b. High risk chromosomal abnormalities by FISH = Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Source: (Palumbo & Anderson, 2011).

10.14. Appendix 14: Prior Lines of Therapy

The following guidelines (adapted from (Rajkumar SV, 2015)) 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, include, but are not limited to; end of planned therapy.

- **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.

10.15. Appendix 15: Kidney Safety Monitoring Guidelines

10.15.1. 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.

10.15.2. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.15.3. Age-Specific Kidney Function Calculation Recommendations

10.15.3.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	SCr *(mg/dL)*	Scys *(mg/L)*	Recommended eGFR Equation
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (SCr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (SCr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (SCr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (SCr/0.9)^{-1.200} \times (0.9938)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49. (Inker et al, 2021)

10.15.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to CTCAE criteria.

10.16. Appendix 16: Anti-infectious Prophylaxis and Monitoring

Participants should receive antimicrobial prophylaxis as per the guidelines below.

Prophylaxis	Therapy	Start	Stop
REQUIRED			
Hypogammaglobulinemia/ Immunoglobulin replacement [eg, subcutaneous or intravenous immunoglobulin (IVIG) (required)	Monitor immunoglobulin levels for the occurrence of hypogammaglobulinemia.	Administer immunoglobulin for IgG level ≤400 mg/dL. Can be given before or after elranatamab.	Until resolution of hypogammaglobulinemia
Antiviral (required)	Acyclovir or alternative	Antiviral prophylaxis within 1 week after starting treatment is required to prevent HZV reactivation	Continue for 3 months following the end of treatment
CMV (required)	CMV testing by PCR is required prior to study drug administration at study entry. On-study testing should be performed every 1 to 3 cycles depending on risk factors and baseline CMV viral load: • Valganciclovir 900 mg PO BID • Alternative antiviral (ganciclovir IV, foscarnet IV) or other approved agents.	For participants with CMV copy number ≥1000/mL, initiation of antiviral treatment is recommended (other risk factors including the rise in CMV copy number should be considered). Treatment should be given for symptomatic participants irrespective of viral load.	Continue therapy until 2 consecutive measurements at least 14 days apart show viral load <1000/mL and resolution of symptoms (if present).
Pneumocystis Pneumonia (PCP) (required)	PCP prophylaxis is required for all participants for at least 6 months. Trimethoprim-sulfamethoxazole DS 1 tablet PO daily, 3 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: 6 months OR 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.

Prophylaxis	Therapy	Start	Stop
RECOMMENDED			
Anti-Bacterial (recommended)	Fluoroquinolones (levofloxacin 500 mg PO or IV daily, or equivalent)	For all participants, administration of an initial 3-month prophylactic course of fluoroquinolones is recommended.	Stop after 3 months of initial prophylaxis if ANC ≥1000/µL.
	Suggested alternative for participants with allergy to quinolones: Cefpodoxime 200 mg PO twice a day	After initial 3-month treatment, administer for participants with ANC <1000/µL	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.
Anti-Fungal (recommended)	Fluconazole 400 mg daily (or equivalent)	Recommended for participants with 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.
	Consider switch to posaconazole or equivalent	Prolonged ANC <500/µL >3 weeks	Until neutropenia resolution (ANC ≥500/µL)
Neutropenia/G-CSF Prophylaxis (recommended)	Prophylactic administration of G-CSF[a,b] in a participant who is experiencing neutropenia or therapeutic use in participants with serious neutropenic complications should be considered by investigators consistent with the ASCO guidelines (2015) (Smith et al, 2015) 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.

a. Eligibility restricts use within 7 days of first elranatamab dose.
b. Prophylactic use not allowed during DLT evaluation period.
References: (Smith et al, 2015; Dimopoulos et al, 2021; NCCN, 2022a; NCCN, 2022b; NCCN, 2022c; Raje et al, 2022)

10.17. Appendix 17: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 7 (28 July 2022)

Overall Rationale for the Amendment: Alignment and consistency with global clinical practice and across the elranatamab clinical program.

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
Section 2.2.3.2. Clinical Overview	Updated data from C1071001 study and added data from C1071003 study	To reflect current available clinical data on elranatamab and provide update on clinical experience with elranatamab in the target patient population.	Y
Section 2.2.3.2.5. Other Elranatamab Studies	Added a new section about other elranatamab studies	To provide current information.	Y
Section 8.1. Efficacy Assessments	Updated the disease assessment duration by removing the condition of "start of new anti-cancer therapy".	To align across the elranatamab clinical program	Y
Section 8.1.2. Bone Marrow Sample Assessments for Evaluation of Disease Status	Updated the evaluation for screening BMA samples and collection requests for BMA and BMB samples.	To align with information provided in the sub-study protocols.	Y
Section 8.1.3. Imaging Assessments (PET/CT, CT,	Added explanation about evaluation of radiologic progression observed within	To avoid incorrect declaration of progressive disease due to pseudo-	Y

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
MRI, or low-dose CT)	the first month following the first dose of elranatamab.	progression, which is a class effect that can occur with BCMA CD3 engagers	
Section 8.6.1. Bone Marrow Aspirate for Minimal Residual Disease (MRD)	Added instructions for both screening sample and on-treatment sample collection.	To provide detailed instructions for sample collection and align with information provided in the sub-study protocols.	Y
Section 8.6.2. Bone Marrow Biopsy for Protein Profiling	Added explanation for BMB sample collection and its purpose.	To provide detailed instructions for sample collection and align with information provided in the sub-study protocols.	Y
Section 8.6.8. Blood Sample for Circulating Free (cf) DNA	Added instructions for collection blood sample for cfDNA examination.	To provide instructions about cfDNA examination.	Y
Section 10.9. Appendix 9: Alternative Measures During Public Emergencies	Specified window for positive test result for SARS-CoV-2 infection.	To clarify allowed window	Y
Section 10.11. Appendix 11: IMWG Response Criteria for Multiple Myeloma	Updated criteria for serum FLC assay and listed the full modified IMWG criteria	To align across the elranatamab clinical program	Y
Section 10.15 Appendix 15: Kidney Safety	Added new section.		Y

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
Monitoring Guidances		To provide guidance for kidney injury safety monitoring	
Section 8.2.5 Clinical Safety Laboratory Assessments	Added reference to the new appendix: Appendix 15: Kidney Safety Monitoring Guidances		N
Section 10.16 Appendix 16: Anti-infectious Prophylaxis and Monitoring Recommendation	Added new section.	To provide guidance for infection monitoring and treatment	Y
Title page and Section 2.	Added ClinicalTrial.gov ID and updated the brief title.	To update study information.	N
Section 2.2.1 Multiple Myeloma	Updated literature reports about study results from RRMM patients	To provide current information.	N
Section 7.1. Discontinuation of Study Intervention	Modified reasons for permanent discontinuation of study intervention by adding "breastfeeding", "Medication error without associated adverse event", "Withdrawal by participant"; "Investigator decision"; and "Study completed"; removed "Completed".	To provide additional reasons for discontinuing study treatment.	N
Section 7.2. Participant Discontinuation/Withdrawal From the Study	Removed "Refused further study procedures" and "Completed"; added "Withdrawal by participant", and "Study completed".	To provide additional reasons for participant discontinuation/withdrawal.	N
Section 8.1.1. Laboratory Assessment for Evaluation of Disease Response	Updated the measurement requests for SPEP, SIFE, and 24-hour UPEP.	To align across the elranatamab clinical program	N

Section # and Name	Description of Change	Brief Rationale	Substantial (Y/N)
Section 8.2.2. Vital Signs	Extended window for vital sign monitoring during hospitalization.	To provide increased flexibility.	N
Section 8.2.5. Clinical Safety Laboratory Assessments	Added explanation about laboratory report reviewing on days of study drug administration.	To provide clarifications.	N
Section 8.3.6. Cardiovascular and Death Events	Added instructions to refer to Appendix 7 for ECG findings of clinical significance and to Appendix 3 for reporting of deaths.	To provide clarifications.	N
Section 8.4.1. Elranatamab	Clarified for pre-dose PK samples, "collection should occur prior to administration of pre-medications, and prior to elranatamab alone or elranatamab and any combination partner on that day."	To clarify for the process of sample collection.	N
Section 8.6.4. Serum Sample to Assess Circulating Proteins and/or Metabolite Analysis	Updated the purpose for serum samples collected for circulating protein analysis, M protein analysis and/or metabolomic analysis.	To provide detailed instructions for sample collection and align with information provided in the sub-study protocols.	N
Global	Minor and editorial updates throughout	To provide clarifications and improve readability	N

Amendment 6 (02 December 2021)

Overall Rationale for the Amendment: Alignment and consistency with global clinical practice and across the elranatamab clinical program

Section and Name	Description of Changes	Brief Rationale
Section 8.3.8.3 (Peripheral Neuropathy)	New section; wording was moved from Section 8.2.9 to Section 8.3.8.3	Peripheral neuropathy is considered an Adverse Event of Special Interest
Section 8.1.2 (Bone Marrow Sample Assessments for Evaluation of Disease Status); Section 10.11 (Appendix 11: IMWG Response Criteria for Multiple Myeloma)	Added immunofluorescence and flow cytometry for the determination of sCR; Made BMB sampling optional; Added criteria for VGPR, and additional notes to Appendix 11	To align with global clinical practice and add clarity to IMWG response criteria for MM
Section 8.6.1 (Bone Marrow Aspirate for Minimal Residual Disease (MRD))	Added allowance of alternate bone marrow sample types for MRD analysis	To facilitate MRD analysis
Title page	Added EudraCT number	C1071004 is a global study
Section 2.2.1 Multiple Myeloma (Table 1)	Added footnote indicating that Pepaxto was withdrawn from the US market on 22 October 2021	Provide notification that a therapy previously available has been removed from the US market
Section 7 (Discontinuation of Study Intervention and Participant Discontinuation / Withdrawal)	Added statement that interim analyses results can be used by the sponsor for decision-making; Added additional discontinuation reasons	Clarification of data use regarding study decision-making
Section 8.1.1 (Laboratory Assessment for Evaluation of Disease Response)	Deleted the use of urine specimens should be used for M-protein (M-spike) laboratory assessments	Clarified that only serum specimens should be used for M-protein (M-spike) laboratory assessments
Section 8.2.2 (Vital signs)	Added statement that vital signs associated with AEs are recorded on the CRF	Clarification of data collection
Section 10.1.7 (Data Quality Assurance)	Added definition of QTLs	Provided for completeness regarding monitored study parameters.
Section 10.7 (Appendix 7: ECG Findings of Potential Clinical Concern)	Added information in footnote regarding enumerated list of major events of potential clinical concern	Provided for completeness
Section 10.9.3.2 (Imaging) and Section 10.9.3.3 (Electrocardiograms)	Added sub-section regarding imaging and renumbered subsequent sub-section	Clarification of instruction regarding imaging assessments

Section and Name	Description of Changes	Brief Rationale
Section 10.14 (Appendix 14: Prior Lines of Therapy)	New appendix added	Guidance to quantitate number of prior therapies for eligibility criteria
Appendix 16: Abbreviations	Updated abbreviations	Abbreviations revised as applicable
Global	Minor and editorial updates throughout	To provide clarifications and improve readability

Amendment 5 (08-November-2021)

Updated Appendix 15 (List of Abbreviations). No content changes were made to Master Protocol under Protocol Amendment 5.

Amendment 4 (09-August-2021)

Updated Appendix 15 (List of Abbreviations). No content changes were made to Master Protocol under Protocol Amendment 4.

Amendment 3 (29-July-2021)

No changes to Master Protocol.

Amendment 2 (17-June-2021)

Overall Rationale for Amendment 2: Restructured protocol.

Section # and Name	Description of Change	Brief Rationale
Global	Restructured and reformatted content in the master protocol and sub-study protocols.	To simplify future revision and review of sub-studies, and facilitate each sub-study functioning as an independent study.
Section 2.2 (Background)	Updated background information and clinical data from C1071001 First in Human study.	To provide current information and align with the updated elranatamab Investigator's Brochure.
Section 7.1.1 (Follow-Up Visits (28/90 Days); Section 8.3.1 (Time Period and Frequency for Collecting AE and SAE Information)	The safety reporting period after last dose of study intervention was increased from 28 days to 90 days.	To align across the elranatamab clinical program by capturing all potential AEs, including late onset immune-related neurologic AEs.

Section # and Name	Description of Change	Brief Rationale
Section 8.2 (Safety Assessments)	Added text describing peripheral neuropathy and requirements for the neurological examinations.	To align across the elranatamab clinical program per regulatory requirements for the new important potential risk of peripheral neuropathy.
Section 10.10 (Appendix 10 Subcutaneous Injection Site Location)	Added that injection site location will be recorded in the CRF.	To align across the elranatamab clinical program.
Global	Minor and editorial updates throughout; References and Abbreviations updated.	To provide clarifications; To align with information provided in the sub-study protocols and revised protocol template (company standards).

Amendment 1 (14-February-2021)

Overall Rationale for the Amendment:

Changes included incorporating regulatory-required (US FDA) updates during the IND submission; elranatamab clinical program alignment changes; and general updates for clarification/correction. Due to the restructuring and reformatting in Protocol Amendment 2, the detailed list of Amendment 1 Summary of Changes can be found in Protocol Amendment 1. There were no site activations under Protocol Amendment 1, and no participants will be allowed to enroll under Protocol Amendment 1.

10.18. Appendix 18: Abbreviations

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

Abbreviation	Term
AABB	American Association of Blood Banks
ABC	antigen binding capacity
14C	carbon-14 (radioactive isotope of carbon with an atomic nucleus containing 6 protons and 8 neutrons)
ADA	anti-drug antibody(ies)
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AIDS	Acquired Immune Deficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen-presenting cell
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASH	American Society of Hematology
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration versus time curve
AUC_{last}	area under the concentration versus time curve from time 0 to the last measurable concentration
Auto-HSCT	autologous hematopoietic stem cell transplantation
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	Beta human chorionic gonadotropin
BCMA	B-cell maturation antigen
BICR	blinded independent central review
BID	twice a day
BiPAP	Bilevel Positive Airway Pressure
BLRM	Bayesian Logistic Regression Model
BM	bone marrow
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BMMC	bone marrow mononuclear cells

Abbreviation	Term
BOR	best overall response
BP	blood pressure
bpm	beats per minute
BRR	biochemical response rate
BsAb	bispecific antibody
BUN	blood urea nitrogen
CAR T	chimeric antigen receptor T-cell
CBC	complete blood count
CD#	cluster of differentiation #
CDC	Centers for Disease Control and Prevention
cf	circulating free
cfDNA	circulating-free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIPN-20	chemotherapy-induced peripheral neuropathy questionnaire
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-EPI	chronic kidney disease-epidemiology collaboration
C_{max}	maximum observed concentration
$C_{max-24h}$	Cmax within 24 hours post first dose
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRR	complete response rate
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CSR	clinical study report
CT	computerized tomography, clinical trial
CTCAE	Common Terminology Criteria for Adverse Events(per National Cancer Institute [NCI])
CTIS	Clinical Trials Information System

Abbreviation	Term
C_{trough}	predose trough concentration
CV	cardiovascular
CxDx	Cycle and Day (eg, Cycle 1 Day 1 = C1D1)
CYP3A	cytochrome P450 3A
DDI	drug-drug interaction
Dex	dexamethasone
DILI	drug-induced liver injury
DL(-x)	dose level minus x (eg, dose level minus 1 = DL(-1))
DLT	dose-limiting toxicity
DLx	dose level x (eg, dose level 1 = DL1)
DNA	deoxyribonucleic acid
DOCR	duration of complete response
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
DS	double strength
DT	desmoid tumor
DVT	deep vein thrombosis
E	elranatamab
EBMT	European Society for Blood and Marrow Transplantation
EC	Ethics Committee
EC50	half maximal effective concentration
ECC	emergency contact card
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EMD	extramedullary disease
EMG	electromyography
EMN	European Myeloma Network
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - 30

Abbreviation	Term
EORTC-QLQ-CIPN20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CIPN 20-item scale
EOS	end of study
EOT	end of treatment
ePRO	electronic Patient Reported Outcomes
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	escalation with overdose control
FDA	Food and Drug Administration (United States)
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FLC	free light chain
FSH	follicle-stimulating hormone
FU	follow-up
GB	Guillain Barré
GBS	Guillain Barré Syndrome
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
gDNA	genomic deoxyribonucleic acid
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Clinical Practice
GS	Gamma secretase
GSI	gamma secretase inhibitor
GVHD	graft versus host disease
h	hour, hours
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio, heart rate
HRT	hormone replacement therapy
HSCT	hematopoietic stem-cell transplantation

Abbreviation	Term
HZV	herpes zoster virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICANS	immune effector cell-associated neurotoxicity syndrome
ICD	Informed Consent Document
ICE	immune effector cell encephalopathy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP	intracranial pressure
ICU	intensive care unit
ID	identification
Ig#	immunoglobulin (eg, IgM, IgA)
IHC	immunohistochemistry
IL-#	interleukin (eg, interleukin 6)
IMiD	immunomodulatory drug
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
IND	investigational new drug
IP	investigational product
IPAL	Investigational product accountability log
IR	immune-related
IRB	Independent review board
IRT	interactive response technology
ISR	injection site reaction
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
LDH	lactic dehydrogenase
Len	lenalidomide
LFT	liver function test
LLQ	lower left quadrant; lower limit of quantification
LPLV	last participant last visit
LTFU	long-term follow-up
LUQ	left upper quadrant
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody

Abbreviation	Term
MAD	maximum administered dose
CCI [redacted]	
mbBCMA	membrane-bound BCMA
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
mITT	modified intent-to-treat
MM	multiple myeloma
MQI	qualified medical personnel
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
MY20	myeloma quality of life questionnaire
N	total number, number of DLT-evaluable participants
N/A	not applicable
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NCV	nerve conduction velocity
NDMM	newly diagnosed multiple myeloma
NE	not evaluable
NGF	next-generation flow
NGS	next generation sequencing
NIMP	non-investigational medicinal product
NSAID	nonsteroidal anti-inflammatory drug
OD	overdose
ORR	objective response rate
OS	overall survival
OvGCT	ovarian granulosa cell tumors
PACL	Protocol Administrative Change Letter
$PaCO_2$	partial pressure of arterial carbon dioxide
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PD	progressive disease, pharmacodynamic(s)
PE	pulmonary embolism

Abbreviation	Term
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI	proteasome inhibitor
PJP	pneumocystis jirovecii pneumonia
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	oral(ly)
POC	proof of concept
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PPP	pregnancy prevention programme
PR	partial response, pulse rate
PRO	patient-reported outcome
PS	performance status
PT	preferred term
PT/INR	prothrombin time/international normalized ratio
PVC	premature ventricular contraction/complex
Q#	every # (eg, Q28 days = every 28 days)
Q#W	every # week (eg, Q2W = every 2 weeks)
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QD	once daily
QoL	quality of life
QSP	quantitative systems pharmacology
QT interval	start of the Q wave to the end of the T wave
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
QW	once every week
RECIST	Response Evaluation Criteria in Solid Tumours
REMS	risk evaluation and mitigation strategy
R-ISS	Revised International Staging System
RLQ	right lower quadrant
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RRMM	relapsed/refractory multiple myeloma
RUQ	right upper quadrant

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sBCMA	soluble BCMA
SC	subcutaneous(ly)
SCR	screening
sCR	stringent complete response
SCr	Serum creatinine
SCT	stem cell transplant
Scys	serum cystatin C
SD	stable disease
SEER	Survival Epidemiology and End Results
SEM	standard error of the mean
SIFE	serum immunofixation electrophoresis
SJS	Stevens-Johnson syndrome
SJS	Stevens-Johnson syndrome
SmPC	summary of product characteristics
SoA	schedule of activities
SOC	standard-of-care
SoC	Summary of Changes
SOP	standard operating procedure
SPD	sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	serum protein electrophoresis
SRSD	single reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	standardized uptake value
T-ALL	T-cell lymphoblastic leukemia
Tbili	total bilirubin
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
T-LBL	T-cell lymphoblastic lymphoma
T_{max}	time to maximum concentration
TMF	trial master file
TMP/SMX	trimethoprim/sulfamethoxazole
TNFr SF 17	tumor necrosis factor receptor superfamily 17

Abbreviation	Term
TOC	table of contents
TSH	thyroid stimulating hormone
TTR	time to response
UIFE	urine immunofixation electrophoresis
UK	United Kingdom
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
USPI	United States Prescribing Information
VGPR	very good partial response
Vpop	virtual population
vs	versus
VTE	venous thromboembolism
WBC	white blood cell
WOC	withdrawal of consent
WOCBP	women of childbearing potential

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