NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	MagnetisMM-16: An International, Multicenter, Non-Interventional Post-Authorization Safety Study (PASS) to Evaluate the Effectiveness and Safety of Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Treated in Real-World Settings
Protocol number	C1071016
Protocol version identifier	1.0
Date	31 August 2023
EU Post Authorization Study (PAS) register number	EUPAS106401
Active substance	PF-06863135
Medicinal product	ELREXFIO® (elranatamab-bcmm)
Research question and objectives	**Research questions:** - What is the effectiveness of elranatamab in patients with RRMM treated in real-world clinical settings? - What is the frequency of adverse events in patients with RRMM treated with elranatamab in real-world clinical settings? **Objectives:** 1. To evaluate the effectiveness of elranatamab through the collection and analysis of the following clinical outcomes [defined according to the International Myeloma Working Group (IMWG) consensus criteria for response in multiple myeloma (MM)]: • Overall response rate (ORR) • Time to response (TTR) • Duration of response (DOR) • Progression free survival (PFS) • Overall survival (OS)

	• Time to next treatment (TTNT) 2. To characterize the safety of elranatamab in real-world settings through the solicited collection and summary of adverse events. **Patient Reported Outcomes (Germany only):** 1. To evaluate patient quality-of-life (QoL) by assessing the impact of elranatamab on patient-reported symptoms and functioning, in a real-world setting using the following patient-reported outcome (PRO) instruments: • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) • European Organization for Research and Treatment of Cancer Multiple Myeloma Questionnaire (EORTC QLQ-MY20)
Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADC	antibody drug conjugate
AE	adverse event
AEM	adverse event monitoring
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical
BsAb	bispecific antibody
BCMA	B-cell maturation antigen
BICR	Blinded Independent Central Review
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CD3	cluster of differentiation 3
CD38	cluster of differentiation 38
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSA	clinical study agreement

Abbreviation	Definition
DMP	data management plan
DOR	duration of response
DRL	drug reference list
EC	Endpoint Committee
EDC	Electronic Data Capturing
EDP	exposure during pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EORTC QLQ-MY20	EORTC Multiple Myeloma Questionnaire
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GBS	Guillain Barré Syndrome
GPP	Good Pharmacoepidemiology Practices
ICANS	immune effector cell-associated neurotoxicity syndrome
IEC	Independent Ethics Committee
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology

Abbreviation	Definition
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISS	International Staging System
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MR	minimal response
NIS	non-interventional study
OS	overall survival
OR	objective response
ORR	overall response rate
PASS	Post-Authorization Safety Study
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PII	personal identifiable information
PN	peripheral neuropathy
PR	partial response
PRO	patient-reported outcome

Abbreviation	Definition
PV	pharmacovigilance
R-ISS	Revised International Staging System
RRMM	Relapsed/refractory multiple myeloma
RWD	Real-world data
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
STD	standard deviation
SMM	smoldering multiple myeloma
TCR	triple class refractory
TTNT	time to next treatment
TTR	time to response
VGPR	very good partial response

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Country Coordinating Investigators

Name, degree(s)	Job Title	Affiliation	Address
To be identified			United States
To be identified			Switzerland
To be identified			Germany
To be identified			United Kingdom
To be identified			Brazil
To be identified			Sweden

4. ABSTRACT

Title

MAGNETISMM-16: An International, Multicenter, Non-Interventional Post-Authorization Safety Study (PASS) to Evaluate the Effectiveness and Safety of Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Treated in Real-World Settings

Version and Date of Protocol:

Version 1.0, 30 August 2023

Rationale and background:

Multiple myeloma (MM) remains an incurable disease despite recent advances in treatment. Globally, there are approximately 160,000 new cases and 106,000 deaths per year attributed to MM. [1] Nearly all patients, even those who initially respond to treatment, are expected to relapse. MM patients typically cycle through many lines of treatment, either relapsing or becoming refractory to various therapeutic approaches. Newer and more effective therapies have substantially increased patient benefit; however, the most recent 4-year survival is only 75%. [2] The lack of effective therapeutic options led to the development of elranatamab (PF-06863135), a novel bispecific antibody (BsAb) that targets both B-cell maturation antigen (BCMA) on MM cells and cluster of differentiation 3 (CD3) on T-cells, for the treatment of relapsed/refractory MM (RRMM).

The efficacy of elranatamab monotherapy was evaluated in patients with RRMM in an open-label, non-randomized, multi-center, Phase 2 study (MagnetisMM-3). [3] The study included patients who were refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and one anti-CD38 monoclonal antibody. [3] MagnetisMM-3 included 123 patients naïve to prior BCMA-directed therapy (pivotal Cohort A) and 64 patients with prior BCMA-directed antibody drug conjugate (ADC) or chimeric antigen receptor (CAR) T-cell therapy (supportive Cohort B). [4] Eligible patients received subcutaneous (SC) elranatamab administration at step-up doses of 12 mg on Day 1 and 32 mg on Day 4 of treatment, followed by the first full treatment dose of elranatamab (76 mg) on Day 8 of treatment. Thereafter, patients received 76 mg once weekly. After 24 weeks, in patients who achieved an IMWG response category of partial response or better with responses persisting for at least 2 months, the dose interval was changed from every week to every 2 weeks. [4]

Among the 123 patients treated in pivotal Cohort A, the median age was 68 (range: 36 to 89) years with 19.5% of patients ≥75 years of age. 44.7% were female; 58.5% were White, 13.0% were Asian, 7.3% were Black or African American. [4]

Efficacy results were based on response rate and (DOR), as assessed by Blinded Independent Central Review (BICR) based on the IMWG criteria. Efficacy results in pivotal Cohort A included confirmed ORR by BICR of 61.0% (95% CI: 51.8, 69.6), 35.0% of patients achieved complete response or stringent complete response (CR or sCR), and 56.1%

achieved very good partial response (VGPR). Among patients who achieved an objective response (n = 75), median time to response was 1.2 (range, 0.9−7.4) months. As of the data cut-off of 14 March 2023, median duration of follow-up was 14.7 (range, 0.2−25.1) months and median duration of treatment was 5.6 (range, 0.03−24.4) months.Forty-eight percent (48.0%) of patients had been treated for >6 months and and 35.8% of patients had been treated for >12 months.

The median duration of response (mDOR) has not been reached (95% CI NE−NE) and the Kaplan-Meier (KM) probability of maintaining response at 15 months was 71.5% (95% CI 58.8−80.9). Median PFS and OS had not been reached at the time of data cut-off, with KM rates of 50.9% (95% CI, 40.9-60.0) and 56.7% (95% CI, 47.4-65.1) at 15 months. [4]

The efficacy and safety of elranatamab monotherapy in patients with RRMM and prior exposure to BCMA-directed therapy (CAR-T and/or ADC) was evaluated in a pooled analysis of 4 MagnetisMM studies (MM-1, -2, -3 and -9). [5] After a median follow-up of 11.3 (range: 0.3-32.3) months, ORR was 46.0% (95% CI, 35.2-57.0) (n = 87). Among patients who achieved an objective response (n = 40), median time to response was 1.7 (range: 0.3-9.3) months Median DOR was 17.1 (95% CI, 9.8-NE) months, although not yet mature after censoring data for 23 (57.5%) patients. Median PFS and OS were 5.5 (95% CI, 2.2-10.0) months and 12.2 (7.5-NE) months, respectively.

Elranatamab received accelerated approval by the Food and Drug Administration (FDA) on 14 August 2023. [6] Long-term, non-interventional studies (NIS) that reflect routine care are desirable to continue monitoring the effectiveness and safety of elranatamab after product approval. The existing evidence has been generated from interventional studies; however, the participants enrolled in such interventional studies may not be representative of the real-world population of patients who will receive elranatamab treatment in routine care (i.e., racial/ ethnic diversity). Therefore, this NIS aims to evaluate the effectiveness and safety of elranatamab in real-world clinical settings and has been designated as a voluntaryPASS by the Sponsor.

Research question and objectives:

Research questions:

- What is the effectiveness of elranatamab in patients with RRMM treated in real-world clinical settings?

- What are the frequency of adverse events in patients with RRMM treated with elranatamab in real-world clinical settings?

Objectives:

1. To evaluate the effectiveness of elranatamab through the collection and analysis of the following clinical outcomes (defined according to the IMWG consensus criteria for response and minimal residual disease assessment in MM).

- Overall response rate (ORR)
- Time to response (TTR)
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)
- Time to next treatment (TTNT)

2. To characterize the safety of elranatamab in real-world settings through the solicited collection and summary of adverse events.

Patient Reported Outcomes (Germany only):

1. To evaluate patient QoL by assessing the impact of elranatamab on patient-reported symptoms and functioning, in a real-world setting using the following PRO instruments:

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) [7, 8]
- EORTC Multiple Myeloma Questionnaire (EORTC QLQ-MY20) [9]

Study design:

This prospective, international, longitudinal cohort study will evaluate the effectiveness and safety of elranatamab in routine clinical practice in patients 18 years and older who are treated with elranatamab by their treating physician for up to 3 years. Approximately 340 patients will be recruited from primary care centers, hematology/oncology clinics, and academic centers from the US, Switzerland, Germany, the United Kingdom, Brazil and Sweden. This NIS will aim to enroll patients with a diverse distribution of characteristics (e.g., race, ethnicity, sex) that is representative of the real-world patient population being treated with elranatamab in clinical practice. Thus, both urban/university hospitals and rural community centers will be included in this study. Enrollment will begin after elranatamab is approved by Health Authorities in the respective planned country and last for up to 2 years after the product launch date in the United States.

Each patient's treatment will be consistent with routine practice, corresponding with the recommendations in the local Health Authority approved product label and at the discretion of the treating physician.

Patients will be followed for up to 3 years after enrollment in the study or until withdrawal, physician discretion (i.e., patient health), loss to follow up, death, or study termination, whichever occurs the earliest. Follow-up eCRFs will be completed when a patient returns for clinic visits as per routine clinical practice.

Effectiveness outcomes will be evaluated and non-serious and serious adverse events will be reported by the treating physician or other research staff during each follow-up visit. By maintaining simplicity in study procedures, including the study's inclusion/exclusion criteria, patients' use of concomitant medications, and the frequency of patient monitoring, this study will minimize the artificiality imposed by the requirements of pre-marketing randomized trials, thus allowing an approximation of real-world practice. Additionally, the simplified study procedures will allow for enrollment of a more clinically diverse and larger number of patients in this observational study than in the Phase 2 clinical trial.

Population:

The study will prospectively enroll patients with RRMM who receive elranatamab according to the local Health Authority approved product label (routine-care). Patients must meet the following criteria to be eligible for inclusion in the study:

1. Male or female patients age ≥18 years
2. A diagnosis of MM, as defined according to IMWG criteria
3. New treatment with elranatamab at the time of enrollment
4. A signed and dated informed consent [or electronic (e-consent)] or hardcopy informed consent form from sites which do not allow e-consent, indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Patients meeting the following criteria will not be included in the study:

1. Prior treatment with elranatamab in an investigational setting.

Variables:

The drug exposure of interest will be elranatamab. Consistent with routine practice, patients will be followed regardless of whether s/he changes treatment regimen during follow up. There will not be a comparator group. All treatment will be received via standard medical practice and not determined by this study protocol.

The outcomes of interest will be effectiveness (i.e., ORR, TTR, DOR, PFS, OS, TTNT), safety [i.e., non-serious adverse events (AEs), serious adverse events (SAEs)], and, for Germany only, QOL status during follow up.

Baseline characteristics will be evaluated at the time of study enrollment and will include patient demographics, medical history, and medication use. Additional characteristics will be evaluated during follow up, including treatment patterns, concomitant medications, and comorbidities.

Data sources:

Designated site personnel will enter data collected directly from the patient or using the patients' medical records into the eCRFs (primary data collection) for all patients. In Germany, QOL questionnaires will be provided as part of patients routine standard of care and will be self-administered. Patients will be recruited from sites from the US, Switzerland, Germany, the United Kingdom, Brazil and Sweden.

Study size:

Based on Pfizer country feasibility discussions and the anticipated elranatamab launch strategy, the projected sample size is approximately 340 patients: 125 patients will be recruited from the US, 45 from Switzerland, 70 from Germany, 50 from the United Kingdom, 25 from Brazil, and 25 from Sweden.

Data analysis:

The characteristics captured during baseline and follow up will be summarized using descriptive statistics. Frequencies and percentages will be used for categorical variables and mean (standard deviation [STD]) and median (interquartile range [IQR]) will be used for continuous variables.

For the effectiveness outcomes of interest, ORR will be summarized using frequencies and percentages and time-to-event outcomes (DOR, TTR, PFS, OS, TTNT) will be evaluated using Kaplan-Meier (KM) methods. KM curves will be illustrated and the median and landmark survival and corresponding 95% confidence interval (95% CI) will be computed. To evaluate the safety of elranatamab, AEs and SAEs will collected on an eCRF and structured data collection tool [Adverse Event Monitoring (AEM) form] and will be characterized by type, grade, timing, seriousness, and relationship to elranatamab. Crude cumulative incidence will be calculated as appropriate.

Subgroup analyses may be conducted by line of therapy since initial treatment, prior BCMA exposure, age, race/ethnicity, year of enrollment, enrollment country, and other key subgroups pending sufficient sample size. In line with label changes in the course of time, additional subgroup analyses may be performed if data permits.

All analyses will be further detailed in a separate Statistical Analysis Plan (SAP).

Milestones:

- Start of data collection: 01 November 2023
- End of data collection: 01 November 2028
- Registration in the EU PAS register: 15 September 2023
- Final study report: 30 May 2029

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	01 November 2023
End of data collection	01 November 2028
Registration in the EU PAS register	15 September 2023
Final study report	30 May 2029

7. RATIONALE AND BACKGROUND

MM is a hematological B-cell malignancy characterized by dysregulated proliferation of bone marrow plasma cells. Globally, there are approximately 160,000 new cases and 106,000 deaths per year attributed to MM. 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. The median time to relapse is only 16.4 months for patients treated with novel PI-based or IMiD-based combination regimens as frontline treatment. Moreover, MM patients typically cycle through many lines of treatment, becoming relapsed/refractory to various therapeutic approaches. Patients with RRMM who respond poorly to PI-based or IMiD-based regimens show a median OS of only 1.5 years. Newer and more effective therapies have substantially increased patient benefit; however, the most recent 4-year survival is only 75%. [2]

The lack of effective and durable therapeutic options led to the development of elranatamab (PF-06863135), a novel BsAb that targets both BCMA on MM cells and CD3 on T-cells. Elranatamab is a heterodimeric humanized full-length bispecific IgG2 kappa antibody derived from 2 mAbs, the anti-BCMA mAb (PF-06863058) and the anti-CD3 mAb (PF06863059). 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.

7.1. Clinical Study C1071003

7.1.1. Overview of Study C1071003

Study C1071003, MagnetisMM-3, is an ongoing, open-label, multicenter, non-randomized Phase 2 study to evaluate the efficacy and safety of elranatamab monotherapy in patients with MM who are refractory to at least one PI, one IMiD and one anti-CD38 antibody. [3] The study included 123 patients naïve to prior BCMA-directed therapy (pivotal Cohort A) and 64 patients with prior BCMA-directed antibody drug conjugate (ADC) or chimeric antigen receptor (CAR) T-cell therapy (supportive Cohort B). [4] Eligible patients received subcutaneous (SC) elranatamab administration at step-up doses of 12 mg on Day 1 and 32 mg on Day 4 of treatment, followed by the first full treatment dose of elranatamab (76 mg) on Day 8 of treatment. Thereafter, patients received 76 mg once weekly. After 24 weeks, in patients who achieved an IMWG response category of partial response or better with responses persisting for at least 2 months, the dose interval was changed from every week to every 2 weeks. [4]

7.1.2. Demographic Characteristics and Disease History

In Cohort A, the median (range) age of participants was 68.0 years (36 - 89); 94.3% of participants had an ECOG performance score of 0 or 1. [4] Participants had a median (range) of 5.0 (2, 22) prior lines of treatment, 96.7% were triple-class refractory and 42.3% were penta-drug refractory (2 PIs, 2 IMiDs, and 1 anti-CD38 antibody) with 95.9% of participants being refractory to the last line of therapy. There were 25.2% of participants with high cytogenetic risk (defined by the presence of t(4;14), t(14;16) or del(17p)); 31.7% had EMD at baseline by BICR. Overall, participants enrolled in Cohort A of Study C1071003 displayed characteristics representative of patients with RRMM and multiple lines of prior treatment.

7.1.3. Summary of Findings

The efficacy of elranatamab monotherapy was evaluated in patients with RRMM in an open-label, non-randomized, multi-center, Phase 2 study.

Efficacy results were based on response rate and DOR, as assessed by BICR based on the IMWG criteria. Efficacy results in pivotal Cohort A included confirmed ORR by BICR of 61.0% (95% CI: 51.8, 69.6); 35.0% of patients achieved CR or sCR, and 56.1% achieved VGPR. Among patients who achieved an objective response (n = 75), median time to response was 1.2 (range, 0.9−7.4) months As of the data cut-off of 14 March 2023, median duration of follow-up was 14.7 (range, 0.2−25.1) months and median duration of treatment was 5.6 (range, 0.03−24.4) months. Forty-eight percent (48.0%) of patients had been treated for >6 months and and 35.8% of patients had been treated for >12 months.

The mDOR has not been reached (95% CI NE−NE) and the Kaplan-Meier (KM) probability of maintaining response at 15 months was 71.5% (95% CI 58.8−80.9). Median PFS and OS had not been reached at the time of data cut-off, with KM rates of 50.9% (95% CI, 40.9-60.0) and 56.7% (95% CI, 47.4-65.1) at 15 months. [4]

The efficacy and safety of elranatamab monotherapy in patients with RRMM and prior exposure to BCMA-directed therapy (CAR-T and/or ADC) was evaluated in a pooled analysis of 4 MagnetisMM studies (MM-1, -2, -3 and -9). [5] After a median follow-up of 11.3 (range: 0.3-32.3) months, ORR was 46.0% (95% CI, 35.2-57.0) (n = 87). Among patients who achieved an objective response (n = 40), median time to response was 1.7 (range: 0.3-9.3) months. Median DOR was 17.1 (95% CI, 9.8-NE) months, although not yet mature after censoring data for 23 (57.5%) patients. Median PFS and OS were 5.5 (95% CI, 2.2-10.0) months and 12.2 (7.5-NE) months, respectively. [5]

Elranatamab received accelerated approval by the FDA on 14 August 2023. [6] Long-term, NIS that reflect routine care are desirable to continue monitoring the effectiveness and safety of elranatamab after product approval. Current evidence on the effectiveness and safety of elranatamab is limited to interventional studies. However, the patients enrolled in such interventional studies may not be representative of the real-world population of patients who receive elranatamab treatment in routine care (i.e., racial/ ethnic diversity). This study will also have a larger sample size than the ongoing pivotal Phase 2 study in patients with RRMM, offering the potential to perform additional subgroup analyses. Furthermore, the purpose of the elranatamab NIS is to evaluate the effectiveness and safety of elranatamab in patients with RRMM in real-world settings.

This NIS is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Research questions:

- What is the effectiveness of elranatamab in patients with RRMM treated in real-world clinical settings?

- What are the frequency of adverse events in patients with RRMM treated with elranatamab in real-world clinical settings?

Objectives:

1. To evaluate the effectiveness of elranatamab through the collection and analysis of the following clinical outcomes (defined according to the IMWG consensus criteria for response and minimal residual disease assessment in MM):

- Overall response rate (ORR)
- Time to response (TTR)
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)
- Time to next treatment (TTNT)

2. To characterize the safety of elranatamab in real-world settings through the solicited collection and summary of adverse events.

Patient Reported Outcomes (Germany only) :

1. To evaluate patient QoL by assessing the impact of elranatamab on patient-reported symptoms and functioning, in a real-world setting using the following patient-reported outcome PRO instruments:

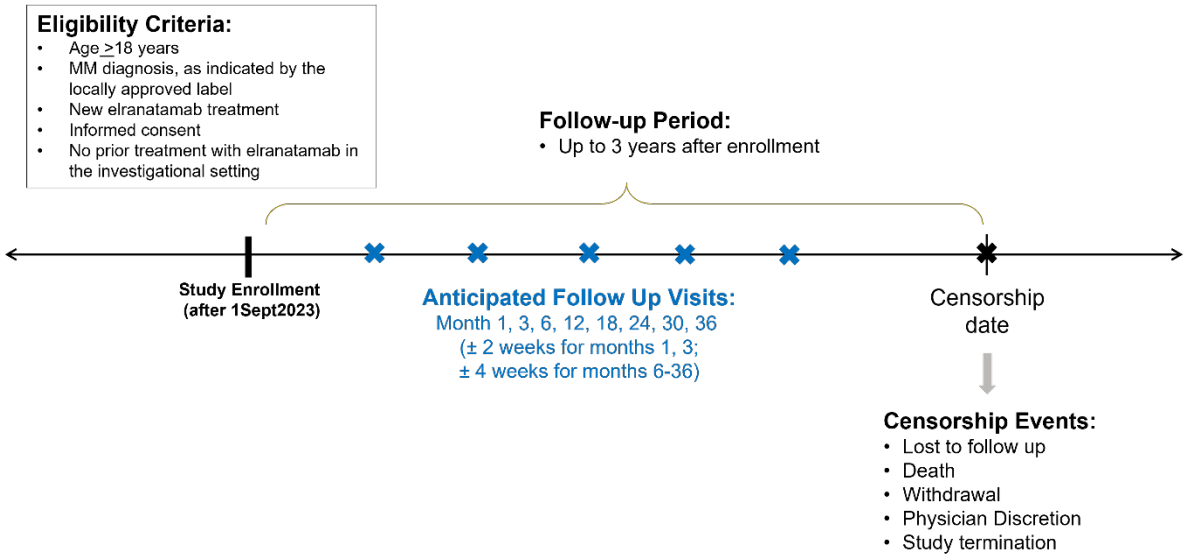
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) [7, 8]
- EORTC Multiple Myeloma Questionnaire (EORTC QLQ-MY20) [9]

9. RESEARCH METHODS

9.1. Study Design

This prospective, international, longitudinal cohort study will evaluate the effectiveness and safety of elranatamab in routine clinical practice in patients 18 years and older who are treated with elranatamab by their treating physician for up to 3 years. Eligible RRMM patients with RRMM will be enrolled and treated according to the current standard of care at the study site. An overview of the study design is depicted in Figure 1.

Figure 1. Study Design Diagram



Approximately 340 patients recruited from primary care centers, hematology/oncology clinics, and academic centers in the US, Switzerland, Germany, the United Kingdom, Brazil and Sweden will be followed for up to 3 years. This NIS will aim to enroll patients with a diverse distribution of characteristics (i.e., race, ethnicity, sex) that is representative of the real-world patient population being treated with elranatamab in clinical practice. Thus, both urban/university hospitals and rural community centers will be included in this study. Approximately 125 patients will be recruited from the United States, 45 from Switzerland, 70 from Germany, 50 from the United Kingdom, 25 from Brazil, and 25 from Sweden. Enrollment will begin after elranatamab is approved by Health Authorities in the respective study country and last for up to 2 years after the product launch date in the United States.

Each patient's treatment will be consistent with routine practice, corresponding with the recommendations in the local Health Authority approved product label and at the discretion of the treating physician. Consistent with routine practice, patients are free to change regimens and dosing during follow up. Only patients treated with elranatamab will be enrolled, so the study will not collect data on a comparator group.

Patients will be followed prospectively for up to 3 years after enrollment in the study or until withdrawal, physician discretion (i.e., patient health), loss to follow up, death, or study termination, whichever occurs the earliest. Patients will continue to be followed regardless of elranatamab discontinuation and/or treatment switches, unless consent is withdrawn. If patients are lost to follow up, then the end of follow up will be defined as the date of the last visit.

Information on patient characteristics, medical history, and MM treatment history will be collected at the time of enrollment into the study (baseline). Follow-up eCRFs will be

completed when a patient returns for office visits as per routine clinical practice with data collection at months 1, 3, 6, 12, 18, 24, 30, and 36. Data collection should be completed within ± 2 weeks for the visits in months 1 and 3, ± 4 weeks for the visits in months 6-36. At each follow-up visit, the treating physician or other designated member of the medical care team will collect and record information on factors such as patient characteristics, treatment patterns, concomitant medications, MM disease characteristics, effectiveness outcomes, adverse events and serious adverse events. In real-world routine clinical practice, patients may not align to the IMWG-defined visit schedule or may require diagnostic testing not widely used in real world settings; methods details for handing these cases are described in the SAP. [10, 11] At each follow-up visit in Germany (only), the patient will be asked to complete an electronic PROs survey on their quality of life. The complete list of variables is available in Table 2.

During follow up, several effectiveness, safety and QOL outcomes will be evaluated as follows:

- To evaluate the primary objective of effectiveness, ORR, TTR, DOR, PFS, OS, and TTNT, will be summarized using descriptive statistics.

- To evaluate the safety objective, all AEs and SAEs that occur during follow up will be summarized using descriptive statistics. There will not be any *a priori* specified safety outcomes, but careful attention will be placed on the known safety concerns for elranatamab. All AEs will be reported.

- To evaluate the Germany-specific objective of assessing the impact of elranatamab on patient-reported symptoms and functioning, PROs will be collected via the following questionnaires: EORTC QLQ-C30 and EORTC QLQ-MY20, and summarized using descriptive statistics.

By maintaining simplicity in study procedures including the study's inclusion/exclusion criteria, patients' use of concomitant medications, and the frequency of patient monitoring, this study will minimize the artificiality imposed by the requirements of pre-marketing randomized trials, thus allowing an approximation of real-world practice. Additionally, the simplified study procedures will allow for enrollment of a more clinically diverse and larger number of patients in this observational study than in the clinical development randomized Phase 2 clinical trial.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this NIS is being conducted. No assessment is required if considered by the enrolling physician to be outside standard clinical practice for the treatment of MM, in accordance with the approved label.

In the United States (only), patients may also opt-in to allow data collection linked to real-world data (RWD) via a universal ID, or a "token", which is de-identified and provides an opportunity to acquire additional data beyond what is collected in the eCRF.

9.2. Setting

9.2.1. Study Population

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

The study population eligible for enrollment in the prospective NIS includes any MM patient who receives at least one dose of elranatamab and satisfies the inclusion and exclusion criteria. Patients will be recruited from primary care centers, hematology/oncology clinics, and academic treatment centers to ensure broad physician and patient representation. Recruitment of sites will begin with invitations to hematologists/oncologists who are most likely to treat patients with MM and will continue until the target number of sites has been met or 2 years after the US product launch date, whichever occurs the earliest.

9.2.2. Diversity of Study Population

Diverse representation in clinical trials allows Pfizer to gain insights necessary to develop medicines and vaccines that will be effective and safe for all patients of any racial or ethnic origin. However, inclusion of a diverse study population in pre-approval drug development is complex and an evolving process; health disparities and stigma surrounding clinical trial participation, among other factorsposea significant challenge. Therefore, this NISwill aim to enroll patients with a diverse distribution of characteristics that is representative of the real-world patient population with MM in clinical practice (see Table 1). [12]

Table 1. Patient Population Metrics for Multiple Myeloma in the United States

	Proportion (%)
Race	
Black/African American	19
American Indian or Alaska Native	1
Asian or Pacific Islander	6
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

Source: Surveillance, Epidemiology, and End Results (SEER)

As a global study, sites will be included from diverse populations in the US, Switzerland, Germany, the United Kingdom, Brazil and Sweden. Sites will include both urban/university hospitals and rural community centers.

Also, Pfizer Inc will employ several strategies to recruit underserved populations, including the following:

- Investigators will be informed of Pfizer's commitment to diverse enrollment;
- To ensure this study is accessible, Pfizer is offering travel reimbursement to patients throughout study participation (as approved by site Institutional review board (IRB)/Independent ethics committee (IEC); and
- Any recruitment and retention materials created for the study will use imagery, and culturally and linguistically appropriate language to resonate with underrepresented populations. For example, in the United States, all patient facing materials will be available in English and Spanish; in the United Kingdom, all patient facing materials will be available in British English, Urdu and Punjabi

9.2.3. Inclusion Criteria

The study will prospectively enroll patients with RRMM who receive elranatamab according to the local Health Authority approved product label (routine-care). Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Male or female patients age ≥18 years
2. A diagnosis of MM, as defined according to IMWG criteria
3. New treatment with elranatamab at study enrollment
4. Evidence of a personally signed and dated informed consent [or electronic (e-consent)] indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

9.2.4. Exclusion Criteria

Patients meeting the following criteria will not be included in the study:

1. Prior treatment with elranatamab in an investigational setting.

9.3. Variables

9.3.1. Exposure

The exposure of interest is elranatamab. Information on dose, duration, line of therapy, date of treatment initiation, and reason for treatment initiation will be collected at baseline. Elranatamab treatment patterns over time will be captured at follow up visits by collecting detailed information on factors such as changes to treatment drug, schedule, dose, and line of

therapy. All treatment will be received consistent with the approved label independent of this study. Patients will remain in follow-up regardless if they discontinue elranatamab.

9.3.2. Patient Characteristics

In the baseline assessment (occurring at the time of enrollment into the study), patient characteristics will be collected including patient demographics, MM disease characteristics (e.g., current International Staging System (ISS) or Revised-ISS (R-ISS) disease stage, cytogenic risks, etc.), MM treatment history [e.g., line of therapy, previous (autologous stem cell transplantation (ASCT), previous MM-related radiation therapy], medical history, concomitant medications, factors associated with treatment initiation, and the Charlson comorbidity index (Table 2). Variables are reflective of a combination of sources including: patient self-reported, physician derived, and/or electronic medical record extracted.

Key patient characteristics, such as comorbidities and reasons for changes to the treatment regimen, will also be captured during follow-up visits.

9.3.3. Study Outcomes

Study effectiveness, safety and QOL outcomes will be collected during follow up visits (Table 2).

9.3.3.1. Effectiveness Outcomes

The effectiveness outcomes will be defined as ORR, TTR, DOR, PFS, and OS according to the IMWG consensus criteria for response in MM. TTNT will be defined as the time from elranatamab initiation to next treatment. Full definitions of each effectiveness variable are included in Table 2.

9.3.3.2. Safety Outcomes

Safety will be continuously monitored throughout the study. The enrolling physician or other treatment team member will report AEs and SAEs for all patients to Pfizer for up to 90 calendar days after the last dose of elranatamab. These outcomes may be identified from routine clinic visits, from other treating physicians and/or from hospital records. In addition, for patients lost to follow-up, outcomes may be identified through standard measures used in cohort studies, such as alternative contacts.

9.3.3.3. Patient-Reported Outcomes

PROs will be administered electronically for patients enrolled in Germany (only). PRO translations in the official language(s) will be provided. PROs should be completed at the beginning of the study visit prior to receiving elranatamab. However, if it's not possible to complete the PROs at the beginning of the study visit, it is acceptable to have the patient complete the PROs before the end of the indicated study visit. The PROs will be administered at the time points specified in the schedule of activities (SoA). Cancer-specific global health status and quality of life, functioning, and symptoms data will be collected using the EORTC QLQ-C30 and MY20 questionnaires. EORTC QLQ-C30 is a well-known, reliable and valid self-administered questionnaire used in oncology trials. The QLQ-C30

contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale. All the scales and single-item measures range in score from 0 to 100. Higher scores on the functional scales represent higher levels of functioning. Higher scores on the global health status/quality of life scale represent higher health status/quality of life. Higher scores on symptom scales/items represent a greater presence of symptoms. The EORTC MY20 is a myeloma-specific module developed by the EORTC group specifically to assess quality of life in patients with multiple myeloma. [9] It contains 20 items which can be grouped into a disease symptom subscale (6 items), side effects of treatment subscale (10 items), body image (1 item) and future perspective subscale (3 items).

Table 2. Schedule of Activities and Definition of Patient Characteristics and Study Outcomes

Variable	Role	Baseline Visit	Follow-up Visits[b]	Operational Definition
Patient eligibility and informed consent	Patient characteristic	X		
Patient demographics[a]	Patient characteristic	X		Year of birth, ethnicity, race, sex
General examination	Patient characteristic	X		Height, weight
Medical history[a]	Patient characteristic	X		CRAB symptoms (hypercalcemia, renal insufficiency, anemia, and bone lesions), current ISS or R-ISS disease stage, cytogenic/ fluorescence in situ hybridization (FISH) risks, date of first MM diagnosis, extramedullary disease, history of monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (SMM), immunoglobin subtypes, refractory status
ECOG performance status	Patient characteristic	X	X	
Comorbidities[a]	Patient characteristic	X	X	Amyloidosis, cardiac events, cataracts, hypertension, peripheral neuropathy, pneumonia, skeletal-related events, thrombocytopenia, thromboembolism
Charlson comorbidity index	Patient characteristic	X	X	Defined as per Quan et al.[13]
Concomitant medications[a]	Patient characteristic	X	X	List of concomitant medications (including other treatments for MM)

Table 2. Schedule of Activities and Definition of Patient Characteristics and Study Outcomes

Variable	Role	Baseline Visit	Follow-up Visits[b]	Operational Definition
MM treatment history[a]	Patient characteristic	X	X	Date of initiation, date of treatment discontinuation, duration of each prior line of therapy, line of therapy, MM-related radiation therapy, previous ASCT, reason for discontinuation, therapy type/combination (e.g., ImiD, PI, etc.), treatment sequences, treatments to which disease is refractory
Elranatamab treatment at baseline	Patient characteristic	X		Date of initiation, elranatamab dose, line of therapy, therapy duration, reason for treatment initiation
Elranatamab treatment during follow up	Patient characteristic		X	Date and reason for changes to elranatamab treatment, schedule, dose, line of therapy, discontinuation date, duration, reason for discontinuation
Subject Summary	Patient characteristic		X	Patient Status, Date patient withdrawn, If withdrawn, reason for withdrawal, date last known to be alive
Adverse event or serious adverse event reporting[a,c]	Outcome: Safety		X	All nonserious and serious adverse events
ORR	Outcome: Effectiveness		X	Proportion of patients with confirmed sCR, CR, VGPR, PR based on clinician-assessed documentation (per IMWG criteria)
TTR	Outcome: Effectiveness		X	Time from elranatamab initiation to first documentation of objective response (OR; per IMWG criteria)
DOR	Outcome: Effectiveness		X	Time from first documentation of objective response (OR; per IMWG criteria) until the first noted disease progression or death due to any cause, whichever occurs first, or the end of treatment if no progression occurred
PFS	Outcome: Effectiveness		X	Time from elranatamab initiation to clinician-documented disease progression (per IMWG criteria) or death from any cause, whichever occurs first
OS	Outcome: Effectiveness		X	Time from elranatamab initiation to death from any cause
TTNT	Outcome: Effectiveness		X	Time from enrollment to next treatment

Table 2. Schedule of Activities and Definition of Patient Characteristics and Study Outcomes

Variable	Role	Baseline Visit	Follow-up Visits[b]	Operational Definition
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30)[a]	Outcome: QOL	X	X	Quality of life (i.e., patient-reported symptoms and functioning) of cancer patients questionnaire
RTC Multiple Myeloma Questionnaire (EORTC QLQ-MY20)[a]	Outcome: QOL	X	X	Multiple myeloma questionnaire

Abbreviations: quality of life, QOL; electronic case report form, eCRF; objective response rate, ORR; time to response, TTR; duration of response, DOR; progression free survival, PFS; overall survival, OS; time to next treatment, TTNT.
a Denotes data collected via patient self-report
b Follow-up eCRFs will be completed when a patient returns for office visits as per routine clinical practice with data collection permissible at months 1, 3, 6, 12, 18, 24, 30, 36. eCRFs and QOL questionnaires must be completed within ± 2 weeks for visits at months 1 and 3, ± 4 weeks for visits at months 6-36.
c Adverse event or serious adverse event reporting should be performed as needed anytime over the course of the study.

9.4. Data Sources

The primary data source for this study will be patient medical records. All patient data relating to the study will be recorded in an electronic case report form (eCRF). Guidance on completion of eCRFs will be provided in the eCRF Completion Requirements document. An electronic PRO for will also be administered for German sites

9.5. Study Size

Based on Pfizer country feasibility discussions and the anticipated elranatamab launch strategy, the projected study size for the study is approximately 340 patients globally, including approximately 125 patients from the US, 45 from Switzerland, 70 from Germany, 50 from the United Kingdom, 25 from Brazil, and 25 from Sweden.

There are no *a priori* hypotheses specified in this study. Therefore, there will not be formal hypothesis testing; all analyses are descriptive in nature.

9.6. Data Management

Detailed methodology of the data management software programs that will be used in the study will be documented in a separate data management plan (DMP) document, which will be dated, filed, and maintained by the sponsor. This document will include details about the coding dictionary used for each data element (e.g., Anatomical Therapeutic Chemical (ATC) classification system, Medical Dictionary for Regulatory Activities (MedDRA) terminology, etc.).

United States (only):

Connecting study data to other data about a patient collected through a variety of other sources (e.g., RWD) can be beneficial for better understanding a treatment intervention, efficiently conducting long-term follow-up, improving clinical operations, and more. Pfizer is seeking to connect study data and RWD to answer those additional questions. However, patient IDs numbers in EDCs are unique to each individual study, and do not provide a way to connect to RWD.

In order to ensure the ability to link these study data to other RWD sources, a common, universal ID (herein named a "token") that is unique to each study patient, but also consistent and available in real-world datasets is created. A token is a universal, de-identified key that can be used to reference patient across datasets, created based on elements of patient personal identifiable information (PII) using an industry-leading privacy-preserving technology. The key features below make tokens a secure and consistent mechanism for linking disparate healthcare data sources at the patient level, without compromising the privacy of study patients.

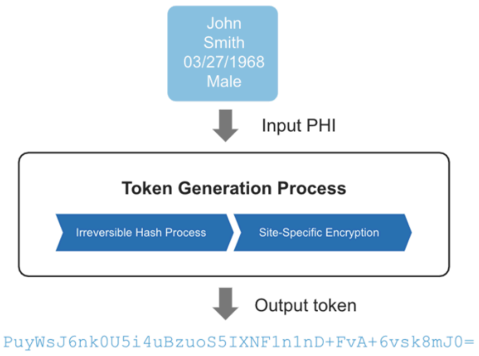
- **Tokens are irreversible and blinded**: Hashing by technology destroys the input PII, which makes tokens de-identified. The input PII cannot be backward engineered from the output token.

- **Tokens are unique**: Each token is unique to the input PII, avoiding false matches. In addition, multiple tokens can be created from different PII elements, improving the precision and granularity of matching.

- **Tokens are consistent**: The same set of input PII will always create the same tokens. Tokens created in any dataset are compatible and can be matched to one another.

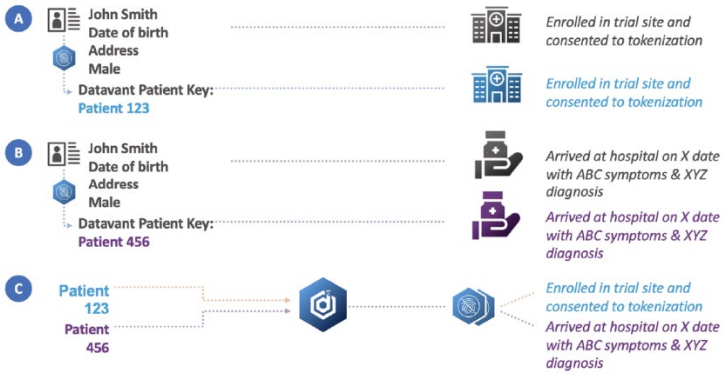
Multiple tokens derived from different PII elements are created for each patient to enable accurate matching (avoiding false positives and limiting false negatives). Tokenization software is used in hundreds of data sources and has been used to tokenize more than 100 billion records, for over 200 million patients. Figure 2 provides a schematic of the tokenization process.

Figure 2. Schematic of the Generation of an Irreversible Token Using Tokenization Technology.



Tokenization enables traditional study data to be used in the future to answer questions not yet conceived and eliminate the need for follow-up studies, expediting future results. Ultimately, the time and costs saved will benefit patients awaiting the development of treatments and ensure Pfizer can get a more holistic, longitudinal view of study patients, by linking tokenized clinical study data with RWD (prescription data, EHR, medical claims, etc.), further elucidating safety signals and our understanding of the benefits of treatment interventions in the real world. Figure 3 provides an illustrative example of the study schematic and RWD linkage, using hospital/EHR records as the example RWD source; patient numbers are intended for illustrative purposes only. Tokenization participation will be documented via a separate electronic informed consent from the primary prospective elranatamab study. Tokenization participation is optional and completely voluntary for patients. Patients may decide to opt out at any time.

Figure 3. Tokenization De-identification and Matching Allows for Patient-Level Data Linkage, While Preserving Patient Privacy.



9.6.1. Case Report Forms (CRFs)/Electronic Data Record

CRFs will be administered electronically through the Electronic Data Capturing (EDC) system in this study. After a patient or a legally acceptable representative agrees to participate in this study by signing and dating an electronic informed consent (e-consent), the treating physician or an authorized staff member will complete the patient baseline CRF at enrollment. As used in this protocol, the term eCRF should be understood to refer to an electronic data record.

The follow-up eCRFs will be completed when a patient returns for office visits as per routine clinical practice. Patient data should be entered in the eCRFs within 5 business days of each visit.

An eCRF is required and should be completed for each enrolled patient. The completed original eCRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the eCRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, and safety data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the eCRFs must match those charts.

In some cases, the eCRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the eCRF, and for which the eCRF will stand as the source document.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed e-consent documents, copies of all eCRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study unless Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

The safety analysis set will include all enrolled patients who received at least one dose of elranatamab. The safety analysis set will be used for all analyses unless specified otherwise.

9.7.1. Data Cleaning

A data cleaning specifications document will be developed before patient enrollment begins. It will be dated, filed, and maintained by the sponsor. The specifications will include consistency and plausibility checks on the data, as well as guidelines for handling the data. Guidelines for handing the data will include a process for query creation/closure and categorization, process for listing data review, process for missing and non-conformant data review, process for flagging data in the clinical data management system, process for SAE reconciliation, process for data handling and validation of electronic records, process for medical coding of data and application of coding conventions (if applicable), process for collection of investigator signature, process for transferring a patient from one site to another, and process for freeze/lock of the clinical database.

9.7.2. Patient Characteristics and Treatment Patterns

Patient characteristics will be analyzed using descriptive summary statistics. The characteristics captured during baseline and follow up will be summarized using frequencies

and percentages for categorical variables and the mean (STD) and/or median (IQR) for continuous variables.

Additionally, treatment patterns over follow up will be described using the previously described summary statistics.

9.7.3. Effectiveness Analyses

ORR will be summarized using frequencies and percentages. Time-to-event outcomes (DOR, TTR, PFS, OS, TTNT) will be evaluated using KM methods. KM curves will be illustrated and the median and landmark survival and corresponding 95% confidence interval will be computed. Additionally, the frequency and percentage of patients in the following response categories will be summarized: sCR, CR, VGPR, PR, minimal response (MR), stable disease (SD), progressive disease (PD), not evaluable, objective response (sCR+CR+VGPR+PR), and clinical benefit response (sCR+CR+VGPR+PR+ MR).

9.7.4. Safety Analyses

AEs and SAEs, both type and grade (when available), will be characterized by type, severity, timing, and seriousness. Crude cumulative incidence will be calculated as appropriate.

9.7.5. Patient Reported Outcome Analyses (Germany only)

The details of PRO analyses will be described in a statistical analysis plan (SAP).

9.7.6. Subgroup Analyses

Subgroup analyses may be conducted by line of therapy since initial treatment, prior BCMA exposure, age, race/ethnicity, year of enrollment, enrollment country, and other key subgroups pending sufficient sample size. Further exploratory analyses may be developed as necessary.

9.7.7. Additional Details

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

During study conduct, Pfizer (or their designee) will perform routine remote oversight of the sites' data collection activities and may also conduct periodic onsite monitoring visits of sites to ensure that the protocol is being followed. During onsite visits, the monitors may review source documents to confirm that the data recorded is accurate. All information recorded on the eCRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

Data entered into the clinical database and some integrated data from third parties (if applicable), will be verified/validated as documented in components of the DMP, which will

be dated, filed, and maintained by the sponsor. After completion of these activities, the investigator will be required to sign off the CRFs electronically.

All analytical datasets and statistical programs owned by Pfizer will be available for audit and inspection purposes. To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigators will agree to keep records, including the identity of all participating patients (sufficient information to link records, such as hospital records), all original signed informed e-consent forms, serious adverse event forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the CSA, whichever is longer.

If an investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. An investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.9. Limitations of the Research Methods

First, the lack of an internal comparator group may pose a challenge for contextualizing the safety, effectiveness, and QoL findings from this study. This study will only enroll patients treated with elranatamab. Comparative analyses will not be possible without collecting the same data for MM patients who were eligible for elranatamab but received a different treatment. Therefore, the findings from this study will be descriptive. To help contextualize the findings from this study, external comparator groups of patients taking other MM treatments can be obtained from existing real-world data studies that capture information on the same outcomes as the elranatamab study.

Second, the findings from this study may not be generalizable to patient populations that are not captured in this elranatamab study. The global, multi-site design of this study is intended to minimize the impact of this potential limitation. Patients will be recruited from different types of clinics (e.g., academic hospitals, community clinics, etc.) with the intention of capturing a diverse population with respect to factors such as geographic region, race/ethnicity, socioeconomic status, and MM disease severity.

Finally, as with all primary data collection or de novo studies, there is potential for misclassified and/or missing data on exposure, outcomes, and patient characteristics. To minimize the possibility of outcome misclassification, effectiveness outcomes will be defined based on established IMWG criteria and QoL outcomes will be assessed using validated PRO instruments. Missing data will be addressed using valid analytic techniques, such as multiple imputation.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic 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 shall 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 natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written or electronic informed consent from each patient before any study specific activity is performed.

10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral,

or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

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

Distinction should be made between discontinuation of elranatamab treatment and discontinuation of study participation. Study patients discontinuing elranatamab treatment will continue to be followed to the end of the 3 year study period from enrollment, voluntary withdrawal from the study, withdrawal at the discretion of the treating physician or sponsor, death, or loss to follow-up due to other reasons (e.g., cannot be located through alternative contact), whichever occurs first.

10.4. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed e-consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by the investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), [14] Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), [15] Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, [16] International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS), [17] European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, [18] ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, [19] FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, [20] FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, [21] and FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. [22]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The table below summarizes the requirements for recording safety events on the CRFs and for reporting safety events on the NIS AEM Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) SAEs; (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Table 3: Requirements for Recording Safety Events

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to elranatamab**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with

this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE 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 patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of elranatamab, and lasts through the end of the observation period of the study, which must include at least 90 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 90 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed e-consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to elranatamab, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to elranatamab, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that elranatamab caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether elranatamab caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that elranatamab did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as a SAE with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are 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.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) elranatamab, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to elranatamab (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to elranatamab prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study patient or study patient's partner becomes, or is found to be, pregnant during the study patient's treatment with elranatamab, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to elranatamab in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes 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 investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study patient will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study patient was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

11.1. Single Reference Safety Document

The elranatamab USPI will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The country-specific product label should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Pfizer has no objection to publications by participating investigators of any information collected or generated by investigator, whether or not the results are favorable to elranatamab. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, participating investigators will be required to provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed. Investigators will also be required to provide manuscripts, abstracts, or the full text of any other intended disclosure (e.g., poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator will agree to delay the disclosure for a period not

to exceed an additional 60 days. Investigators will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

Investigators will agree that the first publication is to be a joint publication covering all study sites. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, then investigators are free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals established by the International Committee of Medical Journal Editors.[23] Publication of study results will also be provided for in the Clinical Study Agreement between Pfizer and institutions.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, 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 patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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14. LIST OF TABLES

15. LIST OF FIGURES

Figure 2. Schematic of the Generation of an Irreversible Token Using Tokenization Technology.

Figure 3. Tokenization De-identification and Matching Allows for Patient-Level Data Linkage, While Preserving Patient Privacy.

16. ANNEX 1. LIST OF STAND ALONE

None.

17. ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

18. ANNEX 3. ENCEPP Checklist for Study Protocols

ENCePPChecklistforStudyProtocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Chiecklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: MagnetisMM-16: An International, Multicenter, Non-Interventional Post-Authorization Safety Study (PASS) to Evaluate the Effectiveness and Safety of Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Treated in Real-World Settings

EU PAS Register® number: EUPAS106401
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.
1.1.2 End of data collection[2]	☒	☐	☐	6.
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6.
1.1.6 Final report of study results.	☒	☐	☐	6.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.
2.1.2 The objective(s) of the study?	☒	☐	☐	8.
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.5

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.8
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.8
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.75

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3/9.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.7.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.7.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.6
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.8
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☐	☒	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6/10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year 30/August/2023

Signature: