NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-World (RW) Elranatamab Administration: Step Up Dosing (SUD), Treatment Patterns, Safety and Effectiveness in the United States Epic Cosmos Data (SUMMIT-2)
Protocol number	C1071052
Protocol version identifier	1.0
Date	16 February 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000853
Active substance	L01FX32, elranatamab
Medicinal product	ELREXFIO™ (elranatamab)
Research question and objectives	**Research Question**: What are the patient characteristics, treatment patterns (including step-up dosing and maintenance frequency), effectiveness, and safety of patients with relapsed/refractory multiple myeloma (RRMM) who initiate elranatamab using Epic Cosmos database? The following objectives will be assessed among patients with RRMM receiving elranatamab: **Primary objectives**: 1) To describe demographics, clinical history, and treatment history of multiple myeloma (MM) patients treated with elranatamab. 2) To describe and characterize elranatamab utilization, including the timing of treatment initiation, step-up dosing (SUD) schedule, administration patterns, treatment duration, and dosing during the SUD and post SUD period. 3) To describe the use of supportive medications during the SUD and post SUD periods as well as subsequent MM treatments after elranatamab discontinuation. 4) To describe the tolerability and safety of elranatamab, specifically the incidence of cytokine release syndrome (CRS), immune effector cell associated neurotoxicity (ICANS), and cytopenia during the SUD and post SUD period. 5) To describe infection incidence during the SUD and post SUD period.

	6) To describe effectiveness of elranatamab in terms of real-world overall survival (rwOS), death, time to next treatment (TTNT), time to next treatment or death (TTNT or death), and time to discontinuation (TTD). **Secondary objectives**: 1) To explore heterogeneity in elranatamab utilization, safety/tolerability, infections, and effectiveness outcomes across prespecified and clinically relevant subgroups, including SUD care setting (inpatient, outpatient), prior BCMA-directed therapy exposure, renal impairment (e.g., Estimated Glomerular Filtration Rate/ Chronic Kidney Disease (eGFR/CKD) categories), prior COVID-19 vaccination status at baseline, and age categories (e.g., <65, 65–69, 70–74, ≥75 years).
Country(ies) of study	United States
Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BCMA	B-cell maturation antigen
BMI	Body Mass Index
BOSS	Bispecific outpatient safe step-up
CAR-T	Chimeric Antigen Receptor (CAR) T cell therapy
CCI	Charlson Comorbidity Index
COVID-19	Coronavirus Disease 2019
CPT	Current Procedural Terminology
CRS	Cytokine release syndrome
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
eGFR/CKD	Estimated Glomerular Filtration Rate/ Chronic Kidney Disease
EC	Ethics Committee
EHR	Electronic health record
EMA	European Medicines Agency
GPP	Good Pharmacoepidemiology Practices
HIPAA	Health Insurance Portability and Accountability Act
HMA	Heads of Medicines Agencies
ICANS	Immune effector cell–associated neurotoxicity syndrome
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification

IMiD	Immunomodulatory drug
IQR	Interquartile Range
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVIG	Intravenous immunoglobulin
IRB	Institutional Review Board
LOT	Lines of therapy
mAb	Monoclonal antibody
MM	Multiple myeloma
OS	Overall survival
PASS	Post-authorization safety study
PFS	Progression-free survival
PI	Proteasome inhibitor
PJP	Pneumocystis jiroveci pneumonia
Q2W	Once every two weeks
Q4W	Once every four weeks
RRMM	Relapsed/refractory multiple myeloma
RWD	Real-World Data
RWE	Real-world evidence
rwOS	Real-world Overall Survival
SAP	Statistical analysis plan
SD	Standard Deviation
SUD	Step-up dosing

TTD	Time to discontinuation
TTNT	Time to next treatment
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title

Real-World (RW) Elranatamab Administration: Step Up Dosing (SUD), Treatment Patterns, Safety and Effectiveness in the United States Epic Cosmos Data (SUMMIT-2)

Version: 1.0
Date: 16 February 2026
Author: [redacted]
Affiliation: Pfizer Inc.

Rationale and background

Despite treatment advancements, many MM patients experience relapse or refractory disease, leading to poor prognosis and limited options. Elranatamab is a B-Cell Maturation Antigen (BCMA) bispecific antibody that was approved August 14, 2023, in the United States (US) for patients with MM who have been treated with at least four lines of therapy, including a proteasome inhibitor (PIs), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody (mAb). This study will utilize an electronic health record (EHR) dataset to describe patient characteristics, patterns of step-up dosing and maintenance, clinical outcomes such as time to next treatment or death, supportive care, and adverse events associated with elranatamab in the US.

Research question and objectives

Research Question:

What are the patient characteristics, treatment patterns (including step-up dosing and maintenance frequency), effectiveness, and safety of patients with relapsed/refractory multiple myeloma (RRMM) who initiate elranatamab using Epic Cosmos database?

Primary objectives:

- Objective 1: To describe demographics, clinical history, and treatment history of multiple myeloma (MM) patients treated with elranatamab.
- Objective 2: To describe and characterize elranatamab utilization, including the timing of treatment initiation, SUD schedule, administration patterns, treatment duration, and dosing during the SUD and post SUD period.
- Objective 3. To describe the use of supportive medications during the SUD and post SUD periods as well as subsequent MM treatments after elranatamab discontinuation.
- Objective 4 . To describe the tolerability and safety of elranatamab, specifically the incidence of cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), and cytopenia during the SUD and post SUD period.
- Objective 5. To describe infection incidence during the SUD and post SUD period.

- Objective 6. To describe the effectiveness of elranatamab in terms of real-world overall survival (rwOS, i.e., time to death), death, time to next treatment (TTNT), time to next treatment or death (TTNT or death), and time to discontinuation (TTD).

Secondary objectives:

- Objective 1: To explore heterogeneity in elranatamab utilization, safety/tolerability, infections, and effectiveness outcomes across prespecified and clinically relevant subgroups, including SUD care setting (inpatient, outpatient), prior BCMA-directed therapy exposure, renal impairment (e.g., eGFR/CKD categories), prior Coronavirus Disease 2019 (COVID-19) vaccination status at baseline, and age categories (e.g., <65, 65–69, 70–74, ≥75 years).

Study design

This is a retrospective, non-interventional, single arm cohort study with descriptive analyses using secondary structured EHR data in Epic Cosmos database.

Population

The study population will include all adults aged 18 years or older from the US with an MM diagnosis (The International Classification of Diseases, 9th Revision Clinical Modification (ICD-9-CM): 203.0x or International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) C90.0x, C90) using data from the Epic Cosmos EHR database. The study will include patients who received elranatamab on or after August 14, 2023 (Index date as the date of initiation). Patients will be required to have at least one recorded clinical encounter in Epic Cosmos database within the 12 months preceding the index date. Patients will be excluded if they have been enrolled in a clinical trial on the index date.

Variables

The following variables will be summarized and reported:

Exposure: Exposure is defined as at least one record of elranatamab on or after August 14, 2023.

Study outcomes:

- Elranatamab utilization: Elranatamab dose strength; Elranatamab administration timing; number of Elranatamab administrations; time between Elranatamab administrations; duration of Elranatamab treatment; SUD exposure group; Elranatamab treatment sub-periods; SUD care setting; Elranatamab maintenance dosing frequency.

- MM treatment: PIs; IMiDs; Anti-CD38s; Stem-Cell transplant; Chimeric Antigen Receptor (CAR) T cell therapy (CAR-T); Chemotherapies; other bispecific antibodies; antibody-drug conjugate; nuclear export inhibitors.

- Adverse events: CRS incidence, time to First CRS; CRS concomitant medications; ICANS incidence; time to first ICANS; ICANS concomitant medications; Cytopenia Incidence.

- Infections: Infection Incidence; frequency of infections; time to first infection; follow-up antibiotics; follow-up antiviral; follow-up antifungals.
- Overall effectiveness: rwOS (time to death), death, TTNT, TTNT or death, and TTD.
- Supportive medication: Intravenous immunoglobulin (IVIG); dexamethasone; diphenhydramine; acetaminophen; tocilizumab.

Key Covariates:

- Demographics: age; sex; race; ethnicity; marital status; state.
- SUD setting: inpatient, outpatient.
- Clinical characteristics: Height; weight; Body Mass Index (BMI); Charlson Comorbidity Index (CCI); renal failure; liver failure (toxicity); amyloidosis; hypertension; extramedullary disease; malignancy other than hemato-oncology; non-myeloma hematologic malignancy; venous thromboembolism; chronic hepatitis B infection; chronic hepatitis C infection; bronchiectasis; peripheral neuropathy; osteoporosis; autoimmune diseases requiring systemic immunosuppression; major depressive disorder; severe mental illness; PIs; IMiDs; Anti-CD38s; penta-drug exposed; stem-cell transplant; CAR-T; chemotherapies; antibiotics; antiviral; antifungals; health system type; care settings; prior BCMA-directed therapy exposure; renal impairment history; prior COVID-19 vaccination.

Data sources

This study will utilize de-identified, structured EHR data from the Epic Cosmos database. A single, time-bounded data extract will be requested, with parameters defined according to the eligibility criteria and study objectives. The Epic Cosmos database combines 17 billions of clinical data points from approximately 300 million patients, made up of data from across the Epic community, to form the largest database of EHR patient information.

Study size

This is a retrospective descriptive study with no a priori hypotheses; therefore, sample size calculations are not applicable. As of October 23, 2025, Epic Cosmos database included around 500 patients who meet the inclusion and exclusion criteria.

Data analysis

Descriptive statistics for continuous (mean/Standard Deviation (SD); median/ Interquartile Range IQR) and categorical variables (counts/%). Incidence and frequency for event occurrence.
Outcomes and key utilization measures will be summarized for the overall study population and stratified descriptively by prespecified subgroups (e.g., inpatient, outpatient SUD). Missingness will be profiled and reported.

Milestones

The study will be registered in the Heads of Medicines Agencies (HMA)- European Medicines Agency (EMA) Catalogues of Real-World Data (RWD) studies on 23 March 2026, followed with data collection starting on 27 March 2026 and ending on 31 December 2026. The final study report is planned for completion by 01 April 2027.

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Start of data collection	27 March 2026
End of data collection	31 December 2026
Registration in the HMA-EMA Catalogues of RWD studies	23 March 2026
Final study report	01 April 2027

7. RATIONALE AND BACKGROUND

MM is a clonal plasma cell malignancy. Although outcomes have improved with Pis, IMiDs and anti-CD38 mAb, many patients relapse and become triple-class exposed, leaving limited options and poor prognosis. BCMA-directed therapies, including the bispecific antibody elranatamab, have expanded choices for RRMM. In the phase 2 MagnetisMM-3 study, elranatamab showed clinically meaningful activity in heavily pretreated patients and a safety profile characterized by CRS, ICANS, cytopenias, and infections, which are typically low grade and can be managed with appropriate mitigation strategies such as step-up dosing, premedication, and close monitoring (1, 2). With longer follow-up from MagnetisMM-3, median progression-free survival (PFS) of approximately 17 months and median overall survival (OS) of more than two years have been reported, confirming durable activity in this triple-class exposed population (2,3).

As elranatamab use scales in routine U.S. practice, real-world evidence (RWE) is needed to describe pragmatic aspects of care, including settings of SUD, transitions between weekly/Once Every 2 Weeks (Q2W)/ Once Every 4 Weeks (Q4W) maintenance dosing, concomitant and supportive care (e.g., antimicrobial prophylaxis, IVIG), adverse events and rwOS. Early real-world studies, including the French compassionate-use program and single-center experiences, suggest that elranatamab retains clinically meaningful activity in heavily pretreated patients but is associated with substantial infection burden and hematologic toxicity; one-year PFS and OS rates around 30-40% and 40% have been reported in these high-risk cohorts. These studies are largely based in European academic centers, include relatively small samples, and have limited follow-up, so they may not fully characterize rwOS, patterns of care, or safety in broader U.S. community and outpatient settings.

Real-world data on BCMA-directed bispecific antibodies also show evolving practice patterns around step-up dosing and site of care. Multiple observational studies of the related BCMA bispecific teclistamab have evaluated outpatient and hybrid SUD administration models. These report high rates of successful SUD completion, low rates of high-grade CRS/ICANS, and meaningful reductions in hospital length of stay and health care resource utilization, while maintaining effectiveness comparable to clinical trials (8-11). However, most of these teclistamab studies come from selected centers with structured outpatient programs and often focus on early safety outcomes rather than long-term survival.

For elranatamab specifically, data on SUD care models are even more limited. Emerging reports describe institutional pathways such as the bispecific outpatient safe step-up (BOSS) program, which suggest that carefully selected patients can complete elranatamab SUD in ambulatory settings with low rates of severe CRS when supported by standardized monitoring and prophylaxis (12,13). In addition, recent consensus roadmaps and expert reviews highlight growing interest in shifting bispecific antibody administration, including elranatamab, from inpatient to outpatient and community settings, but emphasize that evidence guiding patient selection, monitoring protocols, and supportive-care strategies remains sparse (14,15). To date, there are no large, multi-health-system EHR-based studies that comprehensively characterize rwOS, care setting patterns (inpatient vs outpatient) during SUD, and downstream safety outcomes for patients treated with elranatamab in routine clinical practice. The lack of robust and systematically collected real-world data, particularly in outpatient settings, represents a key evidence gap and is a primary motivation for the current study.

This study leverages Epic Cosmos database, a multi-health-system, de-identified EHR network predominantly in the United States, to provide a descriptive profile of adults treated with elranatamab. The goal is to summarize who receives elranatamab, how it is administered and supported

in practice, and what adverse events, infections, and survival outcomes are observable in structured EHR data, thereby providing much-needed evidence for elranatamab in real-world settings.

This noninterventional study is designated as a Post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question: What are the patient characteristics, treatment patterns (including step-up dosing and maintenance frequency), effectiveness, and safety of patients with RRMM who initiate elranatamab using Epic Cosmos database?

Primary Objectives:

- Objective 1: To describe demographics, clinical history, and treatment history of multiple myeloma (MM) patients treated with elranatamab.
- Objective 2: To describe and characterize elranatamab utilization, including the timing of treatment initiation, SUD schedule, administration patterns, treatment duration, and dosing during the SUD and post SUD period.
- Objective 3. To describe the use of supportive medications during the SUD and post SUD periods as well as subsequent MM treatments after elranatamab discontinuation.
- Objective 4. To describe the tolerability and safety of elranatamab, specifically the incidence of cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), and cytopenia during the SUD and post SUD period.
- Objective 5. To describe infection incidence during the SUD and post SUD period.
- Objective 6. To describe the effectiveness of elranatamab in terms of real-world overall survival (rwOS, i.e., time to death), death, time to next treatment (TTNT), time to next treatment or death (TTNT or death), and time to discontinuation (TTD).

Secondary objectives:

- To explore heterogeneity in elranatamab utilization, safety/tolerability, infections, and effectiveness outcomes across prespecified and clinically relevant subgroups, including SUD care setting, prior BCMA-directed therapy exposure, renal impairment (e.g., eGFR/CKD categories), prior COVID-19 vaccination status at baseline, and age categories (e.g., <65, 65–69, 70–74, ≥75 years).

9. RESEARCH METHODS

9.1. Study Design

Overall research design and rationale:

This is a retrospective, non-interventional, single arm cohort study of adult MM patients treated with elranatamab in the US using secondary, de-identified EHR data from Epic Cosmos database. The cohort includes adult patients with RRMM who initiated elranatamab, with index date being defined as the first medication order date that must be linked to a record of administration on or after 14-Aug-2023. A cohort design is chosen to enable time-anchored description of treatment pattern and events from real-world data at scale. No active comparator group is planned; however, descriptive contrasts will be presented across pre-specified subgroups. The design emphasizes representativeness and feasibility to address the research questions, recognizing that causal inference is not an objective of this protocol.

Study time windows and data collection

The study time windows are summarized in Figure 1 Study Design Schematic. For each eligible patient, data will be organized around the following periods:

- Index date: The first order/administration/initiation of elranatamab treatment on or after August 14, 2023.
- Baseline period: Extends from the date of MM diagnosis to the day before the index date. During this period, we will describe:
    - Clinical characteristics, including disease-related features, prior procedures, and other MM-relevant history.
    - MM treatment history, including prior MM therapy and exposure to major MM drug classes and BCMA-directed therapies.
    - Renal impairment history and prior COVID-19 vaccination status.
    - CCI assessment: Comorbidities, summarized using the Charlson Comorbidity Index (CCI), assessed in the 365-day window prior to index to reflect the current comorbidity burden at the time of elranatamab initiation.
    - Demographics: Age, sex, race, ethnicity, geographic region, and marital status will be assessed as of the index date using the values recorded on or closest to that date. Age will be calculated as the difference between date of birth and index date.
- SUD period: Defined as the interval spanning elranatamab step-up dosing, from the first 12 mg dose through the first 76 mg dose (inclusive). Within this period, we will characterize:
    - Care setting (inpatient, outpatient) during SUD.
    - Patients will also be categorized into SUD pattern groups (e.g., complete and timely SUD, complete but delayed SUD, and alternative SUD patterns) based on the timing and completeness of 12 mg, 32 mg, and 76 mg doses. Detailed operational definitions for these SUD groups will be provided in the Variables section.
- Post SUD elranatamab treatment period: Defined as the time from the first 76 mg dose after SUD through the last observed 76 mg elranatamab administration.

- Elranatamab treatment period (SUD and post SUD periods): Defined as the time from the first 12 mg dose to the last 76 mg elranatamab administration, representing the combined duration of the SUD period and the post-SUD elranatamab treatment period.
    - This period will be further partitioned into fixed calendar-day sub-periods to support detailed descriptive summaries of elranatamab administration patterns:
        - Index date to Day 8;
        - Day 9 to Day 168;
        - Day 169 to end of elranatamab treatment.
    - Adverse Event (AE)s which are observable in structured data, including:
        - CRS and ICANS captured during the Elranatamab treatment period.
        - Cytopenia events captured throughout the Elranatamab treatment period.
        - Infections captured during the Elranatamab treatment period.
    - Elranatamab timing and dosing, including completion and dosing intervals.
    - Ongoing elranatamab dosing frequency (weekly, biweekly, monthly), the time between consecutive elranatamab administrations will be summarized using the median number of days (IQR) to characterize the typical dosing interval during the elranatamab treatment period.
    - Concomitant medications commonly used (e.g., dexamethasone, diphenhydramine, acetaminophen, tocilizumab, and other supportive medications).
    - Use of supportive care during Elranatamab treatment period
    - Within each sub-period we will summarize elranatamab administrations, time between consecutive administrations, and duration of observed treatment at both the administration-level and patient-level.
- Post-elranatamab period: Defined as the time from the last 76 mg elranatamab administration plus 90 days to the last observable encounter activity in Cosmos.
- Overall follow-up period: For time-to-event and longitudinal descriptive analyses, patients will be followed from the index date until the earliest of data cutoff, death, or loss of observable activity in the EHR. This follow-up framework allows estimation of rwOS, death, TTNT, TTNT or death, TTD, while aligning with the time periods portrayed in Figure 1. Also, we will describe the use of other multiple myeloma treatments during the overall follow-up period.

In addition, certain medication-based variables will use focused windows around the index date:

- Anti-infective medications (e.g., antibacterial, antiviral, antifungal agents) will be summarized in the 14-day window prior to index to characterize empiric anti-infective use immediately before elranatamab initiation.

Key study outcomes

Within this design framework, the study will provide:

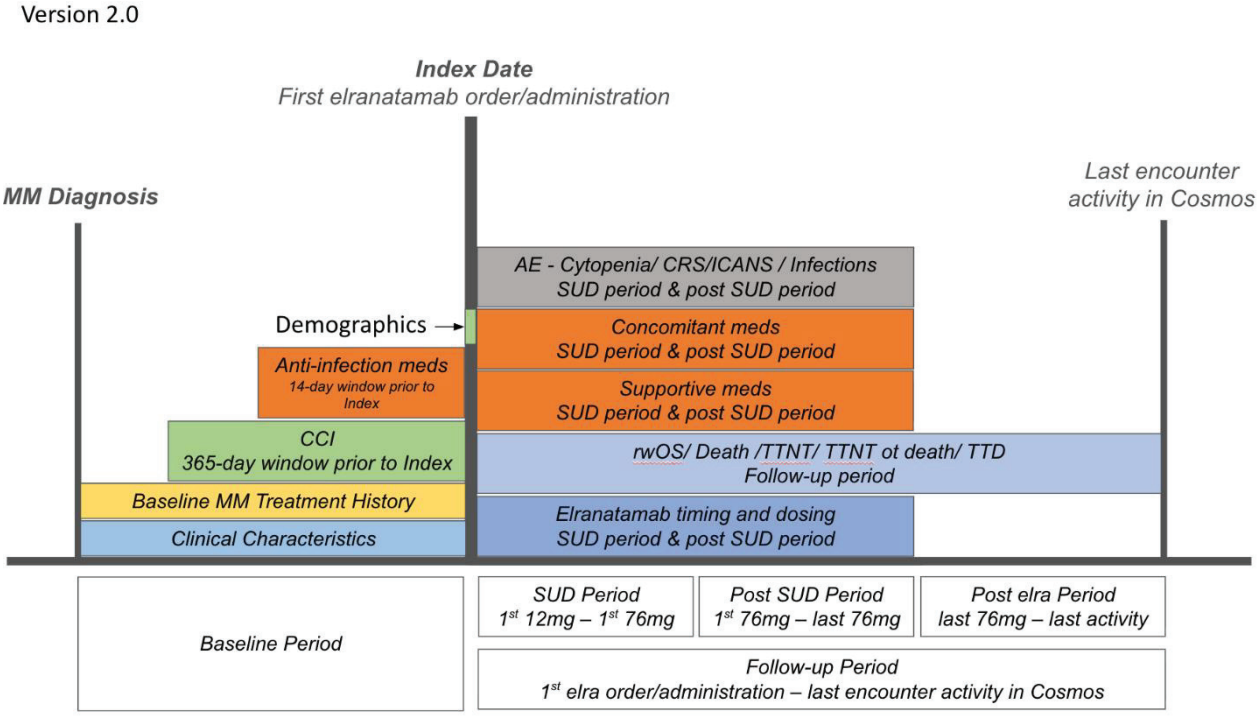
- A detailed baseline profile at index, including demographics, comorbidities (CCI), and MM disease and treatment history.
- A description of elranatamab utilization, including SUD completion and timing, dosing frequency and schedule changes during maintenance, and the distribution of inpatient, outpatient care settings during SUD and subsequent treatment, treatment duration.
- Clinical outcomes, including rwOS, death, TTNT, TTNT or death, and TTD.
- Concomitant and supportive care patterns and AEs observable in structured data, including CRS, ICANS, infections, and neutropenia across the defined study periods.

Strengths of the design:

In this design, patients are first identified at the elranatamab index date and then followed longitudinally until death , loss to follow-up, or database cutoff (regardless of subsequent MM therapy). Baseline information, including demographics measured as of the index date and clinical characteristics, comorbidities, and MM treatment history captured from MM diagnosis up to the day before index, provides context on who receives elranatamab in routine practice. Subsequent events are organized into clearly defined time periods: the SUD period (from first 12 mg dose through first 76 mg dose), the post-SUD elranatamab treatment period (from first 76 mg dose through last elranatamab administration), and the post-elranatamab period (from last elranatamab dose through last encounter). This structure enables consistent description of treatment patterns, supportive care, safety events, infections, and effectiveness outcomes within clinically meaningful windows across the entire follow-up period.

This cohort framework enables (i) large-scale, multiple health system characterization of elranatamab utilization; (ii) direct use of medication administration/order timestamps to profile SUD and maintenance patterns; (iii) pragmatic assessment of clinical outcomes and adverse events in routine practice; and (iv) reproducible definitions, as illustrated in Figure 1, that are suitable for future updates. Limitations (e.g., misclassification, incomplete labs, variability in coding) are acknowledged elsewhere in the protocol.

Figure 1 Study Design Schematic:



9.2. Setting

This study is a secondary analysis of de-identified, structured EHR data consolidated within the Epic Cosmos database, which aggregates data from participating health systems. Available data domains include demographics, diagnoses, procedures, encounters, and medications (orders/administrations, where available).

The Epic Cosmos database combines 17 billion of clinical data points from approximately 300 million patients, made up of data from across the Epic community, to form the largest database of EHR patient information. With over 41,400 Clinics and 1,809 Hospitals participating in Cosmos, researchers can access a representative sample of patients who seek healthcare. Cosmos integrates both inpatient and outpatient charts into a single, comprehensive record, including patients moving between health systems. Participating organizations provide a Health Insurance Portability and Accountability Act (HIPAA)-defined limited data set to the centralized Cosmos database, including demographics, vitals, medications, labs, procedures, encounters, results, care team, allergies, birth history, family history, immunizations, infections, microbiology results, OB history, smart data elements, social history, respiratory data. In addition to diagnoses and medications, it includes patient-generated data and specialty-specific data. For example, a cancer patient's record contains detailed oncology visits, advanced lab results, and hospitalizations as well as standard outpatient visits.

Within this setting, the source population for the current study is adult patients with multiple myeloma receiving care in Epic Cosmos database contributing health systems. The analytic cohort will consist of patients with a diagnosis of multiple myeloma who have at least one elranatamab order with a link to administration recorded in Cosmos on or after August 14, 2023. This first elranatamab order/administration defines the index date. Patients are required to meet protocol specified inclusion

and exclusion criteria to ensure that the cohort represents individuals with relapsed/refractory multiple myeloma (RRMM) treated with elranatamab in routine practice.

For each eligible patient, longitudinal data will be organized into pre-specified time periods as illustrated in Figure 1 study design schematic: a baseline period prior to index (used to characterize clinical profile, treatment history, and comorbidities), a SUD period around initial elranatamab dosing, subsequent elranatamab treatment and post-elranatamab periods, and an overall follow-up period from index until end of observable data. These time periods provide a consistent framework for describing elranatamab utilization, concomitant and supportive treatments, adverse events, and effectiveness outcomes.

9.2.1. Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for inclusion in the study :

1. Received their first elranatamab treatment on or after August 14, 2023.
2. Have a documented diagnosis of MM (ICD-9: 203.0x or ICD-10 C90.0x, C90).
3. Are 18 years of age or older on the index date.
4. Have at least one recorded clinical encounter in Epic Cosmos within the 12 months preceding the index date.

9.2.2. Exclusion Criteria

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

1. Were enrolled in a clinical trial on the index date.
2. Received elranatamab prescription order at a non-US site on the index date.
3. Information on Elranatamab is missing or incomplete, such as details regarding dosage and administration setting.

9.3. Variables

All variables will be queried or derived from de-identified, structured data in Epic Cosmos database, including the patient, encounter, diagnosis, procedure, medication, and vital signs fact tables.

Table 1. Variable for Exposure

Lists the variables for exposure that will be used to identify patients for the study cohort.

Variable	Role	Data Source(s)	Operational Definition	
			Definition	Assessment Period
Elranatamab Initiation	Exposure	Epic Cosmos	Internal code list of generic medication name for elranatamab in Cosmos. • Code list	Index Date

Elranatamab Initiation Time	Exposure	Epic Cosmos	First elranatamab order date. If not available, encounter date will be used. • Timestamp	Index Date
Age at Index	Exposure	Epic Cosmos	Years from birthdate to index (integer years). • Continuous	Index Date
MM Diagnosis	Exposure	Epic Cosmos	MM diagnosis in ICD-10-CM or ICD-9-CM at any time. • Y/N	Baseline Period
12-month Encounter Activity	Exposure	Epic Cosmos	Clinical encounter within 365 days before index. • Y/N	365-day window prior to Index
Enrollment in Clinical Trial	Exposure	Epic Cosmos	Investigational flag indicating enrollment in an interventional clinical study overlapping the index date. • Y/N	Index Date

Table 2. Variables for Primary Objective 1

Primary Objective 1: To describe demographics, clinical history, and treatment history of MM patients treated with elranatamab.

Lists the variables for primary objective 1.

Variable	Role	Data Source(s)	Operational Definition	
			Definition	Assessment Period
Age	Baseline characteristics	Epic Cosmos	Age will be calculated using the birth year index (integer years). • <65 • 65-69 • 70-74 • >=75 • Continuous	Index Date
Sex	Baseline characteristics	Epic Cosmos	Categorical sex • Male	Index Date

			• Female	
Race	Baseline characteristics	Epic Cosmos	Race recorded in Cosmos. • White • African American • Asian or Pacific Islander • Other • Unknown	Index Date
Ethnicity	Baseline characteristics	Epic Cosmos	Ethnicity recorded in Cosmos. • Hispanic • Non- Hispanic	Index Date
Marital Status	Baseline characteristics	Epic Cosmos	Marital status recorded in Cosmos • Married/Partnered/Common law • Separated/Divorced/Widowed/ Never married • Unknown	Index Date
State	Baseline characteristics	Epic Cosmos	State recorded in Cosmos.	Index Date
Care Setting	Baseline characteristics	Epic Cosmos	Derived care setting indicator from Cosmos. • Inpatient • Outpatient	Index Date
Health System Type	Baseline characteristics	Epic Cosmos	Defines healthcare system where available. • Academic • Community	Index Date
Height	Baseline characteristics	Epic Cosmos	Height recorded Cosmos.	Index Date or 30-day window prior to Index
Weight	Baseline characteristics	Epic Cosmos	Weight recorded in Cosmos.	Index Date or 30-day window

				prior to Index
BMI	Baseline characteristics	Epic Cosmos	BMI recorded in Cosmos.	Index Date or 30-day window prior to Index
CCI • Myocardial infarction • Congestive heart failure • Peripheral vascular failure • Cerebrovascular disease • Dementia • Chronic pulmonary disease • Rheumatic disease • Peptic ulcer disease • Mild liver disease • Moderate or severe liver disease • Diabetes w/o chronic complication • Diabetes with chronic complication • Mild or moderate renal disease • Severe renal disease • Hemiplegia or paraplegia • Human immunodeficiency virus • AIDS	Baseline characteristics	Epic Cosmos	Calculated from diagnosis history using the Glasheen algorithm. Higher scores indicate greater comorbidity burden. (categorical) • 0 • 1-2 • 3-4 • >=5	365-day window prior to Index

• Metastatic solid tumor • Malignancy				
Renal failure	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for renal failure • Y/N	Baseline Period
Liver failure (toxicity)	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for liver failure (toxicity) • Y/N	Baseline Period
Amyloidosis	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for amyloidosis • Y/N	Baseline Period
Hypertension	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for hypertension • Y/N	Baseline Period
Extramedullary disease	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for extramedullary disease • Y/N	Baseline Period
Malignancy other than hemato-oncology	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for malignancy other than hemato-oncology • Y/N	Baseline Period
Non-myeloma hematologic malignancy	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for non-myeloma hematologic malignancy • Y/N	Baseline Period
Venous thromboembolism	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for venous thromboembolism • Y/N	Baseline Period
Chronic hepatitis B infection	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for chronic hepatitis B infection • Y/N	Baseline Period
Chronic hepatitis C infection	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for chronic hepatitis C infection • Y/N	Baseline Period

Bronchiectasis	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for Bronchiectasis • Y/N	Baseline Period
Peripheral neuropathy	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for peripheral neuropathy • Y/N	Baseline Period
Osteoporosis	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for osteoporosis • Y/N	Baseline Period
Autoimmune diseases requiring systemic immunosuppression • Rheumatoid arthritis • SLE • Inflammatory bowel disease • Psoriasis	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for autoimmune diseases requiring systemic immunosuppression • Y/N	Baseline Period
Major depressive disorder	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for major depressive disorder • Y/N	Baseline Period
Severe mental illness • Schizophrenia • Bipolar disorder	Baseline characteristics	Epic Cosmos	ICD-9/ICD-10 codes for severe mental illness • Y/N	Baseline Period
Pis • Bortezomib, • Carfilzomib, • Ixazomib	Baseline characteristics	Epic Cosmos	Medication names for Pis: bortezomib, carfilzomib, or ixazomib • Y/N	Baseline Period
IMiDs • Lenalidomide, • Thalidomide, • Pomalidomide	Baseline characteristics	Epic Cosmos	Medication names for IMiDs: lenalidomide, thalidomide, or pomalidomide • Y/N	Baseline Period
anti-CD38 monoclonal antibodies (anti-CD38 mAbs) • Daratumumab,	Baseline characteristics	Epic Cosmos	Medication names for anti-CD38s: daratumumab,	Baseline Period

• Isatuximab, • Elotuzumab			isatuximab, or elotuzumab • Y/N	
Penta-drug exposed • Pis • IMiDs • Anti-CD38 mAbs	Baseline characteristics	Epic Cosmos	Medication names for all the following therapies (Y/N): • 2 distinct records of Pis • 2 distinct records of IMiDs • 1 record of anti-CD38 mAbs	Baseline Period
Other bispecific antibodies • Teclistamab, • Talquetamab, • Linvoseltamab	Baseline characteristics	Epic Cosmos	Medication names for non-elranatamab bispecific antibodies: teclistamab, talquetamab, linvoseltamab • Y/N	Baseline Period
Antibody-drug conjugates • Belantamab mafodotin	Baseline characteristics	Epic Cosmos	Medication names for ADCs: belantamab • Y/N	Baseline Period
Nuclear export inhibitors • Selinexor	Baseline characteristics	Epic Cosmos	Medication names for selinexor • Y/N	Baseline Period
Stem-Cell transplant	Baseline characteristics	Epic Cosmos	Medication names and Current Procedural Terminology (CPT) codes for stem-cell transplant • Y/N	Baseline Period

CAR-T • Idecabtagene vicleucel • Ciltacabtagene autoleucel	Baseline characteristics	Epic Cosmos	Medication names and CPT codes for for idecabtagene vicleucel or ciltacabtagene autoleucel • Y/N	Baseline Period
Chemotherapies • Doxorubicin hydrochloride, • Melphalan, • Bendamustine, • Cyclophosphamid • Etoposide, • Cisplatin	Baseline characteristics	Epic Cosmos	Medication names for chemotherapies: doxorubicin hydrochloride, melphalan, bendamustine, cyclophosphamide, etoposide, or cisplatin • Y/N	Baseline Period
Baseline antibiotics	Baseline characteristics	Epic Cosmos	Medication names for baseline antibiotics • Y/N	14-day window prior to Index
Baseline immunoglobulin	Baseline characteristics	Epic Cosmos	lab test result for baseline immunoglobulin or IVIG administration (Y/N)	90 (30) days pre-index
Baseline serious infection requiring hospitalization	Baseline characteristics	Epic Cosmos	inpatient encounters with infection-related diagnosis codes of the following types (Y/N): • COVID-19 • Adenoviral pneumonia • Cytomegaloviral pneumonitis • COVID-19 pneumonia • Other Pneumonia • Upper respiratory tract infection • Sepsis	365-day pre-index window

			• Cytomegaloviral infection • Pneumocystis jiroveci pneumonia (PJP) • Hepatitis C • Hepatitis B • Other infectious hepatitis • Helicobacter pylori • Candida esophagitis • Urinary tract infection • Sinusitis • Bronchitis	
Baseline antiviral	Baseline characteristics	Epic Cosmos	Medication names for baseline antiviral • Y/N	14-day window prior to Index
Baseline antifungals	Baseline characteristics	Epic Cosmos	Medication names for baseline antifungals • Y/N	14-day window prior to Index
prior BCMA-directed therapy exposure • Idecabtagene vicleucel, • Ciltacabtagene autoleucel, • Belantamab	Baseline characteristics	Epic Cosmos	Medication names/ procedure for idecabtagene vicleucel, ciltacabtagene autoleucel, or belantamab • Y/N	Baseline Period
Renal impairment	Baseline characteristics	Epic Cosmos	Renal impairment will be defined as eGFR < 60 mL/min/1.73 m² based on the most recent eGFR measurement prior to index.	Baseline Period

			• Y/N	
Prior Covid-19 vaccination	Baseline characteristics	Epic Cosmos	Prior COVID-19 vaccination will be defined as receipt of at least one documented COVID-19 vaccine dose prior to the index date, based on vaccination records available in Epic Cosmos. • Y/N	Baseline Period

Variables for Primary Objective 2

Primary Objective 2:

To describe and characterize elranatamab utilization, including the timing of treatment initiation, SUD schedule, administration patterns, treatment duration, and dosing during the SUD and post SUD period.

Patients will be categorized into SUD exposure groups based on the timing and completeness of elranatamab dose administration:

- Group A - Complete and timely SUD: Patients who received one 12 mg dose, followed by one 32 mg dose within 1-7 days after the 12 mg dose, and a subsequent 76 mg dose within 1-7 days after the 32 mg dose.
- Group B - Complete but delayed SUD: Patients who received one 12 mg dose, one 32 mg dose, and a subsequent 76 mg dose, with one or both dose intervals between 8-14 days.
- Group C - Alternative SUD pattern: Patients who:
  - received only one 12 mg or 32 mg dose prior to the first 76 mg dose; or
  - received more than two doses below 76 mg prior to the first 76 mg dose; or
  - had >14 days between the 12 mg and 32 mg doses, or between either the 12 mg or 32 mg dose and the first 76 mg dose.

Excluded from SUD:

- Patients who received only one 12 mg, 32 mg, or 76 mg dose, or only 12 mg and 32 mg doses without a subsequent 76 mg dose.

Patients will also be categorized into fixed calendar-day sub-periods to support detailed descriptive summaries of elranatamab administration patterns, including number of elranatamab administrations, time between consecutive administrations, and duration of observed treatment at both the administration-level and patient-level:

- Index date to Day 8.
- Day 9 to Day 168.
- Day 169 to end of elranatamab treatment.

Table 3. Variables for primary objective 2.

Variable	Role	Data Source(s)	Operational Definition	
			Definition	Assessment Period
Elranatamab dose strength (per administration)	Outcome	Epic Cosmos	Dose strength in mg for each elranatamab administration. • 12 mg • 32 mg • 44 mg • 76 mg • Other	SUD and post SUD period.
Elranatamab administration timing (Days since index)	Outcome	Epic Cosmos	For each elranatamab administration, timing is defined as the number of days from the index date to the administration date, calculated as: administration date − index date. • Continuous (days)	SUD and post SUD period
Number of elranatamab administrations	Outcome	Epic Cosmos	Count of elranatamab administrations (both administration and patient levels) • Integer	SUD and post SUD period
Time between elranatamab administrations	Outcome	Epic Cosmos	Calendar days between consecutive elranatamab administrations per patient, calculated as the difference between administration dates. • Continuous (days)	SUD and post SUD period

elranatamab treatment duration	Outcome	Epic Cosmos	Total calendar duration of elranatamab observation per patient, calculated as days from index to last elranatamab administration. ● Continuous (days)	SUD and post SUD period
SUD exposure group	Outcome	Epic Cosmos	Categorical variable describing elranatamab step-up dosing pattern (detailed definition in the text above this table) ● Group A ● Group B ● Group C	SUD period.
Elranatamab treatment sub-periods	Outcome	Epic Cosmos	Categorical indicator assigning each administration and patient-level summary to one of the fixed calendar-day sub-periods: ● Index date to Day 8 ● Day 9 to Day 168 ● Day 169 to end of elranatamab treatment	SUD and post SUD period
SUD care setting	Outcome	Epic Cosmos	Care setting indicator derived from Cosmos ● All Inpatient ● All Outpatient	SUD period
Elranatamab maintenance dosing frequency	Outcome	Epic Cosmos	For each patient, predominant dosing schedule during the post-SUD period, based on the interval between consecutive 76 mg doses. (weekly, biweekly, monthly) The time between consecutive elranatamab administrations will be summarized using the	Post-SUD period.

			median number of days (IQR) to characterize the typical dosing interval during the elranatamab treatment period.	

Table 4.Variables for Primary Objective 3

Primary Objective 3: To describe the use of supportive medications during the SUD and post SUD periods as well as subsequent MM treatments after elranatamab discontinuation

Lists the variables for primary objective 3 .

Variable	Role	Data Source(s)	Operational Definition	
			Definition	Assessment Period
Pis • Bortezomib, • Carfilzomib, • Xazomib.	Outcome	Epic Cosmos	Medication names for subsequent MM treatment after elranatamab discontinuation - PIs • Y/N	Follow-up Period
IMiDs • Lenalidomide, • Thalidomide, • Pomalidomide	Outcome	Epic Cosmos	Medication names for subsequent MM treatment after elranatamab discontinuation - IMiDs • Y/N	Follow-up Period
Anti-CD38 monoclonal antibodies (anti-CD38 mAbs) • Daratumumab, • Isatuximab, • Elotuzumab	Outcome	Epic Cosmos	Medication names for subsequent MM treatment after elranatamab discontinuation - anti-CD38s • Y/N	Follow-up Period
Stem-Cell transplant	Outcome	Epic Cosmos	Medication names and CPT codes for subsequent MM treatment after elranatamab discontinuation - stem-cell transplant • Y/N	Follow-up Period

CAR-T • Idecabtagene vicleucel • Ciltacabtagene autoleucel	Outcome	Epic Cosmos	Medication names and CPT codes for subsequent MM treatment after elranatamab discontinuation - CAR-T • Y/N	Follow-up Period
Chemotherapies • Doxorubicin hydrochloride, • Melphalan, • Bendamustine, • Cyclophosphamide, • Etoposide, • Cisplatin	Outcome	Epic Cosmos	Medication names for subsequent MM treatment after elranatamab discontinuation - chemotherapies • Y/N	Follow-up Period
Other bispecific antibodies • Teclistamab, • Talquetamab, • Linvoseltamab	Outcome	Epic Cosmos	Medication names for subsequent MM treatment after elranatamab discontinuation - non-elranatamab bispecific antibodies: teclistamab, talquetamab, linvoseltamab • Y/N	Follow-up Period
Antibody-drug conjugates • Belantamab mafodotin	Outcome	Epic Cosmos	Medication names for subsequent MM treatment after elranatamab discontinuation – ADCs: belantamab • Y/N	Follow-up Period
Nuclear export inhibitors • Selinexor	Outcome	Epic Cosmos	Medication names for subsequent MM treatment after elranatamab	Follow-up Period

			discontinuation - selinexor • Y/N	
IVIG	Outcome	Epic Cosmos	Medication names for IVIG • Y/N	SUD and post SUD periods
Dexamethasone	Outcome	Epic Cosmos	Medication name(s) for dexamethasone • Y/N	SUD and post SUD periods
Diphenhydramine	Outcome	Epic Cosmos	Medication name(s) for diphenhydramine • Y/N	SUD and post SUD periods
Acetaminophen	Outcome	Epic Cosmos	Medication name(s) for acetaminophen • Y/N	SUD and post SUD periods
Tocilizumab	Outcome	Epic Cosmos	Medication name(s) for tocilizumab • Y/N	SUD and post SUD periods

Table 5. Variables for Primary Objective 4

Primary Objective 4: To describe the tolerability and safety of elranatamab, specifically cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity (ICANS) during the SUD and post SUD period.

Lists the variables for primary objective 4.

Variable	Role	Data Source(s)	Operational Definition	
			Definition	Assessment Period
CRS Incidence	Outcome	Epic Cosmos	Identified based on either a diagnosis code or algorithmic detection indicative of CRS • For analyses of entire SUD group or the three individual SUD subgroups, CRS will be	SUD and post-SUD periods and within an additional 30-day post-treatment risk window following the last recorded elranatamab dose.

			identified during the following intervals: ○ Between the first and second doses, ○ Between the second and third doses, and ○ After the third dose.	A 30-day washout period will be applied to define incident events
Time to First CRS	Outcome	Epic Cosmos	Time in days from Index to first CRS.	SUD and post-SUD periods and within an additional 30-day post-treatment risk window following the last recorded elranatamab dose. A 30-day washout period will be applied to define incident events.
CRS concomitant medications	Outcomes	Epic Cosmos	Medication names for concomitant medications received on the same day as the CRS event. ● Y/N	SUD and post-SUD periods and within an additional 30-day post-treatment risk window following the last recorded elranatamab dose. A 30-day washout period will be applied to define incident events.
ICANS Incidence	Outcome	Epic Cosmos	Identified based on a diagnosis code of ICANS ● For analyses of entire SUD group, ICANS events will be assessed within 14 days following the index date. ● For analyses of the three individuals SUD subgroups, ICANS will	SUD and post-SUD periods and within an additional 30-day post-treatment risk window following the last recorded elranatamab dose.

			be identified during the following intervals: ○ Between the first and second doses, ○ Between the second and third doses, and ○ After the third dose.	A 30-day washout period will be applied to define incident events.
Time to First ICANS	Outcome	Epic Cosmos	Time in days from Index to first ICANS.	SUD and post-SUD periods and within an additional 30-day post-treatment risk window following the last recorded elranatamab dose. A 30-day washout period will be applied to define incident events.
ICANS concomitant medications	Outcomes	Epic Cosmos	Medication names for concomitant medications received on the ICANS event date or within 1 day after the event. ● Y/N	SUD and post-SUD periods and within an additional 30-day post-treatment risk window following the last recorded elranatamab dose. A 30-day washout period will be applied to define incident events.
Cytopenia Incidence ● Anemia ● Leukopenia ● Lymphopenia ● Neutropenia ● Thrombocytopenia	Outcomes	Epic Cosmos	Identified by disease code or labs value for cytopenias incidence	SUD and post-SUD periods and within an additional 30-day post-treatment risk window following the last recorded elranatamab dose. A 30-day washout period will be applied to define incident events.

Table 6. Variables for Primary Objective 5

Primary Objective 5: To describe infection incidence during the SUD and post SUD period .

Lists the variables for primary objective 5.

Variable	Role	Data Source(s)	Operational Definition	
			Definition	Assessment Period
Infection Incidence	Outcome	Epic Cosmos	Identified based on diagnosis codes for any infection of the following: • COVID-19 • Adenoviral pneumonia • Cytomegaloviral pneumonitis • COVID-19 pneumonia • Other Pneumonia • Upper respiratory tract infection • Sepsis • Cytomegaloviral infection • Pneumocystis jiroveci pneumonia (PJP) • Hepatitis C • Hepatitis B • Other infectious hepatitis • Helicobacter pylori • Candida esophagitis • Urinary tract infection	SUD and post-SUD periods and within an additional 60-day post-treatment risk window following the last recorded elranatamab dose. A 60-day washout period will be applied to define incident events.

			• Sinusitis • Bronchitis.	
Frequency of Infections	Outcome	Epic Cosmos	Total number of infections during the time period per patient (categorical) • 1 infection • 2 infections • 3 or more infections	SUD and post-SUD periods and within an additional 60-day post-treatment risk window following the last recorded elranatamab dose. A 60-day washout period will be applied to define incident events.
Time to First Infection	Outcome	Epic Cosmos	Time from Index to first infection.	SUD and post-SUD periods and within an additional 60-day post-treatment risk window following the last recorded elranatamab dose. A 60-day washout period will be applied to define incident events.
Follow-up antibiotics	Clinical Characteristics	Epic Cosmos	Medication names for follow-up antibiotics • Y/N	SUD and post-SUD periods and within an additional 60-day post-treatment risk window

				following the last recorded elranatamab dose. A 60-day washout period will be applied to define incident events.
Follow-up antiviral	Clinical Characteristics	Epic Cosmos	Medication names for follow-up antiviral • Y/N	SUD and post-SUD periods and within an additional 60-day post-treatment risk window following the last recorded elranatamab dose. A 60-day washout period will be applied to define incident events.
Follow-up antifungals	Clinical Characteristics	Epic Cosmos	Medication names for follow-up antifungals • Y/N	SUD and post-SUD periods and within an additional 60-day post-treatment risk window following the last recorded elranatamab dose. A 60-day washout period will be applied

				to define incident events.

Table 7. Variables for Primary Objective 6

Primary Objective 6: To describe the effectiveness of elranatamab in terms of rwOS, death, TTNT, TTNT or death, and TTD.

Lists the variables for primary objective 6.

Variable	Role	Data Source(s)	Operational Definition	
			Definition	Assessment Period
rwOS (Time to Death)	Outcome	Epic Cosmos	Time to death will be defined as the time from index date to death. Patients without a recorded death will be censored at the last observable encounter or database cutoff date.	Follow-up Period
Death	Outcome	Epic Cosmos	Alive/Deceased status recorded in PatientDim table in Cosmos. Default is alive. • Y/N	Follow-up Period
TTNT	Outcome	Epic Cosmos	Time to next treatment is defined as the number of days from Index date to the initiation of the next non-elranatamab treatment. (Pis, IMiDs, anti-CD48 mAb, stem-cell transplant, Car-T, chemotherapies, other bispecific antibodies, antibody-drug conjugates, and nuclear export inhibitors) Patients without the event will be censored at the last observable encounter or database cutoff date.	Follow-up Period

TTNT or death	Outcome	Epic Cosmos	Time to next treatment or death is defined as the number of days from the index date to the first occurrence of either initiation of the next non-elranatamab MM treatment or death. Patients without the event will be censored at the last observable encounter or database cutoff date.	Follow-up Period
TTD[1]	Outcome	Epic Cosmos	Elranatamab treatment is considered ended at the last observed elranatamab administration if no subsequent elranatamab administration or alternative MM therapy is observed within 180 days. Subsequent MM therapies initiated after this window will be classified as next-line treatment.	Follow-up Period

1. Sensitivity analyses will evaluate alternative gap definitions (e.g., 60-day and 90-day gaps) to assess robustness of the TTD definition.

9.4. Data Sources

This study will utilize de-identified, structured EHR data from the Epic Cosmos database. A single, time-bounded data extract will be requested, with parameters defined according to the eligibility criteria and study objectives. Where applicable, the validity of key variables (e.g., medication administration dosage and date) will be assessed through standard data quality checks.

The Epic Cosmos database combines 17 billion of clinical data points from approximately 300 million patients, made up of data from across the Epic community, to form the largest database of EHR patient information. With over 41,400 Clinics and 1,809 Hospitals participating in Cosmos, researchers can access a representative sample of patients who seek healthcare. Cosmos integrates both inpatient and outpatient charts into a single, comprehensive record, including patients moving between health systems. Participating organizations provide a HIPAA-defined limited data set to the centralized Cosmos database, including demographics, vitals, medications, labs, procedures, encounters, results, care team, allergies, birth history, family history, immunizations, infections, microbiology results, OB history, smart data elements, social history, respiratory data. In addition to diagnoses and medications, it includes patient-generated data and specialty-specific data. For example, a cancer patient's record contains detailed oncology visits, advanced lab results, and hospitalizations as well as standard outpatient visits.

Death information in Epic Cosmos is derived from multiple sources within local health systems. When available, the first populated death date is used, including (1) a verified death date documented in the patient chart, (2) a date of death documented in a flowsheet, or (3) the most recent unconfirmed death date loaded from an external source. If none of these sources contain a death date, the patient will not have a recorded death date in Cosmos. Unconfirmed external death dates are available only for organizations that have upgraded to the Epic November 2023 release.

9.5. Study Size

This is a descriptive study with no formal hypothesis testing planned. Therefore, sample size calculati ons are not applicable. As of October 23, 2025, Epic Cosmos database included around 500 patients w ho meet the inclusion and exclusion criteria.

9.6. Data Management

Data vendor/data store and data source: This study will use Epic Cosmos, a federated, de-identified structured EHR-derived research database hosted by Epic Systems, accessed through the Epic Cosmos Data Science Portal. The analytic team will query the Cosmos structured data domains (e.g., patient demographics, diagnoses, encounters, procedures, medication orders and administrations, laboratory results where available, and death information captured in PatientDim) to construct the study cohort and analysis datasets.

Data acquisition frequency/timepoints and responsible parties: A structured database extract will be generated by the Evidence data science/analytics team via the Cosmos Data Science Portal. Data will be extracted at prespecified timepoints: an initial feasibility/count extract and a final analysis extract using a fixed data cutoff date aligned with the study milestones. No manual chart review is planned, and no Case Report Forms will be used.

Extraction format and process: Cohort construction and variable derivation will be implemented using reproducible, version-controlled query code executed within or against the Cosmos Data Science Portal environment. Output datasets will be exported in analysis-ready formats (e.g., delimited text files and/or native SAS/R/Python formats as applicable) and stored in a controlled-access analytic workspace. An internal data dictionary, cohort flow diagram, and operational definitions (e.g., SUD subgroups, outcome definitions) will be maintained with audit trails and version control. Records will be retained per sponsor policy and applicable law.

Structured extract specifications: The extract will be parameterized to align with the protocol inclusio n/exclusion criteria (MM diagnosis, first elranatamab use on/after the index start date, age ≥18 on inde x, and evidence of clinical activity in the 12 months prior to index), and will include the structured do mains required for the planned analyses (demographics, encounters, diagnoses, procedures, medicatio ns/administrations, laboratory results where available, and mortality). Data will be pulled as a fixed-c utoff extract at prespecified timepoints (feasibility and final analysis) and delivered as analysis-ready datasets compatible with SAS/R/Python workflows.

9.7. Data Analysis

All analyses will be descriptive in nature.

- Continuous variables will be summarized using the mean (standard deviation), and median (interquartile range).
- Categorical variables will be summarized as counts and percentages.
- Event occurrence variables will be summarized using:
    - Frequency, defined as the number of events in a given time window.
    - Incidence, defined as the occurrence of new events among patients at risk during a specified time period, calculated as an incidence rate = (the number of new events during the period) / (total person-time at risk).
- Time-to-event outcomes (e.g., rwOS, TTNT, TTNT or death) will be described using Kaplan-Meier estimates, with the median time-to-event and associated 95% Confidence Intervals (CI) reported where estimable. Censoring will occur at the date of last known clinical encounter or data cutoff, whichever comes first.

No causal inference analyses are planned. Descriptive subgroup analyses will be performed in line with the secondary objectives, including but not limited to subgroups defined by SUD care setting (inpatient, outpatient), prior BCMA-directed therapy exposure, and age categories. The same summary measures described above will be presented within each subgroup. No formal hypothesis testing or interaction testing is planned.

Missing data will be profiled to characterize the extent of missingness. Given the real-world nature of the data source, missingness is expected. No imputation will be performed for missing covariates unless otherwise specified. For categorical variables, key descriptive summaries may include a "missing/unknown" category. For continuous variables, summary statistics (mean, median, SD, etc.) will be calculated based on the number of patients with observed values.

Detailed methodology for summary and statistical analyses of data collected in this study will be docu mented in a statistical analysis plan (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

Programming reviews on cohort entry and key derivations (e.g., SUD completion, rwOS/TTD/TTNT/ TTNT or death) will be performed. Table shells and figure specs will be pre-specified. Internal quality control will include logic checks, extreme value detection, and reconciliation between medication and encounters.

9.9. Limitations of the Research Methods

Variability in EHR coding practices and clinical documentation across healthcare systems may limit the accuracy and completeness of adverse event capture and their severity grading. Mortality information in Epic Cosmos may be incompletely captured, potentially affecting the estimation of

overall survival. In addition, procedure and laboratory data may be incomplete, which could impact the identification of treatments such as CAR-T therapies.

This study relies primarily on structured EHR data and does not incorporate unstructured clinical narratives such as physician notes, pathology reports, or imaging interpretations. As a result, certain clinically nuanced information—such as symptom severity, physician assessments, contextual details of adverse events, and complex disease trajectories—may not be fully captured, which may limit the clinical richness and interpretability of some findings.

Furthermore, while medication orders and administrations can be identified in the EHR, accurately reconstructing complete lines of therapy (LOT) in multiple myeloma remains challenging. EHR data often capture individual drugs rather than standardized regimen groupings, and may not fully reflect treatment intent, combination structures, or sequencing decisions made by clinicians. Consequently, the number, composition, and boundaries of prior or subsequent lines of therapy may be subject to misclassification or uncertainty.

Findings from this study will therefore reflect the experience of patients within participating Epic health systems and may not be fully generalizable to all U.S. healthcare settings.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent.

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

As this study involves a secondary analysis of de-identified, structured data obtained from the Epic Cosmos database, Institutional Review Board (IRB) approval is not required. This determination is based on the fact that the study does not involve the collection, use, or transmission of individually identifiable patient information.

10.4. 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 Guidelines of Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structure data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to lin k (i.e., identify a potential association between) a particular product and medical event for any individ ual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifia ble reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A study report and abstract will be developed. In addition, abstract, poster, and manuscript will be developed and submitted to conferences and peer-reviewed journals of Pfizer's choice with hematology/oncology focus. All external communications will require Pfizer approval. Reporting will be aggregate and de-identified with no patient-level data will be shared.

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 party responsible for collecting data from the participant 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.

13. REFERENCES

1. Lesokhin AM, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023. 29:2259–2267.
2. Tomasson M et al. Long-term efficacy and safety of elranatamab monotherapy in the phase 2 MagnetisMM-3 trial in RRMM. Blood. 2023;142(Suppl 1):3385.
3. Mohty M et al. Long-term Survival After Elranatamab Monotherapy in Patients with Relapsed or Refractory Multiple Myeloma (RRMM): MagnetisMM-3. EHA 2024. Abstract: P932.
4. Malard F et al. Elranatamab monotherapy in the real-world setting in relapsed-refractory multiple myeloma: results of the French compassionate use program on behalf of the IFM. Blood Cancer J. 2024. 14:219.
5. Mohty M et al. Efficacy and safety of elranatamab monotherapy in the real-world setting in Relapsed-Refractory Multiple Myeloma (RRMM): Results of the French compassionate use program on Behalf of the IFM. EHA 2024. Abstract P906.
6. Uzay A et al. Elranatamab in heavily pretreated triple-class refractory multiple myeloma: a single-center experience. Acta Oncologica Turcica. 2025.
7. Mol I et al. Elranatamab versus physician's choice of treatment in triple-class exposed/ refractory multiple myeloma: an updated matching-adjusted indirect comparison. J Comp Eff Res. 2025. 14:e240236.
8. Sandahl TB et al. Real-World Treatment Outcomes of Teclistamab Under an Outpatient Model for Step-Up Dosing Administration. Blood. 2023;142(Suppl 1):5154.
9. Sandahl TB et al. Real-World Safety and Health Care Resource Utilization of Teclistamab Under an Outpatient Model for Step-Up Dosing Administration. JCO Oncol Pract. 2025;21:702-709.
10. Banerjee R et al. Real-World Characteristics, Step-Up Dosing Patterns, and Early Safety Outcomes of Patients with Multiple Myeloma Treated with Teclistamab within Vs. after the First Year of FDA Approval. ASH 2024. Abstract P907.
11. Dhakal B et al. Outcomes of Teclistamab (Tec) Step-Up Dosing in Outpatient/Hybrid Settings among a Large Sample of Relapsed Refractory Multiple Myeloma (RRMM) Patients Treated with Tec. Clin Lymphoma Myeloma Leuk. 2025;25(Suppl):S57-S58.
12. Cirstea D et al. Implementing the bispecific outpatient safe step-up (BOSS) program for elranatamab in ambulatory treatment of multiple myeloma. J Clin Oncol. 2025;43(16 Suppl):e19507.
13. Cirstea D et al. Bispecific Outpatient Step-Up Dosing with Prophylactic Dexamethasone: The BOSS Program Experience in Myeloma. Clin Lymphoma Myeloma Leuk. 2025. 25(Suppl 2):S53-S54.
14. Scott SA et al. Feasibility and Safety of Outpatient Model Administration of Bispecific Antibodies: Proceedings from an International Myeloma Society 21st Annual Meeting Oral Abstract. Clin Lymphoma Myeloma Leuk. 2025. 25:656-660.

15. Garfall AL et al. A roadmap to implementing outpatient administration of bispecific antibodies in multiple myeloma. Front Oncol. 2025. 30:15:1630146.

LIST OF TABLES

LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not Applicable

ANNEX 3. ADDITIONAL INFORMATION

Not Applicable

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