NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Comparative Effectiveness of Elranatamab (PF-06863135) in Clinical Study C1071003 Versus Standard of Care (SOC) in Real-World (RW) External Control Arms in Patients with Triple-Class Refractory (TCR) Multiple Myeloma (MM)
Protocol number	C1071031
Protocol version identifier	1.0
Date	01 May 2023
Active substance	Elranatamab (PF-06863135)
Research question and objectives	**Primary objectives:** • To compare PFS among TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the COTA database. • To compare PFS among TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the Flatiron Health database. **Secondary objective:** • To compare OS in TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the COTA database. • To compare OS in TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients

	receiving SOC therapy from the Flatiron Health database. **Exploratory objective:** • To compare the change of patient-reported outcomes in TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the prospective observational studies C1071013 and C1071014.
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2. LIST OF ABBREVIATIONS

Abbreviation	Term
ADC	Antibody-Drug Conjugate
AE	Adverse Event
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
Anti-CD38 mAb	Anti-CD38 Monoclonal Antibody
AST	Aspartate Aminotransferase
ATE	Average Treatment Effect
ATT	Average Treatment Effect Amongst Treated
BCMA	B-Cell Maturation Antigen
BM	Bone Marrow
CAR	Chimeric Antigen Receptor
CATE	Conditional Average Treatment Effect
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CVD	Cardiovascular Disease
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
EMA	European Medicines Agency
EMD	Extramedullary Disease
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma Questionnaire
EQ-5D	European Quality of Life 5 Dimension
EQ-VAS	EuroQoL – Visual Analog Scale
FCS	Fully Conditional Specification
FDA	Food and Drug Administration
FLC	Free Light Chain
GBS	Guillain-Barre Syndrome
GVHD	Graft Versus Host Disease
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCP	Healthcare Provider
HIV	Human Immunodeficiency Virus
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
IPTW	Inverse Probability of Treatment Weights

Abbreviation	Term
KarMMa-RW	Comparison of Idecabtagene Vicleucel with Real-World Outcomes in Relapsed and Refractory Multiple Myeloma
LVEF	Left Ventricular Ejection Fraction
LOT	Line of Therapy
MAMMOTH	Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure
MAR	Missingness at Random
MI	Multiple Imputation
MICE	Multiple Imputations by Chained Equations
MM	Multiple Myeloma
MMRM	Mixed-Effects Model with Repeated Measures
M-protein	Monoclonal Immunoglobulin Protein
MUGA	Multigated Acquisition Scan
NI	Non-Interventional
NICE	National Institute for Health and Care Excellence
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PGIC	Patient Global Impression of Change
PI	Proteasome Inhibitor
PFS	Progression-Free Survival
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes
PS	Propensity Scores
PRO	Patient-Reported Outcomes
QoL	Quality of Life
QT	Time from the beginning of the QRS Complex to the End of the T Wave
QTcF	Corrected QT (Fridericia Method)
RCT	Randomized Controlled Trial
RW	Real-World
RWD	Real-World Data
RWE	Real-World Evidence
RRMM	Relapsed or Refractory MM
SAP	Statistical analysis plan
SARS-Cov2	Severe Acute Respiratory Syndrome- Coronavirus 2
SLAMF7	Signaling Lymphocytic Activation Molecule Family Member 7
SMD	Standardized Mean Difference
SOC	Standard of Care
SPEP	Serum Protein Electrophoresis
TCR	Triple-Class Refractory

Abbreviation	Term
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
US	United States
VAS	Visual Analog Scale

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Not applicable.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	15 May 2023
End of data collection	22 May 2023
Final study report	26 July 2023

7. RATIONALE AND BACKGROUND

MM is a rare and progressive type of cancer that is characterized by the rapid accumulation of monoclonal plasma cells in the bone marrow (BM). This results in the production of monoclonal immunoglobulin protein (M-protein) and eventually leads to end-organ damage. The global incidence of MM is rising and is estimated at 160,000 in 2018, with 106,000 deaths attributed to MM annually. In the past 3 decades, from 1990 to 2016, the global incidence of MM has increased by 126%, with the highest incidence rates reported in Australia, Western Europe, and the United States (US).[1]

Over the years, advancements have been made in the discovery and utilization of MM therapies, with the current SOC including proteasome inhibitors (PIs) (bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (IMiDs) (thalidomide, lenalidomide, pomalidomide), and anti-CD38 monoclonal antibodies (anti-CD38 mAb: daratumumab and isatuximab).[2]

Despite these treatment advances, a major proportion of MM patients will fail all 3 classes of the current SOC regimens (including PI, IMIDs, and anti-CD38) and become triple class refractory (TCR). The treatment of TCR MM presents a therapeutic challenge because of the inherent clonal heterogeneity and genetic instability of MM tumor cells, influencing the eventual development of therapeutic resistance.[3] Therefore, as TCR patients progress and are exposed to an increasing number of therapies, the duration of response (DOR) decreases along with PFS and OS until the disease is ultimately fatal.[4-6]

Belantamab mafodotin-blmf was the first B-cell maturation antigen (BCMA) therapy approved by the FDA in August 2020,[7] and in November 2022, the US marketing authorization was withdrawn.[8] Since 2020, the FDA has approved 3 other BCMA therapies, including 2 CAR T-cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel) and most recently the first-in-class BCMA bispecific antibody therapy teclistamab-cqyv.[9-11] Pfizer has developed elranatamab (PF-06863135), an investigational B-cell maturation antigen (BCMA) CD3-targeted bispecific antibody, for the treatment of patients with TCR MM. The preliminary results of the Phase 1 study (NCT03269136) demonstrated manageable safety of elranatamab and a response rate of 69% (ie, 9/13 patients) at the recommended dose of 1000 µg/kg.[12] Additionally, elranatamab has been granted Fast Track Designation by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to aid the rapid development and review of this novel agent and thereby address the unmet medical needs of TCR MM patients.[13] Pfizer is currently conducting a Phase 2 study to evaluate the clinical benefit of elranatamab in TCR MM patients (Study C1071003). The updated results from the MagnetisMM-3 study showed an objective response rate (ORR) of 61.0% after a median follow-up of 10.4 months.[14] Based on these results, in November 2022, elranatamab received FDA Breakthrough Therapy Designation for the treatment of patients with relapsed or refractory MM (RRMM).[15] Considering the ethical and practical challenges associated with conducting a randomized clinical trial within a particularly difficult-to-treat population of MM patients with unmet needs and no clear single SOC, a single arm design was adopted for the Phase 2 study.[16] Thus, there is a need to generate evidence on the clinical outcomes of

TCR patients who receive SOC to help contextualize the results from Study C1071003. This has been accomplished by creating an external control arm using real-world data (RWD) to support the ongoing evaluation of elranatamab.

Other studies used the RW data to analyze clinical outcomes in patients with relapsed/refractory MM (RRMM). In the MAMMOTH study,[17] 249 MM patients starting a new treatment after becoming refractory to an anti-CD38 mAb (daratumumab or isatuximab) were identified from 14 US academic institutions. In these patients, the ORR for the first regimen after becoming refractory to anti-CD38 mAb was 31%, and median PFS and OS from the time when patients became refractory to an anti-CD38 mAb were 3.4 months (95% confidence interval, CI: 2.8-4.0) and 9.3 months (95% CI: 8.1-10.6), respectively.[17]

The KarMMa-RW study was a global NI, retrospective study that assessed treatment patterns and outcomes in RW RRMM patients treated with currently available therapies, and whose characteristics were similar to the KarMMa study, a Phase 2 single-arm study of idecabtagene vicleucel in heavily pretreated RRMM patients who were triple-class exposed and refractory to the last regimen.[18] Approximately 43% of the KarMMa-RW population were TCR. The ORR of the 190 eligible RRMM patients in the RW setting was 32% (95% CI: 24.4 - 42.3), and 29.4% (95% CI: 20.2-42.8) in the matched eligible RRMM subset. In the eligible RRMM cohorts, the median PFS was 3.5 months, and the median OS was 14.7 months.

Regulatory Agencies, including FDA and EMA, have recognized the utility of external control arms derived from RWD in decision-making, and have established guidance on conditions that should be satisfied before an external control approach is deemed appropriate, as well as key methodological considerations to be addressed.[19-21] According to these guidelines, an external control approach is considered appropriate under certain conditions, including (a) there is a high unmet need (eg, serious rare diseases), (b) there is a well-documented, highly predictable disease course that can be objectively measured and verified, and (c) there is an expected drug effect that is large, self-evident, and temporally closely associated with the intervention.[22,23] A recently published review of the National Institute for Health and Care Excellence (NICE) appraisals showed that 22 technologies (12 in an oncology indication) were appraised by NICE from 2000 to 2016 based on non-randomized controlled trial (RCT) data; 27% of those used observational data to establish comparative effectiveness;[24] over half of the NICE applications were made in the last 2 years alone.

To contextualize the clinical profile of elranatamab, a retrospective cohort study (Study C1071024; NCT05565391), was conducted to compare the efficacy outcomes observed in the participants of Study C1071003 (with at least 9 months of follow-up) and RW patients selected from 2 US-based oncology electronic health record (EHR) databases, Flatiron Health and COTA. The results of Study C1071024 showed that among TCR MM patients, those treated with elranatamab had significantly higher ORR than those treated with SOC. Thus, in the IPTW analysis comparing participants from Study C1071003 with RW patients from COTA or Flatiron Health, the estimated relative risk (RR) was 2.22 (95% CI: 1.69-2.90, p<.0001) and 1.79 (95% CI: 1.01-3.15, p=.0447), respectively. Differences in the time to

response (TTR) between those treated with elranatamab and SOC were not consistently observed, however, DOR was significantly improved for elranatamab compared to SOC (IPTW hazard ratio [HR] 0.11, 95% CI: 0.06 - 0.22, p<.0001 and 0.21, 95% CI: 0.10 - 0.45, p<.0001 when comparing participants from Study C1071003 with RW patients from COTA or Flatiron Health, respectively). The current study is the continuation of the C1071024 with a longer available follow-up of the Study C1071003 participants and a larger set of outcomes.

This study aims to compare the PFS and OS in participants of Study C1071003 treated with elranatamab versus RW TCR MM patients treated with SOC therapies. To reduce the potential for bias, external control arms will be constructed by selecting fit-for-purpose RWD sources (ie, reliable and relevant),[25] and appropriate comparative effectiveness methods, including statistical techniques (eg, IPTW)[26-28] Additionally, an exploratory analysis of patient reported outcomes (PROs) will be conducted.

8. RESEARCH QUESTION AND OBJECTIVES

This study aims to assess the comparative effectiveness of elranatamab versus SOC treatment in TCR MM patients using external control arms for the open-label, multicenter, non-randomized single-arm Phase 2 Study C1071003.

Primary objectives:

- To compare PFS among TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the COTA database.
- To compare PFS among TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the Flatiron Health database.

Secondary objectives:

- To compare OS in TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the COTA database.
- To compare OS in TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the Flatiron Health database.

Exploratory objective:

- To compare the change of patient-reported outcomes in TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of TCR MM patients receiving SOC therapy from the prospective observational studies C1071013 and C1071014.

9. RESEARCH METHODS

9.1. Study Design

This retrospective cohort study will use patient-level data from single arm clinical Study C1071003 and external control arms identified previously from RWD sources. The relating study protocols are in Annex 1. To maximize comparability, the eligibility criteria for the participants from Study C1071003 have been applied to patients from the RWD sources (see Section 9.2.3 for more detail).

MM patients eligible for selection into external control arms are those patients who are refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb and have started at least 1 new treatment since the documentation of TCR status. Refractory is defined as having disease progression, according to International Myeloma Working Group (IMWG) criteria or clinical assessment, while on therapy or within 60 days of the last dose in any line of therapy (LOT), regardless of response. In Flatiron Health and COTA, if a subsequent LOT was initiated and a progression was observed after at least 30 days of the LOT start, the patient is considered refractory to the subsequent LOT even if the progression occurred within 60 days after the last dose of the preceding LOT. Details on the operational definitions of IMWG criteria for progression used in Flatiron Health, COTA, C1071013, and C1071014 and a side-by-side comparison with the criteria used in Study C1071003 are provided in the related study protocols in Annex 1.

In the RW setting, no single SOC currently exists for TCR MM patients, and combinations of treatments are frequently used in lieu of monotherapy.[29]. For simplicity, in this protocol, the term "SOC" refers to all standard treatment options available for TCR MM patients. Selection of TCR MM patients initiating a new treatment in the external control arm enables comparability of patients at a similar stage in disease progression following TCR documentation.

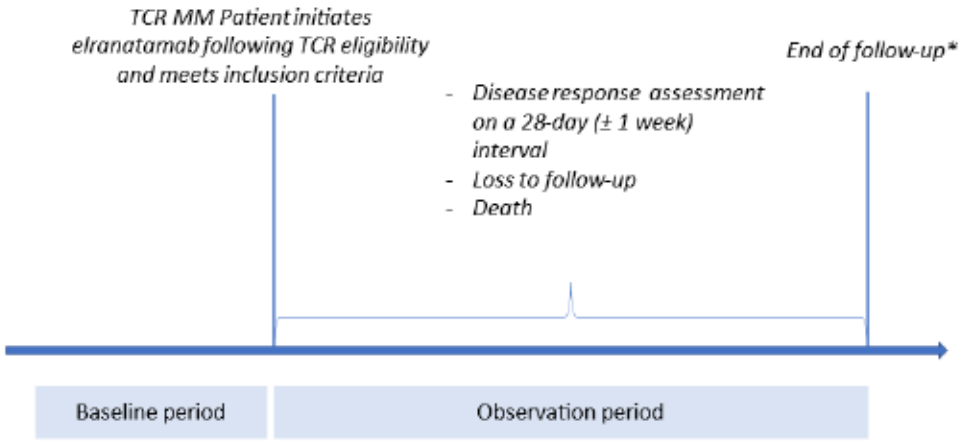
The date of initiation of the first regimen after TCR MM eligibility will be defined as the index date. For the comparative analysis of PFS and OS, only patients with an index date occurring between 16 November 2015, and 30 June 2022 will be selected (the first anti-CD38 mAb therapy was approved by the FDA on 16 November 2015) from COTA and Flatiron Health. CCI [redacted] The study period will be comprised of the baseline period (time preceding the index date) and the observational period (time following the index date). The baseline period (screening period) for the participants of C1071003 is 28 days before the initiation of elranatamab. Due to the observational nature of data, the baseline period for RW patients for the collection of patients' history and lab measurements extends from the time of the first MM diagnosis to the index date. The specific time windows for each assessment are detailed in the respective RW protocols (Annex 1) and in the list of covariates provided in Section 9.3. The observational period will span from the index date to the earliest of death, or the latest available patient record, whichever comes first. The primary clinical outcome of interest will be PFS. The secondary clinical outcome of interest will be OS. It is expected that

the median OS will not be reached in Study C107100 because of insufficient follow-up data used in this analysis. For the exploratory analysis, PROs measured using self-administered questionnaires will be assessed.

In the main analysis comparing PFS and OS, differences in baseline characteristics (demographic characteristics, treatment history, and disease-related characteristics) between patients in Study C1071003 and each external control arm will be balanced using IPTW (see Section 9.7.2). Sensitivity analyses of PFS and OS will be conducted to evaluate the effect of alternative methods to address confounding and selection bias, including the doubly robust method, and using alternative inclusion/exclusion criteria. A quantitative bias analysis (nullification analysis) will be performed to evaluate the robustness of results in the presence of potential threats to internal validity (see Section 9.7.3).

A schematic figure of Study C1071003 and external control arms is provided in Figure 1 and Figure 2, respectively.

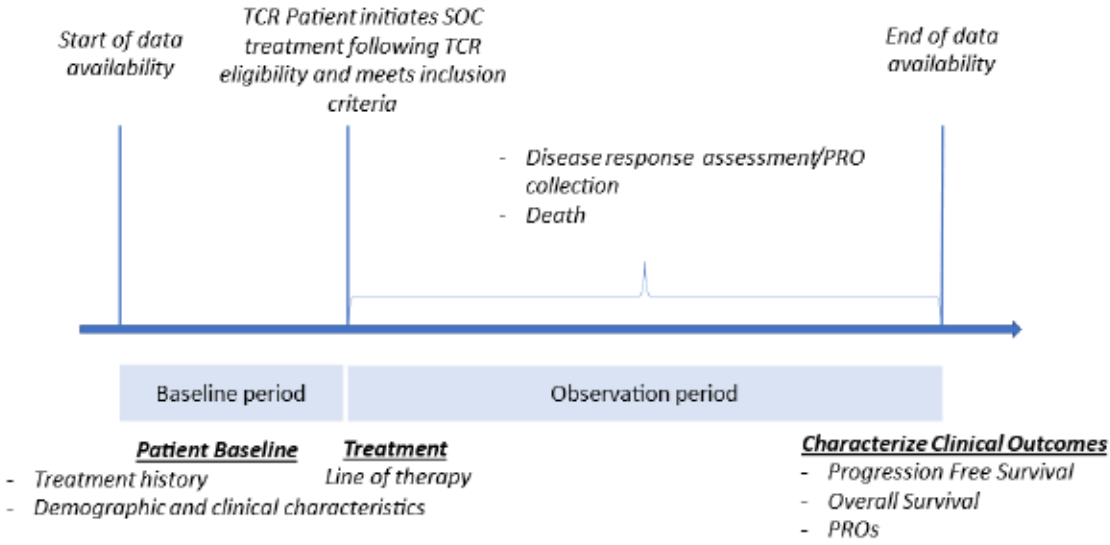
Figure 1. Baseline and Observation Periods in Study C1071003



- *For this protocol, all participants will be followed for about 15 months from the date of enrolment*

Abbreviations: MM=multiple myeloma; TCR=triple -class refractory.

Figure 2. Baseline and Observation Periods in External Control Arms



Abbreviations: MM=multiple myeloma; PRO=patient reported outcome; TCR=triple-class refractory; SOC=standard of care

9.2. Setting

9.2.1. Study C1071003

Study C1071003 is an open-label, multi-center, non-randomized Phase 2 study of elranatamab (PF-06863135) monotherapy, which was initiated in February 2021.[30] To determine the effects of prior BCMA-directed therapy on the response to elranatamab monotherapy, Study C1071003 enrolled 2 independent and parallel cohorts, 1 with patients who are naïve to BCMA-directed therapies (Cohort A; 123 patients) and the other with patients previously exposed to BCMA-directed therapy (Cohort B; 64 patients). Because few patients were exposed to BCMA-directed therapy in our RW database sources, the focus of the comparisons will be on Cohort A in Study C1071003, though additional analyses will include both Cohorts A and B.

9.2.2. Real-World Data Sources

The cohorts of RW TCR MM patients for the external control arm will be identified from EHR databases Flatiron Health and COTA and prospective observational studies C1071013 and C1071014. These databases have been selected according to data availability and as fit-for-purpose for fulfilling study objectives (23). The eligible period for the index dates of patients from each RW database has been selected to align as closely as possible to each other and Study C1071003.

Flatiron Health

The Flatiron Health database is a longitudinal, demographically, and geographically diverse database derived from EHR data. Flatiron includes data from over 280 community cancer centers and academic institutions (~800 sites of care) representing more than 2.4 million US active cancer patients available for analysis. The source population is the overall population reported in the EHR and includes patients managed in at least 1 of the US oncology centers taking part in the Flatiron Health network from 01 January 2011 onwards.

Flatiron Health databases consist of longitudinal data on MM patients, including normalized data from structured EHR, enhanced data on patients' characteristics abstracted from unstructured EHR, and derived data that is created based on Flatiron-specific business rules.[31]

Structured data include information on patients' demographics, visit dates, diagnoses, vitals, medications, the Eastern Cooperative Oncology Group (ECOG) performance status, and laboratory tests. Unstructured data contain additional information on comorbidities, biomarker reports, and details of transplants. Flatiron Health also provides derived data such as progression and response variables where algorithms are developed following adapted IMWG criteria to identify these events throughout the course of a patient's journey.

Details on the identification of the external control arm using Flatiron Health data can be found in the related protocol as Document 001 in Annex 1.

COTA

COTA maintains a multidisciplinary data curation approach. The COTA database is a longitudinal database derived from the EHR of healthcare provider (HCP) sites including academic institutions, community centers, and hospital systems representing 500,000 patients from over 200 sites of care in the US. Data elements are standardized across sources to create a single, structured dataset to cover the full longitudinal history of a patient's clinical care. For each patient, the datasets contain information from the time of initial MM diagnosis to the most recent documentation in the HER.[32]

As with Flatiron Health, COTA collects information from structured and unstructured data sources. Derived data based on adapted IMWG criteria are also provided (eg, disease progression and treatment response). COTA differs from Flatiron Health in the provision of specific databases that are dedicated to reporting factors relevant to the experience of a patient with MM and includes datasets containing abstracted information on bone lesions, plasmacytomas, radiation therapy, and adverse events (AEs).

Details on the identification of the external control arm using COTA data can be found in the related protocol as Document 002 in Annex 1.

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9.2.3. Inclusion and Exclusion Criteria for External Control Arms

Comparability of patients between Study C1071003 and the external control arms is one of the key considerations to minimize bias. Care will be taken to ensure that patients identified from each RW TCR MM cohort are similar to the Study C1071003 patients by satisfying pre-specified inclusion and exclusion criteria. Inclusion and exclusion criteria from Study C1071003 are provided in Table 1 and will be modified for each cohort of RW TCR patients based on data availability. Operational definitions of inclusion and exclusion criteria for each RWD source are summarized in Annex 2.

Due to the missingness present within RWD sources, there is an inherent tradeoff between analyzable sample size and the degree of comparability of patients from Study C1071003 with the external control arm sample. In other words, the more closely the inclusion/exclusion criteria for the external control arms are aligned to Study C1071003, the smaller the available sample size. Therefore, for the comparative analysis of PFS and OS, 2 samples of external control arms (the critical eligibility criteria sample and the expanded eligibility criteria sample) will be selected from each cohort of RW TCR MM patients identified in COTA or Flatiron Health (see Table 1). Both samples will incorporate core inclusion/exclusion criteria from Study C10701003 which represent key clinical variables to define the cohort. Furthermore, the expanded eligibility criteria sample will incorporate additional inclusion/exclusion criteria from Study C1071003 (eg, lab values) at the expense of a smaller sample size.

For the comparative analyses of PFS and OS, the critical eligibility criteria sample will constitute the main analysis set. Sensitivity analyses will be conducted using the expanded eligibility criteria to assess the potential influence of the selection process on the observed effects (ie, main analyses will be repeated using this sample). The number of patients included/excluded at each step of the study will be reported.

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Table 1 provides a tabular view summarizing the inclusion and exclusion criteria of Study C1071003 which are available and will be applied for the selection of critical and expanded eligibility criteria samples of RW patients (signified with a checkmark symbol where the critical and/or expanded selection criteria definitions are applicable).

Table 1. Inclusion and Exclusion Criteria for Study C1071003 and RW Data Sources.

Patient criteria per Study C1071003	Implementation in Flatiron Health		Implementation in COTA		Implementation in C1071013 and C1071014
	Critical eligibility criteria	Expanded eligibility criteria	Critical eligibility criteria	Expanded eligibility criteria	Critical eligibility criteria
Inclusion Criteria					
Male or female patients aged ≥18 years	ü	ü	ü	ü	ü
Willing and able to comply with all scheduled visits, treatment plans, laboratory tests, lifestyle considerations, and other study procedures	N/A	N/A	N/A	N/A	N/A
Prior diagnosis of MM as defined according to IMWG criteria*	ü	ü	ü	ü	ü
Measurable disease, based on IMWG criteria as defined by at least 1 of the following a) Serum M-protein ≥0.5 g/dL by SPEP b) Urinary M-protein excretion ≥200 mg/24 hours by Urine Protein Electrophoresis (UPEP) c) Serum immunoglobulin Free Light Chain (FLC)≥10 mg/dL (≥100 mg/L) and abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65)	ü	ü	ü	ü	ü
Patients are TCR defined as being refractory to all 3 of the following: a) Refractory to at least 1 IMiD b) Refractory to at least 1 PI c) Refractory to at least 1 anti-CD38 mAb Relapsed/refractory to last anti-MM regimen	ü	ü	ü	ü	ü
Initiated at least 1 anti-MM systemic therapy after becoming TCR eligible. The first systemic treatment initiation after becoming TCR eligible must not comprise any study or investigational agent.**	ü	ü	ü	ü	ü
ECOG performance status ≤2	ü	ü	ü	ü	ü
Adequate hepatic function characterized by all of the following: a) Total bilirubin ≤2 x Upper Limit of Normal (ULN) (≤3 x ULN if documented Gilbert's syndrome) b) aspartate aminotransferase (AST) ≤2.5 x ULN c) alanine aminotransferase (ALT) ≤2.5 x ULN	X	ü	X	ü	X
Adequate renal function, defined by an estimated creatinine clearance ≥30 mL/min (according to the Cockcroft Gault formula, by 24 hour urine collection for creatinine clearance, or according to the local institutional standard method)	X	ü	X	ü	X
Adequate BM function characterized by all of the following a) Absolute neutrophil count ≥1.0 × 109/L (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days before planned start of dosing) b) Platelets ≥25 × 109/L (transfusion support is permitted if completed at least 7 days before the planned start of dosing)	X	ü	X	ü	X

Patient criteria per Study C1071003	Implementation in Flatiron Health		Implementation in COTA		Implementation in C1071013 and C1071014
	Critical eligibility criteria	Expanded eligibility criteria	Critical eligibility criteria	Expanded eligibility criteria	Critical eligibility criteria
c) Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 7 days before the planned start of dosing)					
Left ventricular ejection fraction ≥40% as determined by a multigated acquisition scan (MUGA) or echocardiogram	X	X	X	X	X
Resolved acute effects of any prior therapy to baseline severity or Common Terminology Criteria for AE Grade ≤1	X	X	X	X	X
Exclusion Criteria					
Active plasma cell leukemia	ü	ü	ü	ü	ü
Amyloidosis	ü	ü	ü	ü	ü
Previous treatment with an anti-BCMA bispecific antibody.	X	X	X	X	X
Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).	ü	ü	ü	ü	ü
Smoldering MM	ü	ü	ü	ü	ü
Stem cell transplant within 12 weeks before enrolment or active Graft Versus Host Disease (GVHD).	ü	ü	ü	ü	ü
Any other active malignancy within 3 years before enrolment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma *in situ*.	ü	ü	ü	ü	ü
POEMS syndrome	X	X	X	X	ü
Impaired cardiovascular function or clinically significant cardiovascular diseases, defined based on the history of any of the following conditions within 6 months before enrolment: a) Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion) b) Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia) c) Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism) d) Prolonged Time from the beginning of the QRS Complex to the End of the T Wave (QT) syndrome (or triplicate average Corrected QT (Fridericia Method) (QTcF) >470 msec).	X	ü	X	ü	X
Active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2), known Human	ü	ü	ü	ü	ü

Patient criteria per Study C1071003	Implementation in Flatiron Health		Implementation in COTA		Implementation in C1071013 and C1071014
	Critical eligibility criteria	Expanded eligibility criteria	Critical eligibility criteria	Expanded eligibility criteria	Critical eligibility criteria
Immunodeficiency Virus (HIV), or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days before enrolment.					
Other surgical (including major surgery within 14 days before enrolment), medical, or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the patient inappropriate for the study.	X	X	X	X	X
Ongoing Grade ≥2 peripheral sensory or motor neuropathy.	X	ü	X	X	X
History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B).	X	ü	X	ü	X
History of Guillain-Barre Syndrome (GBS) or GBS variants, or history of any Grade ≥3 peripheral motor neuropathy	X	ü	X	X	X
Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.	X	X	X	X	X
Known or suspected hypersensitivity to the study intervention or any of its excipients.	X	X	X	X	X
Live attenuated vaccine must not be administered within 4 weeks of the first dose of the study intervention.	X	X	X	X	X

Abbreviations: AST=aspartate aminotransferase; ALT=alanine aminotransferase; BCMA=B-cell maturation antigen; BM=bone marrow; ECOG=Eastern Cooperative Oncology Group; HCV=hepatitis C virus; FLC=free light chain; GBS= Guillain-Barre syndrome; GVHD=graft versus host disease; HBV=hepatitis B virus; HIV= human immunodeficiency virus; ImiD=immunomodulatory drug; IMWG=International Myeloma Working Group; MM=multiple myeloma; PI=proteasome inhibitor; POEMS=polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; QTcF=corrected QT (Fridericia method); SARS-CoV2=severe acute respiratory syndrome coronavirus 2; SPEP=serum protein electrophoresis; TCR=triple-class refractory; ULN=upper limit of normal; UPEP=urine protein electrophoresis.
Note:
*According to Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-e548. doi:10.1016/S1470-2045(14)70442-5.
**This criterion is not among the inclusion/exclusion criteria of Study C10710003 and is applied only to RW patients.
Legend: ü: this criterion can be applied using this RW dataset;
X: this criterion cannot be applied/assessed due to a lack of information in this RW dataset.

9.3. Variables

Exposure definition

In each comparison, patients will be classified into 1 of the 2 treatment groups according to the therapy received after TCR eligibility, as those treated with elranatamab and those treated with a SOC regimen (any standard treatment option available for RW TCR MM patients).

Study outcomes

Consistency between outcome definitions across data sources is another key consideration to minimize bias. Comparative effectiveness endpoints PFS and OS will be evaluated based on availability within each RWD source. Definitions of the outcomes will be aligned, where possible, with Study C1071003 (Table 2).

Table 2. Definitions of Comparative Effectiveness Outcomes in Study C1071003, Flatiron Health, and COTA

	Outcome	Study C1071003	Flatiron Health	COTA
1	Progression-free survival (PFS)	Time from the date of the first dose until confirmed PD per IMWG criteria or death due to any cause, whichever occurs first.	Time from initiation of the first line after TCR to either the date of progression* or death due to any cause, whichever occurs first.	Time from initiation of the first line after TCR to either the date of progression* or death due to any cause, whichever occurs first.
2	Overall survival (OS)	Time from the date of the first dose until death due to any cause	Time from initiation of the first line after TCR until the date of death due to any cause.	Time from initiation of the first line after TCR until the date of death due to any cause.

Note: *
COTA uses a third-party obituary data source to capture mortality data. COTA defines progression based on IMWG criteria. COTA defines a progression as an increase of ≥25% from the lowest response value in any one or more of the following criteria: SPEP with an absolute increase > 0.5 g/dL; 24-hour UPEP with an absolute increase >200 mg/24 h; in patients without measurable serum and urine M-protein, the absolute increase of >10 mg/dL in the difference between involved and uninvolved FLC levels; or an absolute bone marrow plasma cell percentage >10%.
Flatiron Health's mortality variable is created through an amalgamation of structured data elements, unstructured documents, and linking to external mortality sources and the Social Security Death Index (SSDI). Flatiron Health defines progression based on IMWG criteria. Flatiron Health defines a progression as an increase of ≥25% from baseline/nadir value in any one or more of the following: an absolute increase in serum M-protein by SPEP by ≥0.5 g/dL; serum M-protein ≥1 g/dL if the lowest M component was ≥5g/dL; an absolute increase in urine M-protein by UPEP by ≥200 mg/24 h; in patients without measurable serum and urine M-protein levels, an absolute increase in the difference between involved and uninvolved FLC levels of >10 mg/dL.
Abbreviations: IMWG=International Myeloma Working Group; PD=progressive disease; TCR=triple-class refractory.

CCI [redacted]

CCI

Other variables

Ensuring that baseline factors related to treatment assignment and outcomes are captured is of utmost importance for the validity of external control arms. The availability of these variables in selected RWD sources determines the feasibility of the external control arm.

Baseline covariates will be selected to compare patients from elranatamab and external control arms and to perform further statistical adjustments to control for the baseline confounding (eg, via IPTW).

Baseline covariates to be captured will include those related to patient demographic characteristics, disease characteristics, comorbidity profile, laboratory measurements, and MM treatment patterns, including LOT. Each variable will be taken on or before the index date; if before, the most recent measurement will be used. All variables listed below will be used to describe the study cohorts and to adjust for the baseline confounding. Since a small sample size limits the number of covariates that can be reasonably accounted for in the statistical adjustment (eg, IPTW), a systematic literature review was conducted to identify the variables most strongly and consistently correlated with outcomes in RWD studies conducted among RRMM patients. CCI [redacted]

Additional confounders identified in the previous phase of the study will be included in the analysis to optimize the balance in clinical characteristics between participants from Study C1071003 and each RWD source. These confounders have been selected based on their clinical importance and relevance to the disease prognosis and disease complications (level of serum albumin, serum calcium level, presence of bone lesions, extramedullary disease [EMD], hemoglobin, and serum creatinine), liver dysfunction (levels of bilirubin, aspartate aminotransferase [AST], and alanine aminotransferase [ALT]), and burden of comorbid conditions (Charlson comorbidity index [CCI]). Of note, the presence of EMD is only available for the analyses using combined datasets of Study C1071003 and COTA patients.

Multiple imputations will be used to address the presence of missing values for covariates in RWD.

List of covariates

- Age at index date
- Sex (male; female)
- ISS (International Staging System) stage (I; II; III) within 90 days before or on the index date, if feasible
- ECOG performance status within 90 days before or on the index date, if feasible
- Time since initial MM diagnosis (years)
- Number of pre-index treatment lines
- Penta-refractory status at index date
- High cytogenic risk (yes; no) at index date, if feasible
- EMD identified within 12 months before or on the index date

- Presence of bone lesions in patients with no extramedullary disease within 12 months before or on the index date
- Charlson Comorbidity Index within 12 months before or on the index date
- Aspartate aminotransferase (microkat/L) within 90 days before or on the index date, if feasible
- Alanine aminotransferase (microkat/L) within 90 days before or on the index date, if feasible
- Creatinine clearance (mL/min) within 90 days before or on the index date, if feasible
- Hemoglobin (g/L) within 90 days before or on the index date, if feasible
- Bilirubin (mg/dL) Bilirubin (mg/dL) within 90 days before or on the index date
- Calcium in serum or plasma (mmol/L) reported within 90 days before or on the index date
- Serum albumin (g/dL) reported within 90 days before or on the index date.

9.4. Data Sources

Data integration

Upon constructing the analytical file for the comparison between Study C1071003 and Flatiron Health, Study C1071003 and COTA, Study C1071003, and prospective observational studies, a common data model for Study C1071003 and each of the external control arms will be created with standardized data elements. The variable transformation will include the creation of the common variable type, format, and taxonomy. Consistent definitions will be applied to create derived variables for treatments, index date, outcomes, and comorbidities. All data transformation will be documented for transparency.

Combined study datasets

Combined study datasets will be created from the entirety of the Study C1071003 arm plus the selected external control arm based on the data source and eligibility criteria.

A total of 7 combined study datasets will be created. Each will use the same patients from Study C1071003 along with varying RW patients, depending upon the RWD source and inclusion/exclusion criteria applied to identify them, as indicated below.

For the main analysis and sensitivity analyses to address the primary and secondary objectives:

- Study C1071003 Cohort A arm plus the external control arm selected using critical eligibility criteria from COTA

- Study C1071003 Cohort A arm plus the external control arm selected using critical eligibility criteria from Flatiron Health

For a sensitivity analysis based on alternative inclusion/exclusion criteria:

- Study C1071003 Cohort A arm plus the external control arm selected using expanded eligibility criteria from COTA
- Study C1071003 Cohort A arm plus the external control arm selected using expanded eligibility criteria from Flatiron Health

For the additional analyses:

- Study C1071003 Cohort A and Cohort B arms plus external control arm selected using critical eligibility criteria from COTA
- Study C1071003 Cohort A and Cohort B arms plus external control arm selected using critical eligibility criteria from Flatiron Health
- Study C1071003 Cohort A plus external control arm selected using critical eligibility criteria from prospective observational study C1071013 and study C1071014.

9.5. Study Size

The study sample will be identified from the analysis of secondary data that has already been collected. Accordingly, the sample size will be limited by the duration of the observation window. All patients who meet the inclusion/exclusion criteria defined in Section 9.2.3 will be included in the analyses. Retrospective cohort Study C1071024, referenced in Section 7, identified 342 and 477 TCR MM patients in Flatiron Health and COTA, respectively before applying inclusions and exclusion criteria. CCI [redacted] No formal sample size estimations have been performed for this observational study.

9.6. Data Management

This study will use structured databases from Study C1071003, an open-label, multi-center, non-randomized Phase 2 study of elranatamab (PF-06863135) monotherapy,[30] Flatiron Health, and COTA (the latter 2 databases collect information on MM patients treated across the US), and prospective observational studies C1071013 and C1071014. The RW data sources have been selected according to data availability and as fit-for-purpose for fulfilling study objectives (the US FDA, 2018 Framework). The period for index dates for each RW database has been selected to align as closely as possible to each other and to Study C1071003 which will include approximately 15 months of follow-up.

9.7. Data Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the 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.

Table 3 provides the summary of statistical analyses for the combined study cohorts.

Table 3. Summary of Statistical Analyses for Combined Study Cohorts.

	Critical eligibility criteria samples selected from COTA or Flatiron Health	Expanded eligibility criteria samples selected from COTA or Flatiron Health	Critical eligibility criteria sample selected from C1071013 and C1071014
Main analyses	• IPTW comparison of PFS in elranatamab (Cohort A) versus SOC-treated patients selected from COTA • IPTW comparison of PFS in elranatamab (Cohort A) versus SOC-treated patients selected from Flatiron Health • IPTW comparison of OS in elranatamab (Cohort A) versus SOC-treated patients selected from COTA • IPTW comparison of OS in elranatamab (Cohort A) versus SOC-treated patients selected from Flatiron Health		
Sensitivity analyses	• Doubly robust comparisons of PFS in elranatamab (Cohort A) versus SOC-treated patients selected from COTA • Doubly robust comparisons of PFS in elranatamab (Cohort A) versus SOC-treated patients selected from Flatiron Health • Doubly robust comparisons of OS in elranatamab (Cohort A) versus SOC-treated patients selected from COTA • Doubly robust comparisons of OS in elranatamab (Cohort A) versus SOC-treated patients selected from Flatiron Health • Quantitative bias assessments (using IPTW estimates) when comparing PFS in elranatamab (Cohort A) versus SOC-treated patients selected from COTA • Quantitative bias assessments (using IPTW estimates) when comparing PFS in elranatamab (Cohort A) versus SOC-treated	• IPTW comparison of PFS in elranatamab (Cohort A) versus SOC-treated patients selected from COTA • IPTW comparison of PFS in elranatamab (Cohort A) versus SOC-treated patients selected from Flatiron Health • IPTW comparison of OS in elranatamab (Cohort A) versus SOC-treated patients	

	Critical eligibility criteria samples selected from COTA or Flatiron Health	Expanded eligibility criteria samples selected from COTA or Flatiron Health	Critical eligibility criteria sample selected from C1071013 and C1071014
	patients selected from Flatiron Health • Quantitative bias assessments (using IPTW estimates) when comparing OS in elranatamab (Cohort A) versus SOC-treated patients selected from COTA • Quantitative bias assessments (using IPTW estimates) when comparing OS in elranatamab (Cohort A) versus SOC-treated patients selected from Flatiron Health	selected from COTA • IPTW comparison of OS in elranatamab (Cohort A) versus SOC-treated patients selected from Flatiron Health	
Additional analyses	• Comparisons of PFS in PS matched elranatamab (Cohort A) and SOC-treated patients selected from COTA • Comparisons of PFS in PS matched elranatamab (Cohort A) and SOC-treated patients selected from Flatiron Health • Comparisons of OS in PS matched elranatamab (Cohort A) and SOC-treated patients selected from COTA • Comparisons of OS in PS matched elranatamab (Cohort A) and SOC-treated patients selected from Flatiron Health • IPTW comparison of PFS in elranatamab (Cohort A+Cohort B) versus SOC-treated patients selected from COTA • IPTW comparison of PFS in elranatamab (Cohort A+Cohort B) versus SOC-treated patients selected from Flatiron Health • IPTW comparison of OS in elranatamab (Cohort A+Cohort B) versus SOC-treated patients selected from COTA • IPTW comparison of OS in elranatamab (Cohort A+Cohort		• Number and percentage of participants who completed QLQ-C30 domains, QLQ-MY20 domains, EQ-5D index, EQ-5D-VAS, and PGIC at baseline and each follow-up visit. • Descriptive statistics of QLQ-C30 domains, QLQ-MY20 domains, EQ-5D index, EQ-5D-VAS, and PGIC in elranatamab (Cohort A) and SOC-treated patients, including mean and absolute change in PRO scores (final assessment score minus baseline score) Based on the results of the descriptive analysis of completeness, and the timing of assessments in the two treatment arms, the following analyses may be conducted: • Comparison of change from baseline on the QLQ-C30 domains, QLQ-MY20 domains, EQ-5D index, and EQ-5D-VAS using naïve and adjusted mixed-effect models

	Critical eligibility criteria samples selected from COTA or Flatiron Health	Expanded eligibility criteria samples selected from COTA or Flatiron Health	Critical eligibility criteria sample selected from C1071013 and C1071014
	B) versus SOC-treated patients selected from Flatiron Health • Subgroup analyses to compare PFS and OS in participants of Study C1071003 and patients from Flatiron Health and COTA		

In this study, measures taken to reduce potential bias include a pre-specified and detailed SAP. Additionally, the propensity score (PS) balancing steps will be conducted independently and before availability/knowledge of the outcomes (ie, balancing will be conducted using only baseline characteristic data from a preliminary data cut rather than the final data cut containing Study C1071003 efficacy outcome data).

Multiple imputations

MI will be performed to address missing values only in baseline covariates under the assumption of missingness at random (MAR). MAR assumes that there might be systematic differences between the missing and observed values of prognostic characteristics, but these can be entirely explained by other observed prognostic characteristics, the treatment variable, and the observed overall survival. Multiple imputations by chained equations (MICE) will be performed using the fully conditional specification (FCS) method.[34] This approach imputes multivariate missing data on a variable-by-variable basis, by specifying an imputation model for each variable. The technique is iterative and proceeds via Gibbs sampling if the initial joint distribution defined by the specified conditional distributions exists.[35]

As with other iterative procedures, diagnostics are essential to assess and evaluate the resulting imputation models obtained via MICE and to determine whether convergence has been achieved (36). Visual assessment will be performed using worm plots, strip plots, and density plots to examine the observed and imputed data and compare their distributions. Convergence will be evaluated by plotting the mean and variance of each imputation run across iterations, to confirm that there are no apparent trends. If convergence has not been achieved, the number of iterations will be increased until means and variances stabilize.

For each imputed dataset, the comparative analysis of PFS and OS will be conducted, the individual estimates will be combined using Rubin's rules[24] (the details are provided in the SAP).

Propensity scores and inverse probability of treatment weighting

In analyses of RWD, an important consideration in the identification of potentially causal effects is a control for confounding. IPTW is a well-established method for causal inference in nonrandomized studies, which aims to eliminate the effect of confounding by observed baseline patient characteristics, improve covariate balance, and thereby obtain unbiased estimates of treatment effects. Estimating the PS, on which IPTW relies, is a form of dimensionality reduction, in which several individual characteristics relevant to treatment assignment and the outcome, or those related only to outcome development, are used to estimate the conditional probability that the patient is assigned to a given treatment. IPTW is an approach often used in non-randomized studies to create a pseudo-population in which the covariates are independent of the treatment assignment, thereby permitting an unbiased estimate of the ATE, provided that fundamental assumptions of causal inference are satisfied.

The PS will be estimated using logistic regression models, where the dependent variable is a binary indicator of the treatment arm (elranatamab versus SOC). Covariates described in Section 9.3 will be entered into the logistic regression model. Diagnostics of the estimated PS will be applied by examining the distribution of the PS in each treatment group to identify the degree of overlap and region of common support.[37] The estimated PS will be used to generate IPTWs, which may be stabilized to reduce variance and the effect of very large weights. A standardized mean difference (SMD) of ≥20% will be used as an indicator of covariate imbalance between the treatment arms requiring further investigation and refining the logistic model for deriving the weights.[38,39]

9.7.1. Descriptive Statistics

Tabular summaries of baseline patient demographics and clinical characteristics by treatment arm will be presented. Summary statistics will include frequencies and percentages (categorical variables) and mean/median, minimum/maximum with standard deviation/interquartile range (continuous variables).

PFS and OS will be described using Kaplan-Meier (KM) methods.[40] The estimates of the time-to-event curves will be plotted and the median PFS and OS with 95% CI will be reported. The 95% CI for the median will be estimated using the Brookmeyer and Crowley method.[41] The PFS and OS event rates (the events of PD and death, respectively) will be estimated with corresponding two-sided 95% CIs. The CIs for the survival function estimates will be derived using the log(-log) method according to Kalbfleisch and Prentice.[42] The estimate of the standard error will be computed using Greenwood's formula.[43] For PFS, the frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons for PFS will be presented along with the overall event and censor rates. The total number of deaths and censoring reasons for OS will be presented along with the overall event and censor rates.

9.7.2. Main Analyses

For comparative effectiveness, PFS and OS will be assessed using IPTW comparisons estimating the average treatment effect (ATE).

PFS and OS will be compared between treatment arms using hazard ratios estimated from Cox proportional hazards models. The proportional hazards assumption will be checked, and in case of deviations, a restricted mean survival time model will be applied instead of the Cox proportional hazards regression model.[44] Standard errors and CI for the IPTW estimator will be obtained via a robust sandwich-type estimator of variance.[45]

Because median OS likely will not be reached in Study C1071003, only for the combined study cohorts selected using critical eligibility criteria, IPT weighted survival probabilities will be described using KM estimator and compared between two treatment groups using the log-rank test [46,47] at 12 and 15 months of follow-up.

9.7.3. Sensitivity Analyses

To evaluate the robustness of results from the primary analyses, sensitivity analyses will be conducted.

Doubly robust comparison

A conditional average treatment effect (CATE) and its associated hazard ratio will be estimated using a semi-parametric approach described by Yadlowsky et al.[48,49] This estimator will provide a doubly robust comparison for PFS and OS between treatment arms. Standard errors and 95% confidence intervals are obtained for this estimator using the non-parametric bootstrap. The method is implemented in R in the precmed package, using the atefitsurv function.

Analyses employing a doubly robust estimator require fitting 2 models: a model for treatment or exposure status, and a second model for the outcome of interest. As with other causal inference methods, valid and unbiased estimates require assumptions of no unmeasured confounding (exchangeability), positivity (the experimental treatment assumption), no interference, and consistency.[50] Assuming these assumptions are upheld, if at least 1 of these 2 models is correctly specified, resulting in a doubly robust estimate that may remain consistent and unbiased.[51]

Diagnostics will be applied to assess whether the doubly robust model appears to be well-specified.[52]

Quantitative bias assessment

Quantitative bias assessment will be done using nullification analysis to assess the potential influence of unmeasured confounding on the HR estimates from the main analysis. A shortlist of suspected unmeasured confounders will be identified; these are variables that were observed in Study C1071003 but not available (or only with substantial missingness) in the RWD sources. The E-value will be computed and reflects the minimum strength of association the confounder would need to have with the exposure and outcome, conditional on the measured covariates, to fully explain away the observed treatment effect.[53]

E-values are relatively intuitive and offer a comprehensible, easily communicated summary of the findings. The lowest possible E-value is 1, and as the value increases, so does the implied degree of bias required to explain the results.[54]

Sensitivity analyses based on the RW sample identified using expanded eligibility criteria

To assess the potential influence of population selection on the observed effect estimates, PFS and OS will be compared in elranatamab (Cohort A) versus SOC-treated patients in combined study cohorts selected using the expanded eligibility criteria. IPTWs will be estimated as described in Section 9.7. Descriptive statistics will be reported as described in Section 9.7.1. PFS and OS will be compared between treatment arms using IPT-weighted Cox proportional hazards models. The proportional hazards assumption will be checked, and in case of deviations, a restricted mean survival time model will be applied instead of the Cox proportional hazards regression model.[44]

9.7.4. Additional Analyses

Analysis of patients matched on PS for the estimation of the ATT effect

This analysis will be conducted in the combined study cohorts selected with critical eligibility criteria. To estimate the ATT effect, each patient from the C1071003 trial will be matched to patients from an observational cohort using greedy nearest neighbor matching on 0.2 standard deviation of the logit of the PS.[55] Previous studies showed that this caliper allowed the elimination of about 99% of the bias due to the measured confounders. Patients with no match will be excluded from the analysis. PS will be estimated as described above in Section 9.7. Descriptive statistics will be reported as described in Section 9.7.1. PFS and OS will be compared between treatment arms using hazard ratios estimated from Cox proportional hazards models. The proportional hazards assumption will be checked, and in case of deviations, a restricted mean survival time model will be applied instead of the Cox proportional hazards regression model.[44]

Comparative analyses of PFS and OS including participants from Study C1071003 previously exposed to BCMA-directed therapies

The goal of this analysis is to explore if previous treatment with BCMA-directed therapies may impact the efficacy outcomes observed in Study C1071003. This analysis will be performed using all participants of Study 1071003 (ie, Cohort A and Cohort B) and RW patients selected with critical eligibility criteria. IPTWs will be estimated as described in Section 9.7. Descriptive statistics will be reported as described in Section 9.7.1. PFS and OS will be compared between treatment arms using IPT-weighted Cox proportional hazards models. The proportional hazards assumption will be checked, and in case of deviations, a restricted mean survival time model will be applied instead of the Cox proportional hazards regression model.[44]

Analysis of PROs

For each treatment group (elranatamab or SOC), the number and percentage of participants who completed the instruments at each visit, will be summarized. The timing of PRO completion by treatment group will be described. An instrument will be considered completed if at least one item was answered by the participant.

Descriptive statistics of PROs in elranatamab and SOC-treated patients

Summary statistics will be reported for each of the PROs listed in Section 9.3 by visit (the baseline visit and the follow-up visits) as well as changes in scores from the baseline to the follow-up visits. CCI [redacted]

If the sample size permits, the comparative analyses of PROs described below will be conducted. CCI [redacted] Only patients who completed the PRO instruments at baseline will be included in the analysis.

Comparison of change from baseline in elranatamab and SOC-treated patients

Among patients for whom a baseline and at least two follow-up measures for the same PRO outcome are available, a repeated measures mixed-effects model will be fit to the data to examine the effects of time (visit) among patients treated with elranatamab versus SOC. Mixed-effects model with repeated measures (MMRM) will be carried out for the domains of

QLQ-C30 and QLQ-MY20, EQ-5D index, and EQ-VAS to examine the effects of time (visit) by cohort and overall. In the model, outcomes are post-baseline scores (and change scores separately), the predictor is the treatment group (elranatamab versus SOC), and the controlling covariates are the corresponding baseline PRO score, CCI [redacted]

Subgroup analysis

Because the treatment patterns described in COTA and Flatiron may not generalize to all non-US countries, subgroup analyses will be performed to only include treatments frequently available for this patient population in non-US countries. The list of treatments for sub-group analyses is provided in Annex 3.

Subgroup analyses will be conducted to compare PFS and OS in participants of Study C1071003 Cohort A and patients from Flatiron Health and COTA selected with critical eligibility criteria.

For each treatment subgroup, IPTWs will be estimated as described in Section 9.7. If the sample size is sufficient, PFS and OS will be compared between participants of Study C1071003 and patients from Flatiron Health and COTA using IPT weighted Cox's proportional hazard model.

In case of insufficient sample size, only descriptive analysis will be provided (Section 9.7.1).

9.8. Quality Control

This is a retrospective study, so issues of quality control at study sites, eg, data queries, do not apply. Analyses are programmed according to the specifications in the protocol, and if applicable, the statistical analysis plan and documented in a programming plan. Final deliverables are reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks are documented in the programming plan.

9.9. Limitations of the Research Methods

Unlike clinical trial settings with specific definitions of study outcomes and scheduled assessments described in the protocol, the assessment of treatment response including progressions in RW clinical practice settings may not be made consistently across patients and physicians. Specifically, in real-world observational studies, especially those performed retrospectively, it is not possible to implement consistent monitoring and application of homogenous evaluation criteria (eg, IMWG) that are inherent to clinical trial design. As such, in RW patients, depending on how often clinical assessments are made, the date of disease progression is more likely to be diagnosed later than it would be diagnosed if patients had scheduled assessments similar to clinical study settings.[56,57] This may result in longer PFS and bias the comparative effectiveness estimates in favor of the RW arms.

The use of RWD sources has further limitations. First, missing data and the accuracy of recorded data on disease characteristics, lab results, and comorbidities in RWD may introduce an information bias and residual confounding. Second, patients without sufficient information in their EHRs were excluded from the datasets by the data providers to avoid information bias. However, this may introduce a selection bias. Third, the variability in populations and differences in the proportions of available values of covariates (non-missing values) can result in some discrepancies in the estimates using different RW sources.

To address and/or reduce the impact of potential bias and improve exchangeability between the trial and the external control arms[27,58,59] measures will be taken to align comparable populations, advanced adjustment methods will be employed, and a series of sensitivity analyses will be conducted to evaluate the impact of key assumptions and selection criteria. However, this analysis is still subject to unmeasured confounding. Quantitative bias analysis will attempt to estimate the potential bias from unmeasured confounders, but these estimates are likely to be conservative and may nullify a true treatment effect.

Participation in the C1071013 and C1071014 prospective observational studies was dependent on physicians' and patients' ability and willingness to participate. Hence, there is a possibility that included physicians are not fully representative of the complete targeted physician population, which could impact patient representativeness. Similarly, results may not be translatable to other geographies with vastly different healthcare systems and treatment approaches. In addition, the availability of information in records may vary by physician practice and may reflect differences in practice patterns, recording practices, and medical norms. These areas provide opportunities for future research.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

10.2. Patient Consent

As this study involves 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. Patient Withdrawal

Not applicable.

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

Approval from an institutional review board/independent ethics committee is not required for this study as only de-identified secondary data sources and anonymized medical record data from EHR will be used. Therefore, this study is considered exempt from the requirements for "human subjects research".

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 Guidelines of Good Pharmacoepidemiology Practices (GPP) issued by the Public Policy Committee, 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 is retrospective, it involves data that exist as structured 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 link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For all publications relating to the study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator 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.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
001	001	11 March 2019	CCI [redacted]
002	002	17 May 2022	
003	003	25 October 2021	
004	004	18 October 2021	

ANNEX 2. MAPPING OF ELIGIBILITY CRITERIA BETWEEN STUDY C1071003 AND RWD SOURCES

Supplementary Table 15.1. Inclusion and Exclusion Criteria in Study C1071003, Flatiron Health and COTA.

Patient inclusion criteria per C1071003 Study	Flatiron Spotlight RW alternative approach to be used in the external control arm	*Implementation*	COTA RW alternative approach to be used in the external control arm	*Implementation*
Age and Sex:				
Male or female participants age ≥18 years.	Male or female participants age ≥18 years.	Critical and expanded criteria	Male or female participants age ≥18 years.	Critical and expanded criteria
A female participant is eligible to participate if she is not pregnant or breastfeeding.	Not available.	N/A	Not available.	N/A
Type of Participant and Disease Characteristics:				
Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.	Not applicable.	N/A	Not applicable.	N/A
Prior diagnosis of MM as defined according to IMWG criteria.	Perfect or close match. Patients were extracted by Flatiron based on the presence of a diagnosis code for MM (ICD-9 203.0x or ICD-10 C90.0x) any time prior to the index date. Active MM diagnosis was confirmed by Flatiron via abstraction of unstructured data.	Critical and expanded criteria	Perfect or close match. MM diagnosis confirmed through pathology reports or through clinical diagnosis and supporting documentation such as lab tests.	Critical and expanded criteria

Patient inclusion criteria per C1071003 Study	**Flatiron Spotlight RW alternative approach to be used in the external control arm**	*Implementation*	**COTA RW alternative approach to be used in the external control arm**	*Implementation*
Measurable disease based on IMWG criteria as defined by at least 1 of the following: a. Serum M-protein ≥0.5 g/dL by SPEP b. Urinary M-protein excretion ≥200 mg/24 hours by UPEP c. Serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65)	Perfect or close match. Measurable disease, defined within 90 days prior to or on the index date.	Critical and expanded criteria	Perfect or close match. Measurable disease, defined within 90 days before or on the index date.	Critical and expanded criteria
Refractory to at least one IMiD.	Perfect or close match. Refractory to at least one IMiD defined as disease progression, based on IMWG criteria or HCP assessment, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical and expanded criteria	Perfect or close match. Refractory to at least one IMiD defined as disease progression, based on IMWG criteria or HCP assessment, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical and expanded criteria
Refractory to at least one PI.	Perfect or close match. Refractory to at least one PI defined as disease progression, based on IMWG criteria or HCP assessment, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical and expanded criteria	Perfect or close match. Refractory to at least one PI defined as disease progression, based on IMWG criteria or HCP assessment, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical and expanded criteria

Patient inclusion criteria per C1071003 Study	**Flatiron Spotlight RW alternative approach to be used in the external control arm**	*Implementation*	**COTA RW alternative approach to be used in the external control arm**	*Implementation*
Refractory to at least one anti-CD38 mAb.	Perfect or close match. Refractory to at least one anti-CD38 mAb defined as disease progression, based on IMWG criteria or HCP assessment, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical and expanded criteria	Perfect or close match. Refractory to at least one anti-CD38 mAb defined as disease progression, based on IMWG criteria or HCP assessment, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical and expanded criteria
Relapsed/refractory to last anti-MM regimen. Note: Refractory is defined as having progressive disease while on therapy or within 60 days of the last dose in any line, regardless of response.	Perfect or close match. By design as the index date is the first line after the TCR eligibility date, all patients will be refractory to the last anti-myeloma regimen.	Critical and expanded criteria	Perfect or close match. By design as the index date is the first line after the TCR eligibility date, all patients will be refractory to the last anti-myeloma regimen.	Critical and expanded criteria
Cohort A: Has not received prior BCMA-directed therapy.	Information is collected as baseline covariates.	Baseline covariate	Information is collected as baseline covariates.	Baseline covariate
Cohort B: Has received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy, either approved or investigational.	Information is collected as baseline covariates.	Baseline covariate	Information is collected as baseline covariates.	Baseline covariate

Patient inclusion criteria per C1071003 Study	**Flatiron Spotlight RW alternative approach to be used in the external control arm**	*Implementation*	**COTA RW alternative approach to be used in the external control arm**	*Implementation*
ECOG performance status ≤2.	Perfect or close match. ECOG performance status ≤2 within 90 days prior to or on the index date	Critical and expanded criteria	Perfect or close match. ECOG performance status ≤2 within 90 days prior to or on the index date KPS score to be converted to ECOG if patient's performance status test closest to the index date is KPS	Critical and expanded criteria
LVEF ≥40% as determined by a MUGA scan or ECHO.	Not available.	N/A	Not available.	N/A
Adequate hepatic function characterized by the following: a. Total bilirubin ≤2 x ULN (≤3 x ULN if documented Gilbert's syndrome); b. AST ≤2.5 x ULN; and c. ALT ≤2.5 x ULN	Perfect or close match. Adequate hepatic before study index date.	Baseline covariate, expanded criteria	Perfect or close match. Adequate hepatic function before study index date.	Baseline covariate, expanded criteria
Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min (according to the Cockcroft Gault formula, by 24-hours urine collection for creatinine clearance, or according to local institutional standard method).	Perfect or close match. Adequate renal function before study index date.	Baseline covariate, expanded criteria	Perfect or close match. Adequate renal function before study index date.	Baseline covariate, expanded criteria

Patient inclusion criteria per C1071003 Study	**Flatiron Spotlight RW alternative approach to be used in the external control arm**	*Implementation*	**COTA RW alternative approach to be used in the external control arm**	*Implementation*
Adequate BM function characterized by the following: a. ANC ≥1.0 × 109 /L (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing); b. Platelets ≥25 × 109 /L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and c. Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing).	Perfect or close match. Adequate BM function before study index date.	Baseline covariate, expanded criteria	Perfect or close match. Adequate BM function before study index date.	Baseline covariate, expanded criteria
Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.	Not available.	N/A	Not available.	N/A
Informed Consent:				
Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.	Not applicable	N/A	N/A	N/A

Patient exclusion criteria per C1071003 Study	**Flatiron Spotlight RW alternative approach to be used in the external control arm**	*Implementation*	**COTA RW alternative approach to be used in the external control arm**	*Implementation*
Medical Conditions:				
Smoldering MM.	Not Available. Not identifiable directly in Flatiron Spotlight data, however patients are only included in the data if they have evidence of active MM. Since smoldering MM (SMM) can be a precursor to active MM, patients may have had SMM before progressing to active MM.	Not implemented directly	Perfect or close match. Patient will be excluded if SMM is the type of MM listed for the patient closet to (but not after) the index date	Critical and expanded criteria
Active plasma cell leukemia.	Perfect or close match. Diagnosis of plasma cell leukemia is identified based on the presence of ≥1 diagnosis code within the 365 days prior to or on the index date or based on identification of plasma cell leukemia in enhanced data abstracted from unstructured sources.	Critical and expanded criteria	Perfect or close match. Active plasma cell leukemia within the 365 days before or on the index date can be identified in the secondary disease diagnosis dataset. Patients are censored by COTA and no longer followed in the data after a determination of active plasma cell leukemia.	Critical and expanded criteria
Amyloidosis.	Perfect or close match. Diagnosis of amyloidosis is identified based on the presence of ≥1 diagnosis code within the 365 days prior to or on the index date or based on identification of amyloidosis in enhanced data	Critical and expanded criteria	Perfect or close match. Amyloidosis within 365 days before or on the index date can be identified in the secondary disease diagnosis dataset. Patients are censored by COTA and	Critical and expanded criteria

	abstracted from unstructured sources.		no longer followed in the data after a diagnosis of amyloidosis.	
POEMS syndrome	Not available	N/A	Not available	N/A
Stem cell transplant within 12 weeks prior to enrollment or active GVHD.	Perfect or close match. Diagnosis of GVHD is identified based on the presence of ≥1 diagnosis code within the 12 weeks prior to or on the index date, but there are no specific codes for "active". The indicator of stem cell transplant and the date the patient received the stem cell transplant is provided.	Critical and expanded criteria	Partial match. Stem cell transplants within 12 weeks prior to index date.	Critical and expanded criteria
Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment: a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion); b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia); c. Thromboembolic or	Partial match. Identifiable based on diagnosis codes (except for QT syndrome); enhanced data abstracted from unstructured sources can identify the following CV conditions: angina, atrial arrhythmia, cerebrovascular accident, congestive heart failure, DVT, MI, another arrhythmia, PE, TIA, ventricular arrhythmia. However, for arrhythmias there is no information as to their clinical significance (eg, if the arrhythmia is uncontrolled).	Baseline covariate, expanded criteria	Partial match. Identifiable based on comorbid conditions that are included in the CCI. However, comorbid conditions included in the CCI are only captured once per patient. History of cardiac arrhythmia, QT syndrome, and other forms of acute coronary syndrome are not identifiable.	Baseline covariate, expanded criteria

cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism); d. Prolonged QT syndrome (or triplicate average QTcF >470 msec at screening).				
Ongoing Grade ≥2 peripheral sensory or motor neuropathy.	Partial match. Ongoing Grade ≥2 peripheral sensory or motor neuropathy cannot be identified in the data as there is no information about Grade. However, treatments used to manage neuropathic pain will be used as a proxy to identify presence of more severe neuropathy cases to describe patients	Baseline covariate, expanded criteria	Not available.	N/A
History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B).	Perfect or close match. Sensory and motor neuropathy may be identified based on the presence of ≥1 diagnosis code any time prior to or on the index date. Among patients with prior BCMA-directed therapy only.	Possible exclusion criteria	Perfect or close match. May be identified based on AEs that resulted in BCMA treatment discontinuation	Possible exclusion criteria

History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.	Partial match. GBS could be identified based on diagnosis codes. There is no information about the grade in the data that allows us to identify Grade ≥3 peripheral motor polyneuropathy. Treatments used to manage neuropathic pain will be used as a proxy to identify more severe neuropathy cases.	Baseline covariate, expanded criteria	Not available.	N/A
Active HBV, HCV, SARS-CoV2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 14 days prior to enrollment.	Partial match. Identifiable based on lab tests as well as diagnosis codes. There are no specific codes for "active" or "uncontrolled", but "active" infections will be closely approximated using clinically plausible covariate assessment periods. HBV or HIV any time before index. Other infections within 30 days before index.	Critical and expanded criteria	Partial match. HBV, HCV, and HIV at any time before index (comorbidities including these infections are only captured once per patient). No information for SARS-CoV2. Information on infections is not available through lab data.	Critical and expanded criteria
Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.	Perfect or close match. Will be identified based on the presence of ≥1 diagnosis code of any other malignancy, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ within the 3 years prior to or on the index date. "Adequately treated" is not identifiable therefore all basal or squamous cell skin cancer or carcinoma in situ will be considered adequately treated and not reason for exclusion.	Critical and expanded criteria	Perfect or close match. Any secondary malignancy developed up to 3 years before index treatment. Only secondary malignancies diagnosed between initial MM diagnosis and index date are identifiable. COTA will censor patients who develop secondary cancer after initial MM diagnosis.	Critical and expanded criteria

Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.	Not available.	N/A	N/A	N/A
Prior/Concomitant Therapy:				
Previous treatment with an anti-BCMA bispecific antibody.	Partial match. Only non-investigational agents are identifiable, therefore to ensure no exposure to anti-BCMA bispecific antibody treatment, all patients treated with investigational agents would need to be excluded	N/A	Partial match. Only non-investigational agents are identifiable, therefore to ensure no exposure to anti-BCMA bispecific antibody treatment, all patients treated with investigational agents would need to be excluded	N/A
Prior/Concurrent Clinical Study Experience:				
Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).	Perfect or close match. Previous administration with an investigational drug within 30 days before the index date or on index date.	Critical and expanded criteria	Perfect or close match. Previous administration with an investigational drug within 30 days before the index date or on index date.	Critical and expanded criteria

Other Exclusions:				
Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.	Not applicable.	N/A	N/A	N/A
Known or suspected hypersensitivity to the study intervention or any of its excipients.	Not applicable.	N/A	N/A	N/A
Live attenuated vaccine must not be administered within 4 weeks of the first dose of study intervention.	Not available.	N/A	N/A	N/A

Supplementary Table 15.2. Inclusion and Exclusion Criteria in Study C1071003, C1071013 and C1071014.

Patient inclusion criteria per C1071003 Study	C1071013 RW alternative approach to be used in the external control arm	*Implementation*	C1071014 RW alternative approach to be used in the external control arm	*Implementation*
Age and Sex:				
Male or female participants age ≥18 years.	Perfect or close match. Male or female participants age ≥18 years.	Critical criteria	Perfect or close match. Male or female participants age ≥18 years.	Critical criteria
A female participant is eligible to participate if she is not pregnant or breastfeeding.	Perfect or close match. A female participant is eligible to participate if she is not pregnant or breastfeeding.	Critical criteria	Perfect or close match. A female participant is eligible to participate if she is not pregnant or breastfeeding.	Critical criteria
Type of Participant and Disease Characteristics:				
Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.	Not applicable.	N/A	Not applicable.	N/A
Prior diagnosis of MM as defined according to IMWG criteria.	Perfect or close match. Prior diagnosis of MM as defined according to HCP judgment or confirmed using IMWG criteria	Critical criteria	Perfect or close match. If application of International Myeloma Working Group (IMWG) criteria for diagnosis of MM or assessment of response is not available as part of regular clinical practice, clinician assessment may be used.	Critical criteria

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
Measurable disease based on IMWG criteria as defined by at least 1 of the following: a. Serum M-protein ≥0.5 g/dL by SPEP b. Urinary M-protein excretion ≥200 mg/24 hours by UPEP c. Serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65)	Perfect or close match. IMWG criteria are not always used or documented in RW. When IMWG is not available, HCP judgment is used.	Critical criteria	Perfect or close match. Increase of 25% from the lowest confirmed response value in one or more of the IMWG criteria.	Critical criteria
Refractory to at least one IMiD.	Perfect or close match. IMWG criteria are not always used or documented in RW. When IMWG is not available, HCP judgment is used.	Critical criteria	Perfect or close match. Refractory to at least one IMiD defined as disease progression, based on IMWG criteria while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical criteria

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
Refractory to at least one PI.	Perfect or close match. IMWG criteria are not always used or documented in RW. When IMWG is not available, HCP judgment is used.	Critical criteria	Perfect or close match. Refractory to at least one PI defined as disease progression, based on IMWG criteria, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical criteria
Refractory to at least one anti-CD38 mAb antibody.	Perfect or close match. IMWG criteria are not always used or documented in RW. When IMWG is not available, HCP judgment is used.	Critical criteria	Perfect or close match. Refractory to at least one anti-CD38 mAb defined as disease progression, based on IMWG criteria, while a patient is on therapy or within 60 days of the last therapy dose in any line, regardless of response.	Critical criteria
Relapsed/refractory to last anti-MM regimen. Note: Refractory is defined as having progressive disease while on therapy or within 60 days of the last dose in any line, regardless of response.	Perfect or close match. IMWG criteria are not always used or documented in RW. When IMWG is not available, HCP judgment is used.	Critical criteria	Perfect or close match. By design as the index date is the first line after the TCR eligibility date, all patients will be refractory to the last anti-myeloma regimen.	Critical c

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
Cohort A: Has not received prior BCMA-directed therapy.	Perfect or close match. Information is collected at the time of enrollment when available.	Possible inclusion criteria	Perfect or close match. Information is collected at the time of enrollment when available.	Possible inclusion criteria
Cohort B: Has received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy, either approved or investigational.	Perfect or close match. Information is collected at the time of enrollment when available.	Possible inclusion criteria	Perfect or close match. Information is collected at the time of enrollment when available.	Possible inclusion criteria
ECOG performance status ≤2.	Perfect or close match. ECOG performance status ≤2.	Critical criteria	Perfect or close match. ECOG performance status ≤2.	Critical criteria
LVEF ≥40% as determined by a MUGA scan or ECHO.	Perfect or close match. LVEF ≥40% as determined by a MUGA scan or ECHO.	N/A	Perfect or close match. LVEF ≥40% as determined by a MUGA scan or ECHO.	N/A
Adequate hepatic function characterized by the following: a. Total bilirubin ≤2 x ULN (≤3 x ULN if documented Gilbert's syndrome); b. AST ≤2.5 x ULN; and c. ALT ≤2.5 x ULN	Perfect or close match. Adequate hepatic function characterized by the following: a. Total bilirubin ≤2 x ULN (≤3 x ULN if documented Gilbert's syndrome); b. AST ≤2.5 x ULN; and c. ALT ≤2.5 x ULN	N/A	Perfect or close match a. Total bilirubin ≤2 x ULN (≤3 x ULN if documented Gilbert's syndrome); b. AST ≤2.5 x ULN; and c. ALT ≤2.5 x ULN	N/A

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min (according to the Cockcroft Gault formula, by 24-hours urine collection for creatinine clearance, or according to local institutional standard method).	Perfect or close match. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min	N/A	Perfect or close match. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min	N/A
Adequate BM function characterized by the following: a. ANC ≥1.0 × 10^9 /L (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing); b. Platelets ≥25 × 10^9 /L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and c. Hemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing).	Perfect or close match. a. ANC ≥1.0 × 10^9 /L; b. Platelets ≥25 × 10^9 /L; and c. Hemoglobin ≥8 g/dL	N/A	Perfect or close match. a. ANC ≥1.0 × 10^9 /L; b. Platelets ≥25 × 10^9 /L; and c. Hemoglobin ≥8 g/dL	N/A

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.	Perfect or close match. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.	N/A	Perfect or close match. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.	N/A
Informed Consent:				
Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.	Perfect or close match. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.	Study eligibility criteria	Perfect or close match. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.	Study eligibility criteria
Medical Conditions:				
Smoldering MM.	Perfect or close match. Patients are excluded if SMM is the type of MM listed for the patient closet to (but not after) the index date	Critical criteria	Perfect or close match. Patients are excluded if SMM is the type of MM listed for the patient closet to (but not after) the index date	Critical criteria
Active plasma cell leukemia.	Perfect or close match. Patients with active plasma cell leukemia are excluded	Critical criteria	Perfect or close match. Patients with active plasma cell leukemia are excluded	Critical criteria
Amyloidosis.	Perfect or close match. Patients with amyloidosis are excluded.	Critical criteria	Perfect or close match. Patients with amyloidosis are excluded	Critical criteria

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
POEMS syndrome	Perfect or close match. Patients with POEMS syndrome are excluded.	Study eligibility criteria	Perfect or close match. Patients with POEMS syndrome are excluded.	Study eligibility criteria
Stem cell transplant within 12 weeks prior to enrollment or active GVHD.	Perfect or close match. Prior stem cell transplant within 12 weeks prior to study enrollment or active graft-versus-host-disease (GVHD)	Critical criteria	Perfect or close match. Prior stem cell transplant within 12 weeks prior to study enrollment or active graft-versus-host-disease (GVHD)	Critical criteria
Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment: a. Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion); b. Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia); c. Thromboembolic or	Perfect or close match. History of impaired cardiovascular function or clinically significant cardiovascular diseases (CVDs), defined as any of the following within 6 months prior to study enrollment: a.Acute myocardial infarction (AMI) or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion); b.Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia); c.Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism) d.Prolonged QT syndrome (or triplicate average QTc corrected using Fridericia's formula [QTcF] >470 msec at screening)	Study eligibility criteria	Perfect or close match. History of impaired cardiovascular function or clinically significant cardiovascular diseases (CVD), defined as any of the following within 6 months prior to study enrollment: a.Acute myocardial infarction (AMI) or acute coronary syndromes (e.g., unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion); b.Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia); c.Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a	Study eligibility criteria

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism); d. Prolonged QT syndrome (or triplicate average QTcF >470 msec at screening).			central venous access complication] or pulmonary embolism) d.Prolonged QT syndrome (or triplicate average QTc corrected using Fridericia's formula [QTcF] >470 msec at screening)	
Ongoing Grade ≥2 peripheral sensory or motor neuropathy.	Perfect or close match. . Presence of ongoing Grade >2 peripheral sensory or motor neuropathy	Study eligibility criteria	Perfect or close match. . Presence of ongoing Grade >2 peripheral sensory or motor neuropathy	Study eligibility criteria
History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B).	Perfect or close match. History of any grade peripheral sensory or motor neuropathy, collected among patients with prior BCMA-directed therapy Among patients with prior BCMA-directed therapy only.	N/A	Perfect or close match. History of any grade peripheral sensory or motor neuropathy, collected among patients with prior BCMA-directed therapy	N/A
History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.	Perfect or close match. History of GBS or GBS variants, or history of any Grade >3 peripheral motor polyneuropathy.	N/A	Perfect or close match. History of GBS or GBS variants, or history of any Grade >3 peripheral motor polyneuropathy.	N/A
Active HBV, HCV, SARS-CoV2, HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections	Perfect or close match. Presence of active hepatitis B virus (HBV), hepatitis C virus (HCV), SARS-CoV-2, human immunodeficiency virus (HIV), or uncontrolled	N/A	Perfect or close match. Presence of active hepatitis B virus (HBV), hepatitis C virus (HCV), SARS-CoV-2, human	N/A

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
must be resolved at least 14 days prior to enrollment.	infection. Active infections must be resolved at least 14 days prior to study enrollment.		immunodeficiency virus (HIV), or uncontrolled infection. Active infections must be resolved at least 14 days prior to study enrollment.	
Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.	Perfect or close match. Any other active malignancy within 3 years prior to study enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.	Critical criteria	Perfect or close match. Any other active malignancy within 3 years prior to study enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.	Critical criteria
Other surgical (including major surgery within 14 days prior to enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.	Perfect or close match. Presence of surgical (including major surgery within 14 days prior to study enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the individual inappropriate for the study.	Study eligibility criteria	Perfect or close match. Presence of surgical (including major surgery within 14 days prior to study enrollment), medical or psychiatric conditions including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the individual inappropriate for the study.	Study eligibility criteria

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
Prior/Concomitant Therapy:				
Previous treatment with an anti-BCMA bispecific antibody.	Perfect or close match. Prior or concomitant treatment with an anti-BCMA bispecific antibody, including PF-06863135.	Study eligibility criteria	Perfect or close match. Prior or concomitant treatment with an anti-BCMA bispecific antibody, including PF-06863135.	Study eligibility criteria
Prior/Concurrent Clinical Study Experience:				
Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).	Perfect or close match. Prior or concomitant treatment with an anti-BCMA bispecific antibody, including PF-06863135.	Study eligibility criteria	Perfect or close match. Prior or concomitant treatment with an anti-BCMA bispecific antibody, including PF-06863135.	Study eligibility criteria
Other Exclusions:				
Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff	N/A	N/A	N/A	N/A

Patient inclusion criteria per C1071003 Study	**C1071013 RW alternative approach to be used in the external control arm**	*Implementation*	**C1071014 RW alternative approach to be used in the external control arm**	*Implementation*
otherwise supervised by the investigator, and their respective family members.				
Known or suspected hypersensitivity to the study intervention or any of its excipients.	N/A	N/A	N/A	N/A
Live attenuated vaccine must not be administered within 4 weeks of the first dose of study intervention.	N/A	N/A	N/A	N/A

ANNEX 3. LIST OF SUBGROUPS AND COMPRISING TREATMENTS

Subgroup	Treatments to be included in Subgroup Analysis
Subgroup 1	All regimens except those which include the following therapies: -Selinexor -Belantamab -CAR-T
Subgroup 2	Only including the following regimens: -Carfilzomib+Dexamethasone -Panabinostat+Bortezomib+Dexamethasone -Carfilzomib+Lenalidomide+Dexamethasone -Carfilzomib+Cyclophosphamide+Dexamethasone -Pomalidomide+Dexamethasone -Pomalidomide+Cyclophosphamide+Dexamethasone
Subgroup 3	All regimens except those which include the following therapies: -Selinexor -Belantamab -Panobinostat -Bendamustine
Subgroup 4	All regimens except those which include the following therapies: -Panobinostat -Venetoclax -Selinexor -Hyaluronidase -Abiraterone -Trastuzumab -Dabrafenib -Autologous stem cell transplant
Subgroup 5	Only including the following regimens: -Dexamethasone/Prednisolone+Bortezomib -Cyclophosphamide+Dexamethasone/Prednisolone+Bortezomib -Bendamustine -Pomalidomide

Subgroup	Treatments to be included in Subgroup Analysis
	-Dexamethasone/Prednisolone+Pomalidomide -Dexamethasone+Pomalidomide+Daratumumab -Dexamethasone/Prednisolone+Pomalidomide+Isatuximab -Cyclophosphamide+Dexamethasone/Prednisolone+Pomalidomide -Dexamethasone/Prednisolone+Carfilzomib -Dexamethasone/Prednisolone+Carfilzomib+Daratumumab -Cyclophosphamide+Dexamethasone+Carfilzomib -Dexamethasone+Pomalidomide+Carfilzomib -Dexamethasone/Prednisolone+Panobinostat -Dexamethasone/Prednisolone+Bortezomib+Panobinostat -Daratumumab -Dexamethasone/Prednisolone+Daratumumab -Dexamethasone/Prednisolone+Lenalidomide+Daratumumab -Dexamethasone/Prednisolone+Bortezomib+Daratumumab -Daratumumab+Carfilzomib+Lenalidomide+Dexamethasone/ Prednisolone -Daratumumab+Bortezomib+Cyclophosphamide+Dexamethasone/ Prednisolone -Dexamethasone/Prednisolone+Elotuzumab -Dexamethasone/Prednisolone+Ixazomib -Isatuximab -Dexamethasone/Prednisolone+Carfilzomib+Isatuximab -Isatuximab+Dexamethasone+Pomalidomide+Carfilzomib -Any other regimen containing Isatuximab -Belantamab -Selinexor

Subgroup	Treatments to be included in Subgroup Analysis
	-Selinexor+Dexamethasone/Prednisolone -Venetoclax+Bortezomib+Dexamethasone/Prednisolone -Cyclophosphamide -Pegylated liposomal doxorubicin -Melphalan+Dexamethasone/Prednisolone -Adriamycine+Cyclophosphamide+Dexamethasone/Prednisolone -Cyclophosphamide+Adriaymicine/Pegylated liposomal doxorubicin+Dexamethasone -Vincristine+Adriamycine+Cyclophosphamide+Dexamethasone

Document Approval Record

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