Elranatamab EU Risk Management Plan

RMP Version number: 2.0

Data lock point for this RMP:

- Clinical Trial: 26 March 2024
- Post Marketing: 15 July 2024

Date of final sign off: 21 January 2025

Rationale for submitting an updated RMP: to respond to PRAC comments.
Summary of significant changes in this RMP:

- Part II, Module SI, to add “high income” related text to the RMP
- Part II, Module SVII.3, to include the incidence of participants with all-causality AE PN from LTS data
- Part III, to remove sentence *There are no studies specifically focused on safety risks, but safety data will continue to be collected in ongoing studies*.
- Annex II, to add CSR links in Table 2
- Annex III, to remove protocol for study C1071003

Other RMP versions under evaluation: None

Details of the currently approved RMP:

- Version number: 1.1
- Approved with procedure: EMEA/H/C/005908/IB/0002
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QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ADC	Antibody-Drug Conjugate
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ASC	Antibody Secreting Cell
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BICR	Blinded Independent Central Review
BCMA	B-Cell Maturation Antigen
CAR-T	Chimeric Antigen Receptor T-cell
C1D1,	Cycle 1 Day 1
C1D4	Cycle 1 Day 4
C1D8	Cycle 1 Day 8
CD	Cluster of Differentiation
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMV	Cytomegalovirus
CoV	Coronavirus
COVID	Coronavirus Disease
CRAB	Hypercalcemia, Renal involvement, Anemia and Bone lesions
CrCl	Creatinine Clearance
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
DNA	Deoxyribonucleic Acid
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECHO	Echocardiogram
EEA	European Economic Area
EEIG	European Economic Interest Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FIH	First-in-Human
GBD	Global Burden of Disease
GBS	Guillaine-Barrè Syndrome
GLOBOCAN	Global Cancer Observatory of the International Agency for Research on Cancer
H	Heavy
HBV	Hepatitis B Virus
HCP	Healthcare Professional
HCV	Hepatitis C Virus

HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplant
IBD	Internation Birth Date
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune effector Cell-associated Encephalopathy
ICP	Intracranial Pressure
IFN	Interferon
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
INN	International Nonproprietary Name
IQR	Interquartile Range
IV	Intravenous
IVIG	Intravenous Immune Globulin
L	Light
LVEF	Left Ventricular Ejection Fraction
LTS	Long Term Safety
MA	Marketing Authorisation
MAA	Marketing Authorization Application
mAb	Monoclonal Antibody
MD	Medical Doctor
mDOR	median Duration of Response
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
MR	Minor Response
MRI	Magnetic Resonance Imaging
MUGA	Multigated Acquisition
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	Natural Killer
NR	Not Reported
ORR	Objective Response Rate
OS	Overall Survival
PAM	Post-Authorisation Measure
PFS	Progression Free Survival
PI	Proteasome Inhibitor
PK	Pharmacokinetic
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy

PN	Peripheral Neuropathy
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin abnormalities
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Person-Years
Q1	First Quartile
Q3	Third Quartile
QPPV	Qualified Person for Pharmacovigilance
QT	time from the beginning of the QRS complex to the end of the T wave
QTcF	QT Interval Corrected by the Fridericia Correction Formula
RMP	Risk Management Plan
RP3D	Recommended Phase 3 Dose
RRMM	Relapsed/Refractory Multiple Myeloma
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results
SmPC	Summary of Product Characteristics
SOB	Specific Obligation
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
US	United States

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PART I. PRODUCT(S) OVERVIEW

Active substance (INN or common name)	Elranatamab
Pharmacotherapeutic group(s) (ATC Code)	ATC code not yet assigned
Marketing Authorisation Applicant	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Medicinal products to which this RMP refers	Elranatamab (PF-06863135)
Invented name(s) in the European Economic Area (EEA)	Elrexfio
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class – biologic
	Summary of mode of action - Elranatamab is a heterodimeric humanized full-length IgG2 kappa bispecific antibody derived from 2 monoclonal antibodies (mAbs), an anti-BCMA mAb and an anti-CD3 mAb. Each of these mAbs contributes one distinct heavy (H) chain and one distinct light (L) chain to the bispecific antibody elranatamab. The resulting 4-chain bispecific antibody is covalently linked via 5 inter-chain disulfide bonds. The mechanism of action of elranatamab involves selective therapeutic targeting and activation of T cells re-directed against BCMA-expressing malignant plasma cells.
	Important information about its composition – Elranatamab drug substance is produced using two recombinant Chinese Hamster Ovary cell lines that contain the DNA encoding for an anti-BCMA mAb and an anti-CD3 mAb.
Hyperlink to the Product Information:	Module 1.3.1 (Proposed Product Information)
Indication(s) in the EEA	Current: Elrexfio is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
Dosage in the EEA	Current: The recommended dose of elranatamab is 76 mg administered by subcutaneous injection, once weekly. During the first week of treatment, elranatamab should be administered as a two step-up doses of 12 mg on Day 1 and 32 mg on Day 4, followed by the first full dose of elranatamab (76 mg) administered on Day 8, followed by weekly dosing from week 2 to week 24. For patients who have received at least 24 weeks of treatment and have achieved a response, the dosing interval should transition to an every- two-week schedule.

	Proposed: For patients who have received at least 24 weeks of treatment at the every- two-week schedule, the dose interval should transition to an every four-week schedule.
Pharmaceutical form(s) and strengths	Current: Elranatamab 44 mg of in 1.1 mL solution for injection (40 mg/mL) Elranatamab 76 mg in 1.9 mL solution for injection (40 mg/mL)
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population(s)

Indication: Elrexfio is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

Multiple myeloma (MM) is a hematologic malignancy characterized by excess clonal plasma cells with the potential for uncontrolled growth.[1] Despite novel therapeutics introduced over the past few decades, virtually all patients with MM ultimately relapse, and after each relapse the disease becomes more aggressive with shortened subsequent progression free survival (PFS).[2,3] Relapsed patients typically receive multiple lines of therapy after first-line treatment.[4]

The term relapsed/refractory multiple myeloma (RRMM) is defined by the International Myeloma Workshop Consensus Panel I as "disease that is nonresponsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously before then progressing in their disease course."[5] These definitions were derived from the American Society for Hematology – Food and Drug Administration panel which evaluated endpoints in trials for myeloma.[6]

Summary of Literature Search

A literature review was conducted to evaluate the epidemiology of RRMM among adults in Europe and the United States (US). PubMed was searched to identify all published references that contained potentially relevant information on the epidemiology of RRMM from January 2012 through July 2022. Keywords related to incidence, prevalence, morbidity, mortality, natural history, risk factors and comorbidities were combined with relapsed/refractory multiple myeloma and multiple myeloma. In addition to the literature review on RRMM, a parallel scan of large studies, reviews, systematic reviews, and meta–analyses was carried out to gather a high–level understanding of the epidemiology of MM. Finally, important citations mentioned in these papers were also obtained as relevant. This work represents a targeted, not systematic, review of the literature.

In parallel with the literature review, prevalence and incidence data for MM were queried from the Global Cancer Observatory of the International Agency for Research on Cancer (GLOBOCAN) database and the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) Program database. RRMM data are not available in these resources.

Incidence

Multiple Myeloma

A summary of the annual age-standardized incidence rates of MM worldwide, in European regions and in the US/North America are presented in Table 1, overall and by sex.

Although MM is considered a rare disease, it is typically found to be the second most common *hematological* cancer in high income countries.[7]

GLOBOCAN collects and presents global cancer statistics using the best available data from contributing countries. GLOBOCAN 2020 estimated that there were 176,404 new cases of MM diagnosed in 2020, which translates to a global age-standardized incidence rate of 1.8 per 100,000 person-years (PY).[8] In Europe, the age-standardized incidence rates (per 100,000 PY) were as follows: 3.8 in Northern Europe, 3.6 in Western Europe, 3.0 in Southern Europe and 2.0 in Central-Eastern Europe. North America had an age-standardized incidence rate of 4.7 per 100,000 PY. The regions with age-standardized incidence rates below the 1.8 per 100,000 PY global average were predominantly in Africa and Asia.

Cowan et al. (2018) conducted an analysis of the incidence of MM using data from the Global Burden of Disease Study (GBD) 2016 and estimated that in 2016 there were 138,509 (95% CI 121,000–155,480) incident cases of MM, with an age-standardized incidence rate of 2.1 per 100,000 persons (95% CI, 1.8-2.3).[9] Regional age-standardized rates were found to be highest in Australasia, North America (high income), and Western Europe, with the lowest rates found in Asia, Oceania and sub-Saharan Africa. Globally, from 1990 to 2016, incident MM cases increased by 126%; the largest contributor to this increase was an aging population, followed by population growth and change in age-specific incidence rates.

The US National Institutes of Health (NIH) uses data from the SEER dataset to estimate annual incidence of various cancers and estimated that in 2022 there would be 34,470 newly diagnosed cases of MM in the US, representing 1.8% of all new cancers.[10] Further, the age-standardized (to the US standard population) incidence rate of MM in the US was found to be 7.1 per 100,00 PY in 2019, which was stable between 2010-2019. The lifetime risk of developing MM in the US is estimated to be 0.8% based on 2017-2019 SEER data.

Table 1. Age-standardized incidence of MM

Region	N cases per year (95% CI)	Incidence Rate per 100,000 PY (95% CI)		Year(s)	Reference
		Overall	By Sex		
Global	176,404	1.8	Males 2.2 Females 1.5	2020	GLOBOCAN 2020[8]
	138,509 (121,000-155,480)	2.1 (1.8-2.3)	Males 2.4 (1.9–2.9) Females 1.8 (1.4–2.2)	2016	Cowan 2018[9]
Northern Europe	9,469	3.8	Males 4.7 Females 3.1	2020	GLOBOCAN 2020[8]
Western Europe	18,114	3.6	Males 4.6 Females 2.7	2020	GLOBOCAN 2020[8]
	35,433 (27,371-43,318)	4.6 (3.7-5.5)	Males 5.7 (3.9–7.3) Females 3.7 (2.7–5.0)	2016	Cowan 2018[9]
Southern Europe	12,020	3.0	Males 3.7 Females 2.4	2020	GLOBOCAN 2020[8]
Central-Eastern Europe	11,315	2.0	Males 2.4 Females 1.8	2020	GLOBOCAN 2020[8]
Central Europe	4,036	2.2 (1.7–2.6)	Males 2.5 (1.7–3.0)	2016	Cowan 2018[9]

Table 1. Age-standardized incidence of MM

Region	N cases per year (95% CI)	Incidence Rate per 100,000 PY (95% CI)		Year(s)	Reference
		Overall	By Sex		
	(3026-4688)		Females 2.0 (1.4–2.4)		
Eastern Europe	6,228 (4778-7971)	2.0 (1.6–2.6)	Males 2.1 (1.5–2.9) Females 2.0 (1.3–2.8)	2016	Cowan 2018[9]
North America	35,318	4.7	Males 5.7 Females 3.9	2020	GLOBOCAN 2020[8]
US	34,470[+]	7.1	Males 8.8 Females 5.9	2015-2019	National Cancer Institute 2022[10]

CI: confidence interval; [+]estimated for 2022; GLOBOCAN reference - International Agency for Research on Cancer, 2020[8]

Relapsed Refractory Multiple Myeloma

There were no studies identified in the literature which described the incidence of RRMM, nor were these data captured in GLOBOCAN or SEER.

Prevalence

Multiple Myeloma

Although the majority of epidemiologic data for MM are presented as incidence, available prevalence data on MM identified in the literature and SEER are presented below.

A recent study reviewing the European Medicines Agency database to identify positive orphan designations for MM (and other malignancies) between 2000 to 2015 found a steady rise in the submitted prevalence estimate for MM, from 12 to 36 per 100,000 over the study period.[11] The authors noted that survival for MM had improved during this time, which in turn would be reflected in increasing prevalence. A study of the burden of MM in Portuguese hospital data estimated that the prevalence of MM in 2018 was 18.9 per 100,000 persons.[12] Finally, SEER estimated 159,787 prevalent cases of MM in the US in 2019.[10]

Relapsed Refractory Multiple Myeloma

There were no studies identified which described the prevalence of RRMM in Europe or the US, nor were these data captured in GLOBOCAN or SEER.

Demographics

Age

Multiple Myeloma

MM is a condition that generally affects an older patient population. Indeed, in 2015-2019 US SEER data, approximately 64% of MM cases were diagnosed among patients aged 65 years or older and the median age of diagnosis was 69 years.[10] Median age at MM diagnosis was similar across several European studies: 71 years in Norway (1982-2017),[13] 70 years in Finland (2005-2016),[14] 70 years in Denmark (2005-2012),[15] and 71 years in Sweden (2008-2015).[16]

RRMM

Table 2 presents the mean/median age at diagnosis of MM and RRMM from 4 studies. In individual studies, the reported median age of diagnosis of RRMM ranged from 70 to 72 years;[17,18] mean age at diagnosis ranged from 66.3 to 69.6 years.[19,20]

Table 2. Mean and median age of RRMM patients in European and US studies

Citation	Study Type, Source of data, n (RRMM)	Study Country and Period	Age at Initial MM Diagnosis (Years)	Age at RRMM Onset/Start of 2L therapy (Years)
Lin et al. 2019[20]	Retrospective, Medical records from 40 hematology/ oncology providers in French hospitals; n=200	France 2009-11	Mean±SD 64.5±9.2	Mean±SD 66.3±8.9
Steinmetz et al. 2022[17]	Retrospective nationwide, medical records from 47 hematologists/ oncologists from 47 centers; n=214 2L patients	Germany 2017-20	Median 67 (IQR 59–74)	Median 72 (IQR 64–78)
Touzeau et al. 2021[19]	Retrospective nationwide, French National Healthcare database; n=12,812 2L patients	France 2009-18	NR	Mean 69.6±10.6
Hari et al., 2018[18]	Retrospective nationwide, Humedica electronic medical records; n=628	US 2008-15	NR	Median 70

Gender

Multiple Myeloma

MM is typically found to be slightly more common in males compared to females,[2] as is demonstrated consistently in studies in Table 1. The 2020 GLOBOCAN estimate for

worldwide incidence of MM was 1.8 per 100,000 persons; however, incidence was 2.2 per 100,000 men and 1.5 per 100,000 women.[8] This pattern was consistent across all European regions and North America. In 2015-2019 US SEER data, the age-standardized incidence of MM was 8.8 per 100,000 males compared to 5.9 per 100,000 females.[10]

RRMM

No studies were identified that reported the risk of developing RRMM by gender. However, nearly all patients with MM will eventually relapse,[2] and thus the gender distribution of patients with RRMM is expected to be similar to the overall MM patient population. Indeed, in each of the study populations included in this review, a higher proportion of males, ranging from 51% to 67%, compared to females in the study was noted.[21,22,17,20,19,23,24,18]

Race

Multiple Myeloma

Although data on race/ethnicity are typically limited in European studies, data from the US SEER have identified that the highest incidence of MM is among non-Hispanic Black patients.[10] Between 2015-2019, the US age-standardized incidence of MM among non-Hispanic Blacks was 12.9 per 100,000 in females and 17.0 per 100,000 in males; in contrast, the age-standardized incidence among non-Hispanic Whites was 5.0 per 100,000 females and 8.1 per 100,000 males. Incidence rates among Hispanics, non-Hispanic Asian/Pacific Islanders and non-Hispanic American/Indian Alaskan Natives were similar to those in non-Hispanic Whites. These findings are consistent with an older analysis of US SEER data (1973-2005), which found that the incidence of MM in Black patients was about twice that in White patients.[25] The median age at diagnosis of MM was 66 years in Blacks and 70 years in Whites in that study.

The reasons for this disparity are not well understood and may be multifactorial; possible contributing factors include socioeconomic factors, genetic differences and family history, and other risk factors such as obesity.[26]

RRMM

No studies were identified that reported the risk of RRMM by race/ethnicity.

Risk Factors

Multiple Myeloma

As described above, the risk of MM increases with increasing age, is slightly higher in men than in women, and is higher among non-Hispanic Blacks.[27] Persons with a family history are also at increased risk of MM.[27,26] Additional suspected risk factors include obesity, occupation, chemical exposures, chronic inflammation and inherited genetic variants.[1,7,26]

RRMM

It is believed that nearly all patients with MM will eventually relapse.[2] A better understanding of risk for relapse and lack of therapeutic response in MM is needed. Despite the availability of several risk classification systems, those classified initially as low risk under current systems may indeed become early relapsers.[28] In a study of 511 newly diagnosed patients with MM treated with novel therapies at a single US center between 2006-2014, 82 (16%) experienced early relapse within 12 months of treatment.[29] In multivariable analyses, only low serum albumin and high-risk cytogenetics were predictive of early relapse. Importantly, early relapse was associated with poorer outcomes.

In a study of 141 patients in the Kaiser Permanente Southern California database who received a hematopoietic stem cell transplant (HSCT) for MM between 2008-2012, predictors of early relapse (defined as within 18 months of transplant) included: higher comorbidity burden, failure to use maintenance therapy after HSCT, less than a complete response following HSCT and male sex.[30] In this study, median overall survival (OS) for early relapsers was 31.4 months, compared to 115 months in those who did not relapse before 18 months.

The Main Existing Treatment Options

To date, 6 other drugs were approved globally and are available in the EU for the treatment of adult patients with multiple myeloma who have received at least a PI, an IMiD, and an anti-CD38 mAb.

Selinexor plus dexamethasone was approved based on results of the STORM trial. Selinexor plus dexamethasone demonstrated an ORR of 25.3% and a mDOR of 3.8 months.[31,]

Melphalan flufenamide plus dexamethasone was approved based on results of the HORIZON trial. Melphalan flufenamide plus dexamethasone showed an ORR of 28.8% with a median DOR of 7.6 months.[32]

Idecabtagene vicleucel and ciltacabtagene autoleucel, two autologous CAR-T cell immunotherapies, were granted approval based on the KARMMA-1 and CARTITUDE-1 Studies respectively. Idecabtagene vicleucel showed an ORR of 73.4% (treated population) with a median DOR of 10.6 months.[33] Ciltacabtagene autoleucel showed an ORR of 97.9% (treated population) with a median DOR of 21.8 months.[34]

Autologous CAR-T treatments are limited to patients whose cells are successfully manipulated ex vivo to allow for re-infusion. Additional limitations of patient access to CAR-T therapies include:

1. the limited number of authorized centers currently available for commercial CAR-T-cell treatments,
2. the difficulties in reaching the target dose and/or risk of manufacturing failure,
3. delay in manufacturing times for these treatments,

4. the need for lymphodepletion therapy can increase the risk of developing cytopenias and infections, and
5. performance status, comorbidities, and disease burden as potential challenges for consideration concerning patient eligibility.

Teclistamab, a BCMA-directed bispecific antibody, was granted conditional approval based on the results of the MAJESTEC-1 study. Teclistamab has an ORR of 63.0% and median DOR of 18.4 months after a median follow-up of 14.1 months.[35,36]

Talquetamab,[37] a GPRC5D-directed bispecific antibody, was granted conditional approval based on the MONUMENTAL-1 study. Talquetamab showed an ORR of 74.1% and a median DOR of 9.5 months with the 0.4 mg/kg weekly dosing and an ORR of 71.7% and a median DOR of not reached with the 0.8 mg/kg biweekly dosing.

Natural History

Multiple Myeloma

It is believed that myeloma typically begins from an asymptomatic overgrowth of monoclonal plasma cells which, as a result of genetic and microenvironmental changes, progresses to what is known as the malignant condition of MM. Typically, the first stage is monoclonal gammopathy of undetermined significance (MGUS), which leads to smoldering myeloma and eventually MM.[38,39] Although MGUS is relatively common in the population, the vast majority of cases will remain in the pre-malignant stages and few will progress to MM.[39]

Many patients will present with end-organ damage due to MM, typically referred to as CRAB symptoms, which are characterized by hypercalcemia, renal involvement, anemia and bone lesions.[27] Upon diagnosis, patients are staged based on laboratory values and chromosomal profile.[38] There are several risk models in MM which have been developed to guide initial treatment decisions.[3,2]

Although MM is typically considered to be a singular disease, it is comprised of plasma cell malignancies with different cytogenetics[2] and the clinical course of disease can be quite heterogeneous.[3] Cytogenetic profile may change over the course of disease and the interpretation of the cytogenetic findings is dependent on when the finding is made in the course of the disease.[2] Treatment decision is based on patient age, risk profile, and comorbidity profile; choice of drug treatment is further driven by whether or not the patient is transplant eligible.[38,27]

Survival in MM has improved dramatically over recent decades, following the introduction of newer medications.[2,40,] However, a precise quantification of current survival in the general population with MM is difficult due to rapidly changing treatment strategies and the continued introduction of newer therapeutics.[2] Although randomized controlled trials provide good data on survival, these studies are not necessarily generalizable to the overall MM population who receive varied treatment combinations and who may be higher risk than

patients typically included in trials, all of which necessitates the evaluation of survival data with caution.[2,40]

Further, although there have been overall gains in survival in MM, recent data suggest that these gains are limited to those who are not classified as having high risk disease.[41,40]Additionally, studies suggest that the oldest patients (typically aged 75 or older) did not gain much in survival improvement.[42,43,40] Limited gains in survival among elderly patients may reflect later stage at diagnosis in these patients, inability of these patients to use certain medications, and increased toxicity of certain regimens.[40]

A US study by Binder et. al (2022) found an improvement in OS across the study period (2004-2018) that was more pronounced among patients treated in a tertiary referral center, potentially attributable to better access to care and newer therapeutics.[40] This study also noted a reduction in early mortality, which may be potentially explained by earlier use of effective treatment in the course of the disease.

The age-standardized death rate for MM in the US was estimated to be 3 per 100,000 persons in 2019, using US SEER data, which is lower than the estimated age-standardized death rate in 2009 of 3.3 per 100,000.[10] The National Cancer Institute noted that the age-standardized death rate fell about 1% each year over that decade. Between 2015-2019 the median age at death was 75 years. The 5-year relative survival was 57.9% overall and was higher in those with localized (stage 1) disease (78.5% compared to 57.0% in those with metastatic disease); only 4% of new MM diagnoses are localized.[10]

RRMM

Despite the great advancement of treatments for MM over the past 2 decades, virtually all patients will relapse at some point at variable intervals and there remain significant challenges in the treatment of RRMM.[3] Subsequent treatment decisions are determined by a variety of factors, some of which include the use of maintenance therapy and resistance to potential maintenance therapy (e.g., lenalidomide or bortezomib), use of prior anti-CD38 antibody treatment, comorbidities and treatment goals.[2,3] The increasing number of new therapies available means that patients who are defined as having RRMM may reach that state from a variety of initial treatments, making it difficult to define a single best algorithm for subsequent therapy.[44]

Current recommendations suggest that patients with CRAB symptoms upon relapse should immediately progress to a new line of therapy; however, in patients without clinical symptoms who do experience biochemical relapse, the ideal timing of initiation of treatment is less clear except in cases of patients who are considered to have high-risk disease who should more immediately begin treatment.[45] As discussed above, patients who experience early relapse following initial therapy tend to have poorer prognosis than those who do not.[29,46]

Current gaps in the treatment of RRMM include risk stratification upon relapse as well as numerous questions around appropriate drug therapy, including timing for initiation

following relapse, ideal combinations, and approach to treating patients with specific mutations.[2,45]

Important Comorbidities

Comorbidities are common in MM, in part because the typical MM patient is elderly and therefore may suffer from age-related comorbidities.[47] Further, observed comorbidities may be due to MM itself or may be related to treatment.[45] A large Swedish study of patients newly diagnosed with MM between 1990-2013 found that 54% had at least 1 comorbidity at diagnosis; further, survival following diagnosis decreased with increasing comorbidity burden.[47] In a small Spanish study of 276 RRMM patients, 63.4% had a comorbidity at the time of last relapse.[22] Common comorbidities in MM, which should be considered when selecting a treatment, include cardiovascular disease, venous thromboembolism, peripheral neuropathy, renal impairment, infection, bone disease, and diabetes mellitus.[45,7]

Module SII. Nonclinical Part of the Safety Specification

The nonclinical safety data for elranatamab do not reveal important hazards otherwise unidentified in the Phase 1 and 2 human clinical trials. Therefore, additional nonclinical data are not needed at this time to support the use of elranatamab in advanced cancer patients.

Elranatamab is fully cross reactive with similar binding affinity to monkey and human for both BCMA and CD3, but not pharmacologically active in rodents and rabbit. The safety of elranatamab was comprehensively assessed in repeat -dose toxicity studies of up to 3 months in duration in cynomolgus monkeys. Safety pharmacology and local toleration were assessed as part of the repeat -dose toxicity studies. In lieu of developmental and reproductive toxicity studies, an integrated weight -of -evidence assessment was completed. Genotoxicity and carcinogenicity were not conducted since they are generally not required for biologics.

The key effects of elranatamab in cynomolgus monkeys were considered related to the mechanism of action and included increased cytokines, decreased BCMA-expressing cells (B cells and plasma cells) and associated decrease of immunoglobulins, and fluctuations in the numbers of peripheral T cells and NK cells. Dosing higher and/or longer in the 3-month toxicity study resulted in elective euthanasia between Days 58 to 91. The dose dependent, moribund condition was attributed to immunosuppressive effects leading to secondary infections at clinically relevant and higher exposures. An integrated weight of evidence developmental toxicity assessment identified a risk of fetal harm.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies	Relevance to Human Usage
Transient Increases in Cytokines Elranatamab induced inflammatory cytokines in vitro and in vivo. In an in vitro cytokine release assay using normal human whole blood, elranatamab induced inflammatory cytokines (eg, TNF, IL 2, and IFNγ). Cytokines were also transiently increased in vivo in cynomolgus monkeys; the largest magnitude changes were typically after the first or second dose and	Elranatamab has the potential to cause cytokine release syndrome (CRS) in humans. See Section SVII.3.1 Important Identified Risk – CRS.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies	Relevance to Human Usage
diminished with repeat dosing. These effects were observed at clinically-relevant concentrations.	
Cytopenias Decreases in B cells and antibody secreting cells (ASC) (plasma cells and plasmablasts that express BCMA) were associated with decreased cellularity of germinal centers in lymphoid tissues in monkeys. Elranatamab also reduced ASC counts in the spleen and bone marrow. At high doses in the toxicity study reductions in red blood cells counts were also observed.	Elranatamab has the potential to cause cytopenias in humans. See Section SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP.
Infections At higher doses and/or with longer duration of dosing, monkeys displayed evidence of bacterial and/or viral infections secondary to elranatamab-related immune suppression. Decreases in BCMA+ cells and correlating decreases in serum globulins (IgA, IgM and IgG isoforms) and protein were observed. Predominant microscopic findings included inflammation/infiltration of the gastrointestinal system and kidneys, but also involved other organs. Evidence of bacterial colonies, intranuclear viral inclusion bodies coupled with neutrophilic and or mononuclear inflammation or infiltration and toxic granulation were observed in moribund animals with secondary infections.	Elranatamab has the potential to cause infections in humans. See Section SVII.3.1 Important Identified Risk – Serious infections.
Embryo-Fetal Toxicity No embryo-fetal toxicity studies were conducted with elranatamab. However, an integrated weight of evidence assessment identified a risk of fetal harm with elranatamab due to B cell lymphocytopenia and the potential impact of cytokine release syndrome (CRS) on pregnancy.	Elranatamab has the potential to cause embryo-fetal toxicity in humans. See Section SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP.

Module SIII. Clinical Trial Exposure

The overall safety profile of elranatamab is based on safety data from 372 participants with RRMM, across 6 studies (1001, 1002, 1003, 1004, 1005, 1009), that were exposed to at least one dose of elranatamab and 183 participants that received the approved commercial dose regimen of 12 mg (step-up dose 1), 32 mg (step-up dose 2) and 76 mg (full treatment dose). Safety data from Studies 1004 and 1005 were in the form of CIOMS I narratives only, for participants with SAEs or deaths at the time of the data cutoff date (Study 1004 n=5 and Study 1005 n=30) who are receiving elranatamab in combination with other anticancer therapies and these studies are therefore not included in the pooled safety analyses.

The safety presentation in this RMP includes findings from the original pooled safety analyses included in the original RMP and from new LTS data for study 1003, the latter with a cutoff date of 26 March 2024. The pooled clinical trial exposure tables provide exposure

data from 265 participants with RRMM randomized to receive monotherapy elranatamab from studies 1001, 1002, 1003 and 1009 for the following populations:

- Pool 1: participants with RRMM randomized to receive the recommended dosing regimen of 12 mg (step-up dose 1), 32 mg (step-up dose 2) and 76 mg (full treatment dose) in ongoing open-label Phase 2 Study 1003 as of the cutoff date of 22 October 2022. For this Pool end of study data as of cutoff date of 26 March 2024 are also included (see Table 7).

- Pool 2: all other participants randomized to receive a 76 mg full dose or equivalent dose calculated on a body weight basis (1000 µg/kg) regardless of priming dose(s) (excluding participants randomized to receive the 12 mg/32 mg priming regimen) in ongoing open-label studies 1001, 1002, 1003 and Part 1 of 1009 as of the data cutoff dates.

- Pool 3 (total): all participants randomized to receive 76 mg/1000 µg/kg full dose (Pool 1 + Pool 2).

Details of exposure to elranatamab in these 3 populations is provided by duration, dose, age and gender, and ethnic/racial origin below in Table 4 to Table 8.

Table 4. Duration of Exposure

Pool 1		
Duration of Exposure	**Participants**	**Participants - Months**
< 1 month	38	21
1 to < 3 months	46	81
3 to < 6 months	22	99
6 to < 9 months	13	104
9 to < 12 months	9	98
12 to <15 months	10	135
15 to < 18 months	3	49
18 to < 21 months	6	118
21 to < 24 months	3	70
⩾ 24 months	33	923
Total Participants time (≥ 1 dose)	183	1699
Pool 2		
Duration of Exposure	**Participants**	**Participants - Months**
< 1 month	11	6
1 to < 3 months	16	29
3 to < 6 months	18	87
6 to < 9 months	17	125
9 to < 12 months	2	22
12 to <15 months	4	52
15 to < 18 months	5	81
18 to <21 months	7	134
21 to <24 months	1	24
≥ 24 months	1	24
Total Participants time (≥ 1 dose)	82	583

Table 4. Duration of Exposure

Pool 3		
Duration of Exposure	**Participants**	**Participants - Months**
< 1 month	49	27
1 to < 3 months	62	110
3 to < 6 months	40	186
6 to < 9 months	31	238
9 to < 12 months	48	511
12 to <15 months	21	271
15 to < 18 months	5	81
18 to <21 months	7	134
21 to <24 months	1	24
≥ 24 months	1	24
Total Participants time (≥ 1 dose)	265	1605

The Participants Time on treatment for each individual subject is defined as (last dose - first dose + 1)/30.4375.

The counts under Participants Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are round to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Data cut-off date: C1071001 – 22Jun2022, C1071002 – 27May2022, C1071003 – 14Oct2022 (Pool 3), 26Mar2024 (Pool 1), C1071009 – 29Jul2022

Table 5. Age Group and Gender

Pool 1						
Age Group	**Participants**			**Participants - Years**		
	M	**F**	**Total**	**M**	**F**	**Total**
⩾ 18 years through 64 years	37	33	70	29	28	57
⩾ 65 years through 74 years	41	37	78	30	37	67
⩾ 75 years	17	18	35	7	9	17
Total	95	88	183	67	75	142
Pool 2						
Age Group	**Participants**			**Participants - Years**		
	M	**F**	**Total**	**M**	**F**	**Total**
⩾ 18 years through 64 years	20	20	40	12	10	23
⩾ 65 years through 74 years	16	18	34	9	10	19
⩾ 75 years	5	3	8	4	3	7
Total	41	41	82	25	23	49
Pool 3						
Age Group	**Participants**			**Participants - Years**		
⩾ 18 years through 64 years	57	53	110	29	28	57
⩾ 65 years through 74 years	57	55	112	26	32	58
⩾ 75 years	22	21	43	10	9	19
Total	136	129	265	65	68	134

F=Female, M=Male
The Participants Time on treatment for each individual subject is defined as (last dose - first dose + 1)/365.25.
The counts under Participants Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are round to nearest tenth. This may result in the Total row mismatching the sum of individual counts.
Data cut-off date: C1071001 – 22Jun2022, C1071002 – 27May2022, C1071003 –14Oct2022 (Pool 3), 26Mar2024 (Pool 1), C1071009 – 29Jul2022

Table 6. Dose

Pool 1		
Dose of Exposure	**Participants**	**Participants - Years**
12 mg	183	2
32 mg	180	4
38 mg	2	0.1
44 mg	26	3
76 mg	176	41
76 mg Q2W	75	30
Total Participants time (≥ 1 dose)	183	71
Pool 2		
Dose of Exposure	**Participants**	**Participants - Years**
4 mg	33	0.3
20 mg	33	0.4
32 mg	10	2
44 mg	53	4
76 mg	70	24
76 mg Q2W	20	15
Total Participants time (≥ 1 dose)	82	40
Pool 3		
Dose of Exposure	**Participants**	**Participants - Years**
4 mg	33	0.3
12 mg	183	2
20 mg	33	0.4
32 mg	190	5
38 mg	2	0.1
44 mg	79	7
76 mg	246	65
76 mg Q2W	95	46
Total Participants time (≥ 1 dose)	265	111

The Participants Time on treatment for each individual subject is defined as (last dose - first dose + 1)/365.25.
Doses of 600 µg/kg were mapped to 44 mg and 1000 µg/kg was mapped to 76 mg.
The counts under Participants Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are round to nearest tenth. This may result in the Total row mismatching the sum of individual counts.
Data cut-off date: C1071001 – 22Jun2022, C1071002 – 27May2022, C1071003 – 14Oct2022 (Pool 3), 26Mar2024 (Pool 1), C1071009 – 29Jul2022

Pool 1 is in an ongoing open-label Phase 2 Study 1003. For Pool 1 end of study data as of cutoff date of 26 March 2024 is presented in Table 7.

Table 7. Dose for Pool 1

Dose of Exposure	Participants	Participants - Years
76 mg	183	142

The Participants Time on treatment for each individual subject is defined as (last dose - first dose + 1) / 365.25.
The counts under Participants Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to the nearest tenth.Data cutoff date : 26Mar2024

Table 8. Race/Ethnic origin

Pool 1		
Race	**Participants**	**Participants - Years**
Asian	17	16
Black or African American	11	11
White	112	87
Unknown	1	0.2
Not Reported	42	28
Total	183	142
Ethnicity	**Participants**	**Participants - Years**
Hispanic or Latino	18	14
Not Hispanic or Latino	115	92
Unknown	2	2
Not reported	48	33
Total	183	142
Pool 2		
Race	**Participants**	**Participants - Years**
Asian	27	14
Black or African American	8	6
White	44	29
Not Reported	3	0.4
Total	82	49
Ethnicity	**Participants**	**Participants - Years**
Hispanic or Latino	5	2
Not Hispanic or Latino	76	47
Not reported	1	0.2
Total	82	49
Pool 3		
Race	**Participants**	**Participants - Years**
Asian	44	23
Black or African American	19	12
White	156	81
Unknown	3	1
Not Reported	43	17
Total	265	134
Ethnicity	**Participants**	**Participants - Years**
Hispanic or Latino	23	9
Not Hispanic or Latino	191	104
Unknown	2	0.9

Table 8. Race/Ethnic origin

Not reported	49	20
Total	265	134

The Participants Time on treatment for each individual subject is defined as (last dose - first dose + 1)/365.25.
The counts under Participants Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are round to nearest tenth. This may result in the Total row mismatching the sum of individual counts.
Data cut-off date: C1071001 – 22Jun2022, C1071002 – 27May2022, C1071003 – 26Mar2024, C1071009 – 29Jul2022

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

There have been no studies conducted in pregnant/lactating women, paediatric patients (< 18 years; there is no relevant use in this population) and specific subpopulations were excluded from the clinical studies.

The following are the important exclusion criteria in the pivotal Phase 2 clinical study C1071003:

Medical Conditions Related to Multiple Myeloma

- Smoldering MM.
- Active plasma cell leukemia.
- Amyloidosis.
- POEMS syndrome.

Reason for exclusion: these exclusion criteria were applied to ensure that the study population was specific to RRMM and to ensure that interpretation of safety and efficacy data would not be confounded by a mixed disease population.

Is it considered to be included as missing information? No.

Rationale: These conditions are not considered missing information because elranatamab will not be indicated for use in these populations.

Cardiac Disease

- Impaired cardiovascular function or clinically significant cardiovascular diseases, defined as any of the following within 6 months prior to enrollment:
    - Acute myocardial infarction or acute coronary syndromes (eg, unstable angina, coronary artery bypass graft, coronary angioplasty or stenting, symptomatic pericardial effusion);

- Clinically significant cardiac arrhythmias (eg, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
- Thromboembolic or cerebrovascular events (eg, transient ischemic attack, cerebrovascular accident, deep vein thrombosis [unless associated with a central venous access complication] or pulmonary embolism);
- Prolonged QT syndrome (or triplicate average QTcF >470 msec at screening).

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

Reason for exclusion: these exclusion criteria were primarily applied due to the expectation that participants could experience Cytokine Release Syndrome (CRS) associated with elranatamab treatment and if severe, significant cardiovascular adverse effects could be anticipated. They were designed to protect patients until additional clinical data could be obtained and evaluated.

Is it considered to be included as missing information? No.

Rationale: Use in patients with these types of cardiac disease is not considered missing information because a different safety profile is not expected in these patients based on the clinical trial data which did not demonstrate any negative effects of elranatamab on the cardiac system. The important identified risk of CRS will apply to all patients receiving elranatamab with no specific recommendation for patients with cardiac disease.

Peripheral Neuropathy

- Ongoing Grade ≥ 2 peripheral sensory or motor neuropathy.
- History of any grade peripheral sensory or motor neuropathy with prior BCMA directed therapy (Cohort B).
- History of GBS or GBS variants, or history of any Grade ≥ 3 peripheral motor polyneuropathy.

Reason for exclusion: based on the safety findings from Phase 1 study C1071001 suggesting a potential risk for peripheral neuropathy, this exclusion criterion was applied in all subsequent elranatamab clinical studies to protect participants until additional clinical data could be obtained and evaluated.

Is it considered to be included as missing information? No.

Rationale: Neurological toxicity, including ICANS is considered an important potential risk of elranatamab and data from Phase 2 study C1071003, suggest that participants with a history of PN are not at increased risk for PN when receiving elranatamab.

Active Infections

- 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.

Reason for exclusion: based on the mechanism of action of elranatamab and concerns related to potential immunosuppression and risk for infection exacerbation during treatment.

Is it considered to be included as missing information? No.

Rationale: a recommendation against initiation of treatment in patients with active infections will be included in Section 4.4 of the SmPC. The safety profile of the product per se is expected to be similar in this population and would not require further studies. Overall, a potential higher risk may be compensated by the expected benefit in this very limited subpopulation.

Hepatic and Renal Function

- 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

- 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 local institutional standard method).

Reason for exclusion: these exclusion criteria were applied to protect participants until additional clinical data could be obtained and evaluated.

Is it considered to be included as missing information? No.

Rationale: use in patients with hepatic or renal impairment is not considered missing information because a different safety profile is not anticipated in these patients.

Use in Pregnancy and Breast-Feeding

- A female participant is eligible to participate if she is not pregnant or breastfeeding.

Reason for exclusion: these exclusion criteria were applied to protect participants based on the potential but unknown adverse effects on foetal and infant development.

Is it considered to be included as missing information? No.

Rationale: Use in pregnancy and breast-feeding is not anticipated in the heavily pre-treated RRMM patient population. However, as elranatamab has the potential to cause embryo-fetal toxicity, information on use during pregnancy and breast-feeding and the potential risk to the fetus/infant will be provided in the SmPC, but due to the limited anticipated use, will not be included as an important potential risk or missing information.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 9 lists the patient populations that have been under-represented in clinical trials in the elranatamab development programme.

Table 9. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant and breastfeeding women were not included in the elranatamab clinical development programme. No female participants became pregnant while receiving elranatamab in the clinical studies.
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Participants with severe hepatic impairment were not included in the elranatamab clinical development programme. In the pooled RRMM studies, 15.5% of participants had impaired hepatic function (AST and total bilirubin >ULN). As a monoclonal antibody, elranatamab is expected to be cleared by catabolism following endocytosis by the mononuclear phagocytic system. Since the elimination of monoclonal antibodies does not occur through non-catabolic pathways such as hepatic metabolic enzymes (i.e., cytochrome P450 enzymes) or via small molecule hepatic drug transporters, no effect of hepatic impairment on elranatamab pharmacokinetic (PK) is anticipated. Clinical studies have not been conducted to evaluate the effect of hepatic impairment on the PK of elranatamab as it is not considered clinically relevant for monoclonal antibodies.

Table 9. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
• Patients with renal impairment	Participants with severe renal impairment were not included in the elranatamab clinical development programme. In the pooled RRMM studies, 33.2% participants had impaired renal function (CrCl ≤ 60 mL/min). Renal clearance is not considered important for elimination of monoclonal antibodies due to their large size and inefficient filtration through the glomerulus. The renal clearance of elranatamab was estimated to be <15% of total elranatamab clearance. Elranatamab PK has not been studied in patients with severe renal impairment.
• Patients with cardiovascular disease	Participants with clinically significant cardiac disease were not included in the elranatamab clinical development programme.
• Immunocompromised patients	Participants with RRMM are typically immunocompromised and there were no exclusion criteria related to immune competence in the clinical development programme with the exception of participants with primary immunodeficiency (such as Severe Combined Immunodeficiency Disease), who were excluded from FIH study C1071001.
• Patients with a disease severity different from inclusion criteria in clinical trials	The proposed indication for elranatamab includes participants with RRMM and these were the participants included in the clinical trials.
Population with relevant different ethnic origin	In the pooled RRMM studies, participants were 60.4% white, 7.2% black, 15.1% Asian, 1.1% unknown and the information was not reported in 16.2%. 8.7% were Hispanic or Latino and 72.1% were not Hispanic or Latino.
Subpopulations carrying relevant genetic polymorphisms	Since the elimination of monoclonal antibodies does not occur through non-catabolic pathways such as hepatic metabolic enzymes (i.e., cytochrome P450 enzymes) or via small molecule hepatic drug transporters, no effect of genetic polymorphisms on elranatamab PK is anticipated.

Module SV. Post-Authorisation Experience

The cumulative estimated patient exposure for elranatamab is based on the worldwide mg sales of 161,688 mg. This estimated exposure is based on sales data provided by IQVIA from 2023 through the first quarter of 2024 in kg. Sales data has been calculated by taking the sum of the estimated previous 4 quarters and extrapolating until the end of the reporting period (13 August 2024). The weekly estimated exposure of elranatamab is 44 mg weekly. The estimated 44 mg weekly dosing was selected based on the actual dose intensity mean/median (45 mg and 43 mg weekly, respectively) from Pool 1 (n=183) of C1071003 which takes into consideration every 2-week dosing and interruptions. The cutoff date of the C1071003 data is 26 March 2024. The number of patient-years were calculated by taking the sales data,

converted to mg, and dividing the total mg sales by 44 mg weekly dose; then further divided by 52 to obtain the estimated patient exposure of 71 patient-years.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Elranatamab does not have characteristics that would make it attractive for use for illegal purposes. In addition, elranatamab is available only through prescribing physicians and other healthcare professionals with prescriptive authority. It is an injectable product that will be administered in the healthcare setting and is not available for home use by patients.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns in the initial RMP are listed below:

Table 10. Summary of Safety Concerns in the Initial RMP

Summary of Safety Concerns	
Important identified risks	• Cytokine Release Syndrome (CRS) • Neurologic toxicity including Immune effector cell-associated neurotoxicity syndrome (ICANS) • Serious infections
Important potential risks	• None
Missing information	• Long term safety

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Injection site reaction
- Diarrhea
- Nausea
- Fatigue
- Pyrexia
- Transaminases increased
- Hypokalemia

- Hypophosphatemia
- Decreased appetite
- Arthralgia
- Headache
- Dyspnea
- Rash
- Dry skin

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Hypogammaglobulinaemia
- Anemia
- Neutropenia
- Thrombocytopenia
- Lymphopenia
- Leukopenia
- Febrile neutropenia.
- Embryo-foetal toxicity

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Cytokine Release Syndrome (CRS)

As a CD3-targeting bispecific antibody, elranatamab stimulates cytokine release and CRS has been identified as an ADR. The main signs and symptoms of CRS include fever, hypotension and hypoxia; other accompanying signs and symptoms such as tachypnoea, headache, tachycardia, myalgia, arthralgia, rash and malaise may also be present.

To mitigate the risk for CRS observed in the initial Phase 1 Study C1071001, a two step-up priming dose regimen (which included premedication, and administration of elranatamab on C1D1 and C1D4 before the first full dose of elranatamab) was implemented in Phase 2 study C1071003, after the first 4 participants had been randomized (initial dosing regimen in these participants was 1 priming dose of 44 mg on C1D1 and the first full dose of 76 mg on C1D8). The 2 step-up priming dosing regimen with pre-medications is the recommended dosing regimen in the SmPC and therefore this risk will be characterized based on the 183 participants that received this dosing regimen (Pool 1).

Among the 183 participants who received the recommended dosing regimen, the overall incidence of CRS was 57.9%, with the majority of events being either Grade 1 (43.7%) or Grade 2 (13.7%); one (0.5%) participant had a Grade 3 event. CRS occurred primarily after the first step-up dose (43.2%) or the second step-up dose (19.1%). There were occasional events after the first full dose (7.1%) or the second or later full dose (1.6%), with 12.6% of participants having >1 CRS event.

Serious CRS events were reported in 12.6% of participants. The frequency of permanent discontinuations (0.5%), dose reductions (2.2%), and dose interruptions (3.3%) due to CRS were low. One participant (with concurrent ICANS) permanently discontinued elranatamab treatment due to both CRS and ICANS. The median (range) time to onset of CRS of any grade was 2 days (1, 9) and the median (range) time to resolution was 2 days (1, 19).

As anticipated based on the definition of CRS, 99.0% of participants with CRS had fever; where most were Grade 1 (61.0%) or Grade 2 (36.2%), 2 participants had Grade 3 (1.9%) fever. Hypotension occurred in 21.0% of participants (5.7% Grade 1, 12.4% Grade 2, and 2.9% Grade 3) and 11.4% had hypoxia (1.0% Grade 1, 8.6% Grade 2, and 1.9% Grade 3).

Risk-benefit impact: CRS has the potential to affect the risk-benefit profile of elranatamab because events can be life-threatening and/or lead to the need for hospitalization for treatment. Additional CRS data will be provided from on-going Phase 2 Study C1071003 and on-going Phase 3 Study C1071005 and a Patient Card is included as an additional risk minimization measure.

Important Identified Risk: Neurologic Toxicity including Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

ICANS is defined as a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells and has been observed following treatment with elranatamab. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

To mitigate the risk for ICANS observed in the initial Phase 1 Study C1071001, a two step-up priming dose regimen (which included premedication, and administration of elranatamab on C1D1 and C1D4 before the first full dose of elranatamab) was implemented in Phase 2 study C1071003, after the first 4 participants had been randomized (initial dosing regimen in these participants was 1 priming dose of 44 mg on C1D1 and the first full dose of 76 mg on C1D8). The 2 step-up priming dosing regimen with pre-medications is the recommended dosing regimen and therefore this risk will be characterized based on the 183 participants that received this dosing regimen (Pool 1).

Among the 183 participants who received the recommended dosing regimen 3.3% developed ICANS. Of the 6 participants with ICANS, 1 (0.5%) had a Grade 1 event, 3 (1.6%) had Grade 2 events and 2 (1.1%) had Grade 3 events. No ICANS were Grade 4 or Grade 5. The majority of participants had ICANS after the first step-up dose (5 [2.7%]); 1 (0.5%) of these participants also experienced ICANS after the second step-up dose and 1 (0.5%) participant

initially experienced ICANS after the third (first full dose) and had events after the fourth and sixth doses.

Serious ICANS was reported in 2 participants (1.1%). One (0.5%) participant had a dose interruption and 2 (1.1%) participants permanently discontinued elranatamab treatment due to ICANS (both had Grade 3 events). There were no dose reductions due to ICANS. The median (range) time to ICANS onset relative to the most recent dose of elranatamab was 3 days (1, 4). All ICANS events resolved and the median (range) time to resolution was 2 days (1, 18).

In participants with ICANS, clinical manifestations included changes in the level of consciousness (2 awakens only to tactile stimulus, 2 awakens to voice and 1 awakens spontaneously) and the ICE score (score of 0 in 1 and 3-6 in 3). No participant had seizures, motor findings or elevated ICP/cerebral edema.

Important neurologic ADRs other than ICANS include Peripheral neuropathy. In participants that received the recommended dosing regimen (Pool 1), 19.1% of participants had an AE included in the search criteria for events of potential PN. The majority of participants had Grade 1 (9.3%) or Grade 2 (8.7%) events with 1.1% having Grade 3 AEs and none having a Grade 4 or Grade 5 event. The most frequently reported (≥2%) all causality potential PN PTs were Peripheral sensory neuropathy (4.9%), Paraesthesia (3.8%), and Muscular weakness (2.7%). Following clinical and safety review, the following PTs were determined to be ADRs and were included in the pooled terms defining Peripheral neuropathy in the SmPC; Peripheral sensory neuropathy, Paraesthesia, Peripheral sensorimotor neuropathy, Dysaesthesia, Neuropathy peripheral, Peripheral motor neuropathy, Guillain-Barre syndrome, Hypoaesthesia, Neuralgia, Polyneuropathy.

Risk-benefit impact: Neurologic AEs, including ICANS have the potential to affect the risk-benefit profile of elranatamab because events can be life-threatening and/or lead to the need for hospitalization for treatment. Additional neurotoxicity data, including data on ICANS will be provided from on-going Phase 2 Study C1071003 and on-going Phase 3 Study C1071005 and a Patient Card is included as an additional risk minimization.

Important Identified Risk: Serious Infections

Infections are common in patients with RRMM due to underlying immunosuppression. However, as elranatamab causes plasma cell depletion, and contributes to worsening hypogammaglobulinemia and neutropenia (also common in this patient population), elranatamab treatment increases the risk of infections.

In the overall pooled safety population (Pool 3), 69.1% of participants had an all-causality infection AE, including 66.7% in Pool 1 and 74.4% in Pool 2. Grade 3 or 4 infections occurred in 30.9% of participants with 26.8% Grade 3 and 4.2% being Grade 4. The frequencies of permanent discontinuations and dose reductions due to infection AEs were 5.3% and 2.6%, respectively.

Serious infections were reported in 39.2% of participants. The most frequently reported (≥2%) serious infections were COVID-19 pneumonia (8.3%), Pneumonia (7.5%), Sepsis

(3.4%), *Pneumocystis jirovecii* pneumonia (3.0%), COVID-19 (2.3%), Septic shock (2.3%), and Urinary tract infection (2.3%).

Grade 5 infection AEs were reported in 15 participants (5.7%) and included COVID-19 pneumonia (1.5%), Septic shock (1.5%), Sepsis (0.8%), COVID-19 (0.8%), Adenovirus infection (0.8%), Pneumonia adenoviral (0.4%), and Pneumonia pseudomonal (0.4%).

Opportunistic infections were reported in 9.4% of participants; 4.2% were Grade 3, 0.4% were Grade 4 and 0.8% were Grade 5. The most frequently reported (≥2%) opportunistic infections were Cytomegalovirus infection reactivation (4.2%) and *Pneumocystis jirovecii* pneumonia (3.8%). Serious opportunistic infections were reported in 4.9% of participants. Progressive multifocal leukoencephalopathy (PML) has also occurred during therapy with elranatamab.

Treatment-related infections were reported in 34.0% of participants; 12.1% were Grade 3/4 with 10.9% Grade 3 and 1.1% Grade 4. Three participants (1.1%) had a treatment-related Grade 5 event (Adenovirus infection, Pneumonia pseudomonal, and Septic shock). Treatment related serious infections were reported in 14.7% of participants; the most frequently reported (≥2%) event was Pneumonia (4.2%).

The median (Q1, Q3) time to first onset of infection AEs of any grade was 36 days (12, 95) with the majority of participants (21.9%) having first onset at >8 to ≤24 weeks of treatment. At the time of the data cut, 105/183 (57.4%) participants had resolved infection events and the median (Q1, Q3) time to resolution was 14 days (7, 24). The median (Q1, Q3) duration of infection AEs of any grade was 14 days (7, 29).

Risk-benefit impact: Serious infections have the potential to affect the risk-benefit profile of elranatamab because events can be life-threatening and/or lead to the need for hospitalization for treatment. It is important that HCPs follow the risk minimization measures communicated in the SmPC and that patients seek immediate treatment at the first signs or symptoms of an infection. Additional data on serious infections will be provided from on-going Phase 2 Study C1071003 and on-going Phase 3 Study C1071005.

Missing information: Long-term safety

The initial submission for elranatamab for the treatment of patients with RRMM will be supported primarily by data from Phase 2 Study C1071003 (pivotal). Studies C1071001, C1071002, and C1071009 will be supportive. These studies currently do not provide long term safety data as the median follow-up for participants in Study C1071003 at the time of submission will be approximately 9 months.

Risk-benefit impact: Additional risks may be identified during long term follow-up of ongoing studies and in additional Phase 3 studies. Study C1071005 is proposed to serve as the confirmatory randomized Phase 3 study and will provide long-term safety data and additional safety data will be provided from on-going Phase 2 Study C1071003. New Safety Concerns and Reclassification with a Submission of an Updated RMP.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Study C1071003 met protocol defined end of study criterion as all participants have been followed for at least 2 years from the date of enrollment. The final CSR for this study has been completed. Long-term safety previously classified as missing information is removed from the list of safety concerns as long-term safety data from Study C1071003, included in the RMP, allow for a full characterization of the safety profile of elranatamab monotherapy in patients with RRMM.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

The identified risks of CRS and Neurological toxicity, including ICANS are characterized based on safety data from the 183 participants in pivotal Phase 2 study C1071003 that received the approved dosing regimen, including pre-medications (Pool 1). The identified risk of Serious infection is characterized using the pooled safety data from all participants in monotherapy studies 1001, 1002, 1003 and 1009 (Pool 3) and using LTS data from study 1003 (Pool 1).

Important Identified Risk: Cytokine Release Syndrome (CRS)

Table 11. Important Identified Risk - CRS

Potential mechanisms	As a CD3-targeting bispecific antibody, elranatamab stimulates cytokine release.
Evidence source and strength of evidence	The relationship between elranatamab administration and CRS has been clearly demonstrated in clinical studies. Risk factors important for the management of CRS were identified in Phase 1 study 1001 and measures to mitigate them were implemented in future studies.
Characterisation of the risk	There were no changes in the CRS incidence, severity or occurrence in the LTS data set compared to the initial MAA dataset. Among the 183 participants who received the approved dosing regimen, the overall incidence of CRS was 57.9%, with the majority of events being either Grade 1 (43.7%) or Grade 2 (13.7%); one (0.5%) participant had a Grade 3 event. CRS occurred primarily after the first step-up dose (43.2%) or the second step-up dose (19.1%). There were occasional events after the first full dose (7.1%) or the second or later full dose (1.6%), with 12.6% of participants having >1 CRS event. The main signs and symptoms of CRS include fever, hypotension and hypoxia; other accompanying signs and symptoms such as tachypnoea, headache, tachycardia, myalgia, arthralgia, rash and malaise may also be present. CRS is reversible and can be managed with appropriate supportive care and/or the use of IL-6 inhibitors and/or corticosteroids.
Risk factors and risk groups	The risk for CRS is greatest following the first 2-3 doses of elranatamab; CRS occurs infrequently following later doses. The risk for CRS is dose related. There are no known risk groups for CRS.
Preventability	The risk for CRS can be mitigated with the use of pre-medications, including dexamethasone, paracetamol, and a histamine-1 receptor antagonist prior to the

Table 11. Important Identified Risk - CRS

	first 3 doses of elranatamab and with the use of a 2 step-up priming dose regimen prior to the first full dose. Patients should be instructed to remain within the proximity of a healthcare facility, be monitored daily for 48 hours after administration of the first 2 step-up doses of elranatamab, and to seek medical attention if signs or symptoms of CRS occur. Specific guidelines for the management of CRS by severity are provided in the SmPC.
Impact on the risk-benefit balance of the product	CRS has the potential to affect the risk-benefit profile of elranatamab because events can be life-threatening and/or lead to the need for hospitalization for treatment. It is important that HCPs follow the risk minimization measures communicated in the SmPC and that patients seek immediate treatment at the first signs or symptoms of CRS.
Public health impact	The public health impact is anticipated to be minimal as CRS is limited to the first few doses of elranatamab and can be recognized and medically managed without long-term consequences. However, in some cases hospitalization may become necessary.

Post-Marketing data from the MAH Safety Database

Table 12. Post-Marketing AEs CRS by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome (%)				
				Fatal	Resolved/ Resolving	Resolved with Sequelae	Not Resolved	Unknown/ No Data
Cytokine release syndrome	78 (100)	78 (100)	17 (21.8)	1 (1.3)*	51 (65.4)	0	7 (9.0)	19 (24.4)

Reporting Period: Cumulative Through 15-July-2024
Of note Compassionate use events are excluded.
*The fatal case: the patient's disease had progressed extremely far, and the patient experienced 'serious AEs (probably CRS)'. Cause of death was reported as cytokine release syndrome and disease progression.

Important Identified Risk: Neurologic Toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Table 13. Important Identified Risk – Neurologic Toxicity including ICANS

Potential mechanisms	As a CD3-targeting bispecific antibody, elranatamab engages and activates T-cells. Neurologic toxicity has been reported with other T-cell redirectors, however, the mechanism is unclear. ICANS is defined as a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells.

Table 13. Important Identified Risk – Neurologic Toxicity including ICANS

Evidence source and strength of evidence	The relationship between elranatamab administration and neurologic toxicities including ICANS has been demonstrated in clinical studies. Risk factors important for the management of ICANS were identified in Phase 1 study 1001 and measures to mitigate them were implemented in future studies.
Characterisation of the risk	There were no changes in the ICANS data in the LTS data compared to those included in the initial MAA. Among the 183 participants who received the approved dosing regimen, 3.3% developed ICANS. Of the 6 participants with ICANS, 1 (0.5%) had a Grade 1 event, 3 (1.6%) had Grade 2 events and 2 (1.1%) had Grade 3 events. No ICANS were Grade 4 or Grade 5. The majority of participants had ICANS after the first step-up dose (5 [2.7%]); 1 (0.5%) of these participants also experienced ICANS after the second step-up dose and 1 (0.5%) participant initially experienced ICANS after the third (first full dose) and had events after the fourth and sixth doses. The main signs and symptoms of ICANS can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema. In participants treated with elranatamab, symptoms included only changes in the level of consciousness and the ICE score, no participant had seizures, motor findings or elevated ICP/cerebral edema. ICANS is reversible and can be managed with appropriate supportive care and the use of corticosteroids and IL-6 inhibitors (if associated with CRS). Important neurologic ADRs other than ICANS included Peripheral neuropathy. In participants that received the approved dosing regimen (Pool 1) at the time of the initial MAA, 19.1% of participants had an AE included in the search criteria for events of potential PN. The majority of participants had Grade 1 (9.3%) or Grade 2 (8.7%) events with 1.1% having Grade 3 AEs and none having a Grade 4 or Grade 5 event. Similarly, in the LTS data, the majority of participants had Grade 1 (10.9%) or Grade 2 (10.4%) AEs of potential PN. Three (1.6%) participants had Grade 3 AEs and no participant had a Grade 4 or Grade 5 event. The all causality potential PN AEs in the LTS data were coded to the PTs Peripheral sensory neuropathy (8.7%), Paraesthesia (4.4%), Muscular weakness (3.3%), Areflexia, Gait disturbance, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy (1.6% each), Dysaesthesia, Motor dysfunction, Neuralgia (1.1% each), Burning sensation, Electric shock sensation, Guillain-Barre syndrome, Hypoaesthesia, Muscle atrophy, Myelopathy, Neuropathy peripheral, Paroxysmal extreme pain disorder, Peroneal nerve palsy, Polyneuropathy and Sensory loss (0.5% each). Of note 1 participant may report more than 1 potential PN AEs. The most frequently reported (≥2%) all causality potential PN PTs in both datasets (incidence at initial MAA submission; incidence at LTS) were Peripheral sensory neuropathy (4.9%; 8.7%), Paraesthesia (3.8%; 4.4%), and Muscular weakness (2.7%; 3.3%). At the time of the initial MAA, following clinical and safety review, the following PTs were determined to be ADRs and were included in the pooled terms defining Peripheral neuropathy in the SmPC; Peripheral sensory neuropathy, Paraesthesia, Peripheral sensorimotor neuropathy, Dysaesthesia, Neuropathy peripheral, Peripheral motor neuropathy, Guillain-Barre syndrome, Hypoaesthesia, Neuralgia, and Polyneuropathy. There were no new AEs considered ADRs based on the LTS report data.

Table 13. Important Identified Risk – Neurologic Toxicity including ICANS

Risk factors and risk groups	The risk for ICANS is greatest following the first 2-3 doses of elranatamab and event occurred infrequently following later doses. ICANS occurs commonly in association with CRS but can occur without concurrent CRS. The risk for ICANS is dose related. There are no known risk groups for ICANS. The risk factors for Peripheral neuropathy have not been fully identified. Current data suggest that participants with a history of PN are not at increased risk for PN when receiving elranatamab.
Preventability	The risk for ICANS can be mitigated with the use of a 2 step-up doing regimen of elranatamab prior to the first full dose. The risk for all neurologic events can be mitigated through monitoring for signs and symptoms and prompt treatment. Patients should be instructed to remain within the proximity of a healthcare facility, be monitored daily for 48 hours after administration of the first 2 step-up doses of elranatamab, and to seek medical attention if signs or symptoms of ICANS occur. Specific guidelines for the management of ICANS by severity are provided in the SmPC.
Impact on the risk-benefit balance of the product	ICANS has the potential to affect the risk-benefit profile of elranatamab because events can be life-threatening and/or lead to the need for hospitalization for treatment. Other neurologic events were primarily Grade 1 or Grade 2, non-serious and generally manageable with standard treatments, and are therefore not considered to substantially impact the benefit risk profile. It is important the HCPs follow the risk minimization measures communicated in the SmPC and that patients seek immediate treatment at the first signs or symptoms of neurologic toxicity, including ICANS.
Public health impact	The public health impact is anticipated to be minimal as neurologic toxicity, including ICANS can be recognized and medically managed, typically without long-term consequences. However, in some cases hospitalization may become necessary.

Post-Marketing data from the MAH Safety Database

Table 14. Post-Marketing AEs of Neurologic Toxicity by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved/ Resolving	Resolved with Sequelae	Not Resolved	Unknown/ No Data
Immune effector cell-associated neurotoxicity syndrome	11 (55.0)	11 (100)	8 (72.7)	1 (9.1) *	4 (36.4)	0	3 (27.3)	3(27.3)
Neuropathy peripheral	3 (15.0)	3 (100)	0	0	1 (33.3)	0	1 (33.3)	1 (33.3)

Table 14. Post-Marketing AEs of Neurologic Toxicity by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome N (%)				
				Fatal	Resolved/ Resolving	Resolved with Sequelae	Not Resolved	Unknown/ No Data
Neurotoxicity	3 (15.0)	3 (100)	1 (33.3)	0	1 (33.3)	0	0	2 (66.7)
Muscle atrophy	1 (5)	1 (100)	1 (100)	0	0	0	1 (100)	0
Muscular weakness	1 (5)	1 (100)	1 (100)	0	1 (100)	0	0	0
Paraesthesia	1 (5)	0	0	0	0	0	1 (100)	0

Reporting Period: Cumulative Through 15-July-2024
Total number of Neurologic Toxicity AEs 20. Of note Compassionate use events are excluded.
* fatal case: a 71 years old patient was administered elranatamab for plasma cell myeloma refractory and reportedly experienced 'Grade 4 ICANS' which resulted in a hospital admission. After discharge from hospital the patient passed away. Of note concomitant medications included IV antibiotics, that may suggest systemic infection

Table 15. Important Identified Risk – Serious Infections

Potential mechanisms	Infections are common in patients with RRMM due to underlying immunosuppression. However, as elranatamab causes plasma cell depletion, and likely contributes to worsening hypogammaglobulinemia and neutropenia (also common in this patient population), elranatamab treatment increases the risk of infections.
Evidence source and strength of evidence	The relationship between elranatamab administration and serious infections has been demonstrated in clinical studies.
Characterisation of the risk	In LTS data from study C1071003 (Pool 1), 71.6% of participants had an all-causality infection AE. Grade 3 or 4 infections occurred in 38.8% of participants with 32.8% Grade 3 and 6.0% being Grade 4. Serious infections were reported in 48.1% of participants, with most frequent (≥2%) serious infections of COVID-19 pneumonia (13.1%), Pneumonia (9.3%), Sepsis (4.9%), *Pneumocystis jirovecii* pneumonia (4.9%), COVID-19 (4.9%), Septic shock (3.8%), Pneumonia bacterial (3.3%), and Urinary tract infection (3.3%). Grade 5 infection AEs were reported in 14 participants (7.7%) and included Septic shock in 5 participants (2.7%), COVID-19 pneumonia in 4 participants (2.2%), COVID-19, Sepsis, Adenovirus infection, Pneumonia adenoviral, Adenoviral hepatitis, Pneumonia pseudomonal in 1 participant each (0.5%); one participant had 2 concurrent Grade 5 events reported (Adenovirus infection/Pneumonia adenoviral). Opportunistic infections were reported in 14.8% of participants. The most frequently reported (≥2%) opportunistic infections were Cytomegalovirus infection reactivation (5.5%) and *Pneumocystis jirovecii* pneumonia (3.8%). Serious opportunistic infections were reported in 7.7% of participants. PML has also occurred during therapy with elranatamab.

Table 15. Important Identified Risk – Serious Infections

Risk factors and risk groups	Patients with RRMM are at increased risk for serious infection due to well documented disease related immunosuppression (neutropenia, lymphopenia and hypogammaglobulinemia), which can be worsened with elranatamab treatment and lead to an increased risk for the development of serious infections, including opportunistic infections.
Preventability	The risk for serious infections can be decreased with the appropriate use of prophylactic antimicrobial and/or antiviral agents and through monitoring and treatment of cytopenias and hypogammaglobulinemia. Patients should be monitored for signs and symptoms of infection and appropriate treatment be promptly initiated. Serious infections can also be prevented by not initiating elranatamab treatment in patients with active infection until the infection has resolved.
Impact on the risk-benefit balance of the product	Serious infections have the potential to affect the risk-benefit profile of elranatamab because events can be life-threatening and/or lead to the need for hospitalization for treatment. It is important the HCPs follow the risk minimization measures communicated in the SmPC and that patients seek immediate treatment at the first signs or symptoms of an infection.
Public health impact	The public health impact is anticipated to be minimal as the risk of serious infections can be reduced and treated using standard of care therapy. However, in some cases hospitalization may be necessary.

Post-Marketing data from the MAH Safety Database

Table 16. Post-Marketing AEs of Serious Infection by Outcome

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved/ Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
Escherichia bacteraemia	3 (23.1)	3 (100)	0	0	1 (33.3)	0	0	2 (66.7)
Cellulitis	2 (15.4)	2 (100)	1 (50)	1 (50)	0	0	0	1 (50)
Neutropenic sepsis	2 (15.4)	2 (100)	0	0	2 (100)	0	0	0
Pneumonia	2 (15.4)	2 (100)	0	0	0	0	1 (50)	1 (50)
Enterococcal sepsis	1 (7.7)	1 (100)	0	0	1 (100)	0	0	0
Pneumonia aspiration	1 (7.7)	1 (100)	1 (100)	1 (100)	0	0	0	0
Pneumonia bacterial	1 (7.7)	1 (100)	0	0	1 (100)	0	0	0
Sepsis	1 (7.7)	1 (100)	0	0	0	0	0	1 (100)

Reporting Period: Cumulative Through 15-July-2024
Total number of serious infections AEs 13. Of note compassionate use events are excluded.
*Some cases reported more than 1 relevant AE

SVII.3.2. Presentation of the Missing Information

Missing Information: None

Module SVIII. Summary of the Safety Concerns

Table 17. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Cytokine Release Syndrome (CRS) • Neurologic Toxicity including Immune effector cell-associated neurotoxicity syndrome (ICANS) • Serious infections
Important potential risks	• None
Missing information	• None

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires:**

  None proposed.

- **Other forms of routine pharmacovigilance activities:**

  None proposed but the PSUR will include data on important identified and potential risks, and on other events of interest, including but not limited to tumor lysis syndrome and hepatotoxicity.

III.2. Additional Pharmacovigilance Activities

None proposed.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 18. On-Going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
None				

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Study short name and title:

Study C1071005 - An Open-Label, 3-Arm, Multicenter, Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Elranatamab (PF-06863135) Monotherapy and Elranatamab + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma

Rationale and study objectives:

Part 1: To assess DLTs, safety and tolerability of elranatamab + daratumumab in order to select a RP3D for the combination to be used in Part 2 of this study.

Part 2:

- To compare the efficacy of elranatamab (Arm A) vs daratumumab + pomalidomide + dexamethasone (Arm C) as measured by PFS
- To determine the safety and tolerability of elranatamab monotherapy
- To evaluate the immunogenicity of elranatamab

Study design:

Randomized Phase 3 clinical trial.

Study population:

Part 1: Participants with RRMM who had received at least 3 prior lines of anti-MM therapy including treatment with lenalidomide and a PI

Part 2: Participants with RRMM who had received at least 1, but not more than 3, prior lines of anti-MM therapy including treatment with lenalidomide and a PI. A response of MR or better must have been achieved with any prior anti-MM therapy based on investigator assessment using IMWG criteria

Milestones:

Protocol submission: 09 January 2023

Final report: June 2027

Table 19. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None.				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
C1071005 On-going	Part 2 Primary Objective: To compare the efficacy of elranatamab (Arm A) vs daratumumab + pomalidomide + dexamethasone (Arm C) as measured by PFS. Part 2 Secondary Safety Objectives: To determine the safety and tolerability of elranatamab monotherapy. To evaluate the immunogenicity of elranatamab	Confirmatory and long-term efficacy	Protocol submission: Final report:	09 Jan 2023 June 2027 (submission to EMA)

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 20. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
CRS	Routine risk communication: SmPC Sections 4.2, 4.4, 4.5 and 4.8; Package Leaflet (PL) Sections 2, 3 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation that elranatamab should be administered by a healthcare provider with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in SmPC section 4.2. Recommendation for two step-up doses of elranatamab prior to the first full dose of elranatamab is included in SmPC section 4.2 and 4.4. Recommendation for pre-medications prior to the first 3 doses of elranatamab is included in SmPC section 4.2 and 4.4. Recommendation for patients to remain within the proximity of a healthcare facility, be monitored daily for 48 hours after administration of the first 2 doses of elranatamab, and to seek medical attention if signs or symptoms of CRS occur in SmPC section 4.2 and 4.4. Recommendation to withhold elranatamab treatment until Grade 1, Grade 2, or first Grade 3 CRS has resolved in SmPC section 4.2. Recommendations to discontinue elranatamab treatment for recurrent Grade 3 or Grade 4 CRS is included in SmPC section 4.2. Recommendations for monitoring and treatment of CRS is included in SmPC section 4.2. Information for patients to be on the look out for CRS, including a description of common signs and symptoms in PL section 2. Recommendation for patients to tell their doctor or nurse and to seek medical attention right away if they have any signs and symptoms of CRS in PL section 2 and 4. Recommendation for patients to stay close to a healthcare facility for 48 hours after each of the first two doses in case they have side effects in PL section 3.

Table 20. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Information for patients that they will be given pre-medication prior to the first 3 doses of elranatamab to lower the chance of CRS in PL section 3. Other routine risk minimization measures beyond the Product Information: None
Neurologic toxicities including ICANS	Routine risk communication: SmPC Sections 4.2, 4.4, 4.7 and 4.8; Package Leaflet (PL) Sections 2, 3 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation that elranatamab should be administered by a healthcare provider with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in SmPC section 4.2. Recommendation for two step-up doses of elranatamab prior to the first full dose of elranatamab is included in SmPC section 4.2 and 4.4. Recommendation for patients to remain within the proximity of a healthcare facility, be monitored daily for 48 hours after administration of the first 2 doses of elranatamab, and to seek medical attention if signs or symptoms of ICANS occur in SmPC section 4.2 and 4.4. Recommendation to withhold elranatamab treatment until Grade 1, Grade 2, or initial Grade 3 ICANS has resolved in SmPC section 4.2. Recommendation to discontinue elranatamab for recurrent Grade 3 or Grade 4 ICANS is included in SmPC section 4.2. Recommendations for monitoring and treatment of ICANS is included in SmPC section 4.2. Recommendation to avoid driving and operating heavy or potentially dangerous machinery during the elranatamab step-up dosing schedule and for 48 hours after completing each of the 2 step-up doses of elranatamab, or until any neurologic adverse events resolve in SmPC section 4.4 and 4.7. Information for patients to be on the look out for side effects on the nervous system which could be signs of ICANS, including a description of symptoms, in PL section 2.

Table 20. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Recommendation for patients to tell their doctor or nurse and to seek medical attention right away if they have any nervous system signs including those of ICANS in PL section 2 and 4. Recommendation for patients to stay close to a healthcare facility for 48 hours after each of the first two doses in case they have side effects in PL section 3. <u>Other routine risk minimisation measures beyond the Product Information:</u> None
Serious infections	<u>Routine risk communication:</u> SmPC Sections 4.2, 4.4 and 4.8; Package Leaflet (PL) Sections 2 and 4. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Recommendation to not initiate treatment in patients with active infections in SmPC section 4.4. Recommendation that prophylactic antimicrobials and anti-virals should be administered according to local institutional guidelines in SmPC section 4.2 and 4.4 and that treatment with subcutaneous or intravenous immunoglobulin (IVIG) should be considered, as appropriate in SmPC section 4.4. Recommendation that patients be monitored for signs and symptoms of infection prior to and during treatment and that appropriate treatment be initiated in SmPC section 4.4. Recommendation to monitor immunoglobulin levels during treatment and administer IVIG for IgG levels <400 mg/dL in SmPC section 4.4. Recommendation to monitor patients for neutropenia and provide supportive therapy according to local institutional guidelines in SmPC section 4.4. Provision of dose modification guidelines for management of infections by Grade in SmPC section 4.2. Recommendation that live viral vaccines or live attenuated vaccines are not administered within 4 weeks prior to the first dose of elranatamab, during treatment, and at least 4 weeks after treatment in SmPC section 4.4. Information for patients that they should not receive live vaccines within the four weeks before their first dose of ELREXFIO, while treated with ELREXFIO, and at least 4 weeks after last dose in PL section 2.

Table 20. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Information for patients to be on the look out for serious side effects including infections in PL section 2. Recommendation for patients to tell their doctor or nurse and to seek medical attention right away if they have any signs of infection in PL section 2 and 4. Other routine risk minimisation measures beyond the Product Information: None

V.2. Additional Risk Minimisation Measures

Additional risk minimisation 1 – Patient Card

Objectives:

The objective of the Patient Card is to ensure that patients are reminded of the following regarding the risk for CRS and neurologic toxicities including ICANS:

1. Key signs and symptoms of CRS and neurologic toxicities including ICANS
2. They should remain within proximity of a healthcare facility, and be monitored for signs and symptoms daily for 48 hours after administration of the first 2 step-up doses
3. When to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or neurologic toxicities including ICANS present themselves
4. The prescribing physician's contact details

Rationale for the additional risk minimisation activity:

Due to the risk for CRS and Neurologic toxicities including ICANS, the SmPC will state that patients should be instructed to remain within proximity of a healthcare facility, and be monitored for signs and symptoms daily for 48 hours after administration of the first 2 step-up doses. Therefore, it is important for patients to understand the signs and symptoms of CRS and neurological toxicity, including ICANS and how and when they should seek additional attention from the healthcare provider.

Target audience and planned distribution path:

The target audience is patients that will receive the material via their prescribing physician. The distribution plan may vary by local legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Direct evaluation of the patient population is not planned due to known barriers to recruiting patients for survey research in the EU. The Patient Card is judged effective if no negative trends or worsening outcomes in the risks of CRS and Neurologic toxicities including ICANS are identified.

V.3. Summary of Risk Minimisation Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Table 21. Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
CRS	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.5 and 4.8: PL Sections 2, 3 and 4. Additional risk minimisation measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Neurologic Toxicities including ICANS	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.7 and 4.8: PL Sections 2, 3 and 4. Additional risk minimisation measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None
Serious infections	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8: PL Sections 2 and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Elrexfio

This is a summary of the risk management plan (RMP) for Elrexfio. The RMP details important risks of Elrexfio, and how these risks can be minimised, and how more information will be obtained about Elrexfio's risks.

Elrexfio's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how elranatamab should be used.

This summary of the RMP for Elrexfio should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Elrexfio's RMP.

I. The Medicine and What It Is Used For

Elrexfio is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. It contains elranatamab as the active substance and is given by subcutaneous injection.

Further information about the evaluation of Elrexfio's benefits can be found in Elrexfio's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Elrexfio, together with measures to minimise such risks and the proposed studies for learning more about Elrexfio's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Elrexfio, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Elrexfio is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Elrexfio are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Elrexfio. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term safety of the medicine).

Table 22. List of important risks and missing information

Important identified risks	• Cytokine Release Syndrome (CRS) • Neurologic Toxicity including Immune effector cell-associated neurotoxicity syndrome (ICANS) • Serious infections
Important potential risks	• None
Missing information	• None

II.B Summary of Important Risks

Table 23. Important Identified Risk: Cytokine Release Syndrome (CRS)

Evidence for linking the risk to the medicine	The relationship between elranatamab administration and CRS has been clearly demonstrated in clinical studies. Risk factors important for the management of CRS were identified in Phase 1 study 1001 and measures to mitigate them were implemented in following studies.
Risk factors and risk groups	The risk for CRS is greatest following the first 2-3 doses of elranatamab and occurs infrequently following later doses. The risk for CRS is dose related. There are no known risk groups for CRS.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.5 and 4.8: PL Sections 2, 3 and 4. Additional risk minimisation measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 24. Important Identified Risk: Neurologic Toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Evidence for linking the risk to the medicine	The relationship between elranatamab administration and Neurologic toxicity including ICANS has been clearly demonstrated in clinical studies. Risk factors important for the management of ICANS were identified in Phase 1 study 1001 and measures to mitigate them were implemented in following studies.
Risk factors and risk groups	The risk for ICANS is greatest following the first 2-3 doses of elranatamab; ICANS occurs infrequently following later doses. ICANS occurs commonly in association with CRS but can occur without CRS. The risk for ICANS is dose related. There are no known risk groups for ICANS.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.7 and 4.8: PL Sections 2, 3 and 4. Additional risk minimisation measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None .

Table 25. Important Identified Risk: Serious Infections

Evidence for linking the risk to the medicine	The relationship between elranatamab administration and serious infections has been demonstrated in clinical studies.
Risk factors and risk groups	Patients with RRMM are at increased risk for serious infection due to well documented disease related immunosuppression (neutropenia, lymphopenia and hypogammaglobulinemia), which can be worsened with elranatamab treatment and lead to an increased risk for the development of serious infections.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8: PL Sections 2 and 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorization:

Study name

Study C1071005 - An Open-Label, 3-Arm, Multicenter, Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Elranatamab (PF-06863135) Monotherapy and Elranatamab + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma

Purpose of the study:

Part 1: To assess DLTs, safety and tolerability of elranatamab + daratumumab in order to select a RP3D for the combination to be used in Part 2 of this study.

Part 2: To compare the efficacy of elranatamab (Arm A) vs daratumumab + pomalidomide + dexamethasone (Arm C) as measured by PFS

II.C.2 Other Studies in Post-Authorisation Development Plan

None

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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Follow-up forms

Not Applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Draft key messages of the additional risk minimisation measures

The MAH shall ensure that in each Member State where elranatamab is marketed, all patients/carers who are expected to use elranatamab have access to/are provided with the Patient Card which will inform and explain to patients the risk of CRS and Neurologic Toxicities including ICANS.

- **Patient Card**:

  Objectives:

  The objective of the Patient Card is to ensure that patients are reminded of the following regarding the risk for CRS and neurologic toxicities including ICANS:

  1. Key signs and symptoms of CRS and neurologic toxicities including ICANS
  2. They should remain within proximity of a healthcare facility, and be monitored for signs and symptoms daily for 48 hours after administration of the first 2 step-up doses
  3. When to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or neurologic toxicities including ICANS present themselves
  4. The prescribing physician’s contact details