12 October 2023
EMA/544323/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Elrexfio

International non-proprietary name: Elranatamab

Procedure No. EMEA/H/C/005908/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

~	approximately
%	percent or percentage
A	amperes
AA	accelerated approval
ADA	anti-drug antibodies
ADC	antibody drug conjugate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APCs	antigen presenting cells
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ASTCT	The American Society for Transplantation and Cellular Therapy
ATC2	anatomic therapeutic chemical classification
AUCtau	area under the concentration-time curve at steady state over the dosing interval t
BCMA	b-cell maturation antigen
BICR	blinded independent central review
BLA	biologics license application
BOR	best overall response
BRR	biochemical response rate
BsAb	bispecific antibody
BTD	breakthrough therapy designation
C#D#	cycle # day # (eg, C1D1 = cycle 1 day 1)
CAR-T	chimeric antigen receptor T cell
CD#	cluster of differentiation and number (eg, CD3, CD38, etc.)
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax, 24	maximum observed concentration from time 0 to 24 hours
CMC	chemistry, manufacturing and controls
CO	clinical overview
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance

CRF	case report form
CRR	complete response rate
CRS	cytokine release syndrome
CSR	clinical study report
CT scan	computed tomographic scan
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450
DLT	dose limiting toxicity
DDI	drug-drug interaction
DI	dose intensity
DL	dose level
DOCR	duration of complete response
DOR	duration of response
DP	drug product
DS	drug substance
ECOG	Eastern Cooperative Oncology Group
eDISH	evaluation of the drug-induced serious hepatotoxicity
EMA	European Medicines Agency
EMD	extramedullary disease
EOP1	end of Phase 1
EORTC	European Organisation for Research and Treatment of Cancer
EORTC MY20	European Organisation for Research and Treatment of Cancer, Multiple Myeloma module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer, Quality of Life of Cancer Patients core module
EQ-5D	EuroQol-5 Dimensions
ETASU	elements to assure safe use
EU	European Union
FA	final analysis
Fc	fragment of the immunoglobulin that is encoded by constant (c) genes
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridisation
FLC	free light chain
FMQ	US FDA Medical Query
GCP	good clinical practice
HDAC	histone deacetylase
IA	interim analysis

IAP	integrated analysis plan
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICP	intracranial pressure
Ig#	immunoglobulin (eg, IgM, IgA, etc)
IgG#	immunoglobulin G# (eg, IgG2)
IMiD	immunomodulatory
IMWG	International Myeloma Working Group
IND	investigational new drug
INV	investigator
ISR	injection site reaction
ISS	integrated summary of safety; International Staging System as per context
ITT	intent-to-treat
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
LLN	lower limit of normal
MA	marketing authorisation
MAA	marketing authorisation application
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MHLW	Ministry of Health, Labour and Welfare
MM	multiple myeloma
MOA	mechanism of action
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
N	total number, total sample size
n	number (subgroup or subpopulation)
NAb	neutralising antibodies
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable; not estimable as per context
No.	number
oAECI	other adverse events of clinical interest
OL	open label
OR	overall response

ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s); progressive disease as per context
PET	positron emission tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PMAR	population modelling analysis report
PN	peripheral neuropathy
PopPK	population pharmacokinetics
PR	partial response
PRIME	PRIority MEdicines
PRO	patient-reported outcome
PS	performance status
PT	preferred term
p-value	probability value
Q1; Q3	quartile number
Q#W	every 'x' weeks (e.g., Q2W = every 2 weeks)
QOL	quality of life
QSP	quantitative systems pharmacology
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QW	every week
RD	relative dose
RDI	relative dose intensity
REMS	risk evaluation and mitigation strategy
R-ISS	Revised Multiple Myeloma International Staging System
RP2D	recommended phase 2 dose
RR	relative risk; risk ratio as per context
RRMM	relapse/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sBCMA	soluble BCMA
SBS	summary of biopharmaceutic studies and associated analytical methods
SC	subcutaneous(ly)

SCE	summary of clinical efficacy
SCP	summary of clinical pharmacology studies
sCR	stringent complete response
SCS	summary of clinical safety
SCT	stem cell transplant
SD	stable disease; standard deviation as per context
SEER	surveillance, epidemiology, and end results
SLAMF7	signalling lymphocytic activation molecule family 7
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SOC	System Organ Class
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TMDD	target-mediated drug disposition
TNFRSF17	tumour necrosis factor receptor superfamily member 17
TTR	time to response
ULN	upper limit of normal
US	United States
VGPR	very good partial response

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 4 January 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Elrexfio, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Elrexfio, was designated as an orphan medicinal product EU/3/21/2471 on 19 July 2021 in the following condition: treatment of multiple myeloma.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 27 October 2023. More information on the COMP's review can be found in the orphan withdrawal assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Elrexfio.

The applicant applied for the following indication: treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that elranatamab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0564/2021 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active substance status

The applicant requested the active substance elranatamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Elrexfio was granted eligibility to PRIME on 26 March 2021 in the following indication:
treatment of multiple myeloma.

Eligibility to PRIME was granted at the time in view of the following:

- Despite available treatments, there is still a need for new options for the treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.
- The high-level summary of non-clinical data submitted does not allow evaluation of evidence of anti-tumour activity, but BCMA targeting therapy is known to be effective in the claimed indication.
- The submitted preliminary clinical data offer sufficient evidence of an effective treatment in a heavily pre-treated population.
- The mechanism of action offers an alternative to CAR-T route of activation of T-cells.

Upon granting of eligibility to PRIME, Jan Mueller-Berghaus was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 19 October 2021. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- Quality aspects including the stability plans and the strategy to implement the new drug product process
- Nonclinical development approaches
- Adequacy of the data required to support a conditional marketing authorisation
- Use of minimal residual disease (MRD) as an intermediate efficacy endpoint.
- Strategy to demonstrate significant benefit in the context of orphan maintenance
- The timing of the submission for accelerated assessment

1.7. Scientific advice and protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
25 March 2021	EMA/SA/0000051606	Rune Kjeken and Johanna Lähteenvuo
22 April 2022	EMA/SA/0000082372	Brigitte Schwarzer-Daum and Dieter Deforce
21 July 2022	EMA/SA/0000091448	Dieter Deforce and Sara Galluzzo

The above procedures pertained to the following quality, non-clinical, clinical and significant benefit aspects:

- the analytical comparability strategy to support shelf-life claims for two different drug product presentations;
- the approach of embryo-foetal developmental risk via a non-clinical weight-of-evidence strategy;
- the existence of an unmet medical need in the sought indication and adequacy of study C1071003, to fulfil this need and support a Conditional Marketing Authorisation;
- the approach to contextualise efficacy in the C1071003 trial with real-world datasets, the selected eligibility criteria to compare between populations and the choice of endpoints in the real-world comparator datasets;
- the design elements, including patient population selection, stratification factors, active treatment and comparators, endpoints and associated statistical considerations and patient reported outcome assessment tools for the proposed study C1071005;
- the acceptability of the blinded independent central review efficacy assessment strategy for the development programme and use of multiple sources of the comparator lenalidomide for study C1071005;
- the strategy to demonstrate Significant Benefit at the stage of Marketing Authorisation in the context of the respective orphan medicinal product designation, in particular with regards to the proposed comparative effectiveness plan and the approach against CAR-T therapies;

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Johanna Lähteenvuo

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Nikica Mirošević Skvrce

The appointed CHMP co-rapporteur had no such prominent role in protocol assistance relevant for the indication subject to the present application.

The application was received by the EMA on	4 January 2023
The procedure started on	26 January 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 April 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	2 May 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 April 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 May 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 July 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 September 20233
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 September 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Elrexfio on	12 October 2023
The CHMP adopted a report on similarity of Elrexfio with Darzalex, Imnovid, Farydak, Kyprolis, Ninlaro, Blenrep, Abecma, Carvykti and Talvey on (see Appendix on similarity)	12 October 2023
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	12 October 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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

According to the International Myeloma Working Group (IMWG) criteria (Rajkumar et al. 2011), RRMM is defined as disease that is nonresponsive while on salvage therapy or progresses within 60 days of last therapy. Relapsed and refractory subjects must have had achieved minimal response (MR) or better at some point previously, before then progressing in their disease course.

The course of MM is characterised by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapeutic line. Drug resistance to prior regimens in patients with RRMM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008).

2.1.2. Epidemiology and risk factors

Multiple Myeloma is a rare and incurable plasma cell neoplasm which typically affects adults mostly over 60 years of age. The median age at diagnosis is 65–70 years; MM is very rare in patients younger than 40 years old (2% of cases).

MM accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy (after non-Hodgkin's lymphoma [NHL]) with an estimated incidence in Europe of 4.5-6/100 000/year, with approximately 176.404 new MM cases and 117,077 deaths due to MM anticipated in 2020 worldwide (The Global Cancer Observatory 2020).

MM is characterised by the increased proliferation of malignant monoclonal plasma cells in the bone marrow, with the subsequent bone marrow failure due to replacement of normal bone marrow haematopoiesis, the over-production of monoclonal immunoglobulins (M-protein, either intact immunoglobulins and/or free light chains [FLC]) which could be detected in the serum or urine, and finally the presence of systemic symptoms named as CRAB (hyperCalcemia, Renal impairment, Anaemia and Bone lesions). Increased susceptibility to infections (immunoparesis) and neurological complications are also present (Palumbo 2011).

Based on karyotype, MM is classified as non-hyperdiploid and hyperdiploid, with the latter accounting for 50% to 60% of cases and characterised by trisomies in odd-numbered chromosomes. MM has a heterogeneous progression pathway, with multiple relapses over time, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the evolution of drug-resistance clones [Laubach, 2014].

Drug resistance to prior regimens in patients with relapsed/refractory (RR) MM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008).

2.1.3. Biologic features

B-cell maturation antigen, also known as CD269 and TNFRSF17, is a 20 kilodalton, type III membrane protein that is part of the tumour necrosis receptor superfamily. BCMA is predominantly expressed in B-lineage cells and plays a critical role in B-cell maturation and subsequent differentiation into plasma cells (Tai 2015). B-cell maturation antigen binds 2 ligands that induce B cell proliferation: a proliferation-inducing ligand ([APRIL]; CD256) and B-cell activating factor (BAFF; CD257) (Avery 2003; Darce 2007; Patel 2004). Binding of BCMA monomers to the APRIL trimer triggers activation and phosphorylation of p38MAPK, ELK, and NF-κB through intracellular tumour necrosis factor receptor associated factor molecules leading to pro-survival gene regulation (Bossen 2006; Hsi 2008; Korde 2011). Comparative studies have shown a lack of BCMA in most normal tissues and absence of expression on CD34-positive haematopoietic stem cells (Carpenter 2013; Kimberley 2009). This selective expression and the biological importance for the proliferation and survival of myeloma cells makes BCMA a promising target for the treatment of multiple myeloma. Several BCMA-directed immunotherapies have been developed and four of them are approved in the EU (Belantamab mafodotin, Teclistamab and two CAR-T cell products).

Overall, targeting BCMA in multiple myeloma represents an established approach to improving the treatment of this disease in addition to melphalan, proteasome inhibitors, immunomodulatory drugs and anti-CD38 monoclonal antibodies.

2.1.4. Clinical presentation, diagnosis

Multiple myeloma, a malignant disorder of the plasma cells characterised by uncontrolled and progressive proliferation of a plasma cell clone, and accounts for approximately 10% of haematological malignancies (Rodriguez-Abreu 2007; Rajkumar 2011). The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow haematopoietic precursors and overproduction of monoclonal paraproteins (M-proteins). Characteristic hallmarks of multiple myeloma include osteolytic lesions, anaemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications (Palumbo 2011). Profound intratumoural heterogeneity is observed throughout the disease course but is especially problematic after multiple lines of treatment. The coexistence of different tumour subclones displaying different drug sensitivities contributes to both progression of disease and development of drug resistance (Barlogie 2014).

The criteria for diagnosis of MM as defined by the International Myeloma Working Group (IMWG), requires 10% clonal BM plasma cells or biopsy proven bony or extra-medullary plasmacytoma and evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, or biomarkers of malignancy (60% clonal BM plasma cells or involved/uninvolved serum-free light chain ratio >100 or >1 focal lesion on magnetic resonance imaging studies).

The course of MM is characterised by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy (Moreau, 2017). The treatment of MM has notably progressed with the availability of new drugs and its combinations, such way that survival of patients with newly diagnosed MM has increased from approximately 3 years in the years 1985 to 1998 (Kyle 2003) to 6 to 10 years (Moreau 2015) along the last 15 years. Despite the significant improvement in patients' survival over the past 20 years, only 10%-15% of patients achieve or exceed expected survival compared with the matched general population.

The estimated 5-year survival rate for patients with MM is approximately 54% (Cancer.net 2020). With each successive relapse, symptoms return, quality of life worsens, and the chance and duration of response typically decreases. Therefore, there remains a significant and critical unmet need for new

therapeutic options directed at alternative mechanisms of action that can better control the disease; provide deeper, more sustained responses; and yield better long-term outcomes including maintenance of HRQoL.

Despite advances in therapy, MM remains incurable. Although autologous stem cell transplant (ASCT) has extended survival in newly diagnosed MM, practically all patients eventually relapse, and with each successive relapse, the chance of response and duration of response typically decreases and ultimately the disease becomes refractory and results in cumulative end organ damage (e.g., renal, cytopenias, infections and bone complications).

2.1.5. Management

The treatment landscape for relapsed or refractory multiple myeloma (RRMM) has changed in recent years. Current treatment of MM includes glucocorticoids, chemotherapy, primarily alkylating agents, high dose chemotherapy followed by ASCT, proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies ((mAbs), such as daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat. Common standard regimens include either a PI or an IMiD in combination with dexamethasone with or without a monoclonal antibody such as daratumumab. The triplet combination of bortezomib, lenalidomide, and dexamethasone (VRd) is a standard of Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) treatment guidelines (NCCN 2020 and Moreau 2017). Newer classes of medications including XPO1 inhibitors (selinexor) and antibody drug conjugates targeting BCMA (belantamab mafodotin-blmf) and also CAR-T cell products (Idecaptagene vicleucel, Cilacaptagene autoleucel) have been approved by EMA. The latest was talquetamab, which is a bsAb that targets GPRC5D and CD3.

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities and organ reserve, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e., clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed). Some clinicians switch however treatment even in PR if they expect higher response with alternative treatment. This is to protect organs, especially kidneys.

Despite multiple therapeutic options, MM remains incurable. All patients eventually relapse and become refractory to existing treatments. Median OS in patients who have received at least three prior multiple myeloma lines of therapy and are refractory to both an IMiD and a PI is only 13 months (Kumar 2017). The reported ORR for approved therapies for the population of heavily pre-treated and refractory patients with multiple myeloma, is approximately 30%.

In a chart review, investigators from 14 academic institutions analysed 275 patients to determine the efficacy of subsequent treatments after disease progression on an anti-CD38 monoclonal antibody treatment (Gandhi 2019). This multicentre, retrospective, observational study investigated the natural history and outcomes of patients with multiple myeloma refractory to CD38 monoclonal antibodies (MAMMOTH study). Patients were heavily pre-treated with a median of 4 prior lines of therapy (range: 1-16). Regardless of the particular salvage regimen chosen, the observed efficacy of the next treatment after progression on PI, IMiD, and anti-CD38 monoclonal antibody therapy was dismal.

The median OS for the entire cohort was 8.6 months (95% [CI]: 7.5-9.9), ranging from 5.6 months for penta-refractory patients (refractory to anti-CD38 antibody, 2 PIs, and 2 IMiDs) to 11.2 months for patients not simultaneously refractory to an IMiD and PI. Among patients who received ≥1 subsequent treatment after becoming refractory to anti-CD38 antibody therapy (90% of patients in the study), the response rate averaged 31%, with a median PFS and median OS of 3.4 months and 9.3 months,

respectively. The median OS for patients who received no further treatment was 1.3 months. The results of the MAMMOTH study were derived from real-world data and support the lack of options for patients who had prior exposure to a PI, IMiD, and anti-CD38 monoclonal antibody therapy. Despite new therapeutic achievements with novel mechanisms of action, multiple myeloma remains an incurable disease in which all patients eventually relapse. There remains an unmet medical need for new treatment options beyond the current classes of anti-myeloma therapy.

Chimeric antigen receptor T (CAR-T) cell therapy use modified autologous T cells that are activated in a major histocompatibility complex independent manner upon binding to their target resulting in the lysis of the targeted cells. Immunotherapy using CAR-T technology to target the BCMA receptor has emerged as a highly promising therapy for patients with advanced multiple myeloma who have exhausted available therapies such as PI, IMiD, and CD38 monoclonal antibodies.

Idecaptagene vicleucel (Abecma) is indicated 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 was investigated in the KarMMa study which was an open-label, single-arm, multicentre study that evaluated the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior antimyeloma therapies including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and who were refractory to the last treatment regimen. The ORR in the ITT population was 73.4% (95%CI: 65.8, 81.1), whereas more than half of the responses 53.1% (95%CI: 44.5, 61.8) achieved VGPR or better.

Ciltacaptagene autoleucel (Carvykti) shares the same indication as Abecma. It was investigated in the MMY2001 study which was an open label, single-arm, multicentre, Phase 1b/2 study evaluating the efficacy and safety of CARVYKTI for the treatment of adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or within 12 months after the last regimen. The ORR in the ITT population was 84.1% (95%CI: 76.0, 90.3), whereas more than half of the responses 81.4% achieved VGPR or better.

Teclistamab (Tecvayli) is similar to elranatamab. It shares the MoA as it is also an anti BCMA x CD3 bispecific antibody (bsAb). It has been investigated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multi-centre, Phase 1/2 study (MajesTEC-1). The study included patients who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. ORR was achieved in 63% of patients (95%CI: 55.2, 70.4). VGPR or better has been achieved in 58.8%. Tecvayli is approved under CMA in the indication which is being sought for elranatamab.

More recently talquetamab (Talvey) also received a CMA for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. This is a GPRC5D x CD3 bsAb which was investigated in MonumenTAL-1, a single-arm, open-label, multi-centre, Phase 1/2 study. ORR was reported in 74.1% (66.1, 81.1) and 71.7% (95% CI: 63.7, 78.9) in patients receiving of 0.4 mg/kg weekly and 0.8 mg/kg biweekly respectively.

Belantamab mafodotin (Blenrep) is a humanised IgG1κ monoclonal antibody conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF) that binds to BCMA on myeloma cell surfaces causing cell cycle arrest and inducing antibody-dependent cellular cytotoxicity. The product received a CMA on the basis of the Phase 2, open-label DREAMM-2 study designed to evaluate the efficacy and safety of belantamab mafodotin monotherapy in patients with RRMM who had 4 or more prior lines of treatment, were refractory to a PI, an IMiD, and had failed treatment with an anti-

CD38 antibody. The ORR of DREAMM-2 as assessed by IRC at the time of granting the CMA was 32% (97.5% CI: 20.8, 42.6). As for all CMAs, additional data need to be provided to confirm the safety and efficacy of the product.

Talquetamab (Talvey) is the most recently approved product in this condition, based on MonumenTAL-1 a single-arm, open-label, multicentre study, conducted in patients with relapsed or refractory multiple myeloma. The study included patients who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. ORR was achieved in 74.1% (95% CI: 66.1, 81.1) and 71.7% (95% CI: 63.7, 78.9) of patients in the 0.4 mg/kg QW and 0.8 mg/kg Q2W.

2.2. About the product

Elranatamab (also referred to as PF-06863135 in this report) is a heterodimeric humanised full-length bsAb consisting of a BCMA binding arm and a CD3 binding arm, as well as a modified human IgG2ΔA Fc region. The proposed mechanism of action for elranatamab allows T cells to circumvent the need for the interaction of the T-cell receptor (TCR) and antigen in the context of MHC class I, and instead, directs T cells to myeloma target cells through direct co-engagement of CD3ε expressed on the T cell and BCMA expressed on the myeloma tumour cell surface.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that teclistamab is available on the market, and a positive benefit/risk has been established. While it is agreed that elranatamab addresses the unmet medical need to at least similar extent as teclistamab, elranatamab does not represent major interest from the point of view of public health, and in particular from the viewpoint of therapeutic innovation.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

To confirm results obtained from the pivotal single-arm study (C1071003, also referred to as Study 1003 or MAGNETISMM-3 in this report), the Applicant is conducting an open-label, 3-arm, multicentre, randomised Phase 3 study to evaluate the efficacy and safety of elranatamab monotherapy and elranatamab + daratumumab versus daratumumab + pomalidomide + dexamethasone in participants with RRMM who have received at least 1 prior line of therapy, but not more than 3, including lenalidomide and a PI (MagnetisMM-5 also referred as Study C1071005).

Part 1 of the study has been finalised and the randomised Phase 3 dose (RP3D) of elranatamab in combination has been selected in July 2022. Full enrolment in Phase 3 was expected in August 2023 with IA#2 on PFS 75% events in 2Q 2024 and final PFS analysis in 3Q 2026.

- Unmet medical need will be addressed. To date, 7 drugs were approved globally for the treatment of patients with myeloma who have received at least a PI, an IMiD, and an anti-CD38 mAb. Of these therapies, 4 of the 7 share a mechanism of action directed to BCMA. These 4 BCMA-directed therapies correspond to 3 different BCMA modalities which include belantamab mafodotin (an ADC), idecabtagene vicleucel and ciltacabtagene autoleucel (CAR-T), and teclistamab (BsAb).

Elranatamab efficacy results from C1071003 showed a confirmed ORR by BICR of 61.0% in cohort A patients notably exceeding the ORR of Blenrep, Nexpovio and Pepaxti and similar to that of teclistamab talquetamab, and CAR-T. Elranatamab may offer an alternative treatment to CAR-T considering the following meaningful clinical benefit compared to BCMA CAR-T:

- Ready to use.
- Safety profile of elranatamab seems better compared to CAR-Ts in terms of CRS, ICANS, febrile neutropenia rate, although there are limitations to cross-study safety comparisons

Elranatamab shares with teclistamab the same mechanism of action, potentially addressing the unmet medical need at the same extent (similar efficacy results and similar safety profile).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Based on the positive benefit- risk balance demonstrated in C1071003, immediate availability of elranatamab would provide patients with an important therapeutic option whilst additional data are being generated to confirm safety and efficacy of elranatamab in a randomised Phase 3 study (C1071005).

2.4. Quality aspects

2.4.1. Introduction

Elranatamab, the active substance contained in Elrexfio, is a heterodimeric humanised full-length bispecific IgG2 kappa antibody produced from Chinese hamster ovary (CHO) cell lines with one heavy chain / light chain pair directed against cluster of differentiation 3 (CD3) and one heavy chain / light chain pair directed against B-cell maturation antigen (BCMA). It has diminished Fc effector function.

Elranatamab is provided as a solution for injection for subcutaneous administration in a single-dose vial in two presentations (strength 40 mg/mL): 44 mg of elranatamab in 1.1 mL and 76 mg of elranatamab in 1.9 mL. Elranatamab is formulated with edetate disodium (EDTA), L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

2.4.2. Active Substance

2.4.2.1. General information

Elranatamab is a humanised full-length bispecific IgG2 kappa antibody directed against CD3 and BCMA and therefore acting as T-cell engager directing T cells to myeloma target cells. The resulting 4-chain bispecific antibody is covalently linked via five inter-chain disulfide bonds. It has a diminished Fc effector function. Mutations of aspartic acid (D) to alanine (A) residue at position 259 in anti-BCMA H chain and at position 265 of anti-CD3 H chain were made.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, MA 01810, USA. All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

Description of the manufacturing process and process controls

The commercial manufacturing process, and process controls include a combination of critical process parameters (CPP), non-critical process parameters (non-CPP), critical material attributes (CMA), and in-process tests (IPT). Overall, the manufacturing process has been well defined and sufficient details are provided.

The manufacturing process uses two recombinant CHO cell lines, one that contains the DNA encoding the sequence for anti-BCMA MAb and one that contains the sequence for anti-CD3 MAb, both of which are grown separately in suspension culture using chemically defined, animal-derived component-free media. Cells from each working cell bank (WCB) are thawed, and the cultures progressively expanded.

An elranatamab active substance batch consists of one anti-BCMA MAb and one anti-CD3 MAb production fed-batch bioreactor culture.

Production of anti-CD3 MAb is initiated by thawing cells from the anti-CD3 MAb WCB. According to the manufacturing process description, multiple production fed-batch bioreactor cultures may result from a single thaw of a WCB vial for anti-BCMA MAb and/or a single thaw of a WCB vial for anti-CD3 MAb, depending on the manufacturing campaign duration. The culture is agitated during the batch duration under controlled temperature, dissolved oxygen concentration, and pH conditions.

Anti-CD3 MAb culture expansion and maintenance takes place in seed bioreactors. The cell culture process of the anti-BCMA MAb is comparable to the anti-CD3 MAb process up to the bioreactor stage. The anti-BCMA MAb and anti-CD3 MAb production fed-batch bioreactor cultures are separately harvested and clarified by centrifugation and depth filtration to remove cells and debris followed by a viral inactivation step via detergent addition. After this harvest and detergent virus inactivation step, the anti-BCMA and anti-CD3 MAbs are processed separately through a protein A affinity chromatography step and the eluates are neutralised. The anti-BCMA MAb and anti-CD3 MAb neutralised protein A eluate pools are mixed and the inter-disulfide (HC-HC) bonds between the anti-BCMA MAb and anti-CD3 MAb heavy chains are reduced. Then through oxidation the disulfide bonds reform preferentially between one half of anti-BCMA MAb and one half of anti-CD3 MAb forming the elranatamab bispecific. The reaction mixture is buffer exchanged in an ultrafiltration/diafiltration step before being processed through two additional chromatography steps. Throughout the purification process the material is being processed in one or more cycles.

The product is then processed through a virus retaining filter followed by concentration and buffer exchange in a second ultrafiltration/diafiltration step. At the virus retaining filtration and final active substance filtration reprocessing is potentially possible. Lastly, excipients are added to the product to achieve the final formulation of active substance, followed by final filtration, filling, and freezing.

Control of materials

Information regarding all materials used in the manufacture of elranatamab active substance is presented. Raw materials, filter and membrane materials, chromatography resins and virus retaining filter have been listed together with information on the quality of these materials. Specifications for the non-compendial raw materials and resins used in the manufacture of elranatamab active substance are listed. The raw materials used in the elranatamab active substance manufacturing process are routinely tested, or are accepted based on the Certificate of Analysis from approved suppliers with an identity test. For critical materials, tests and acceptance criteria are provided.

Details of the source and generation of the cell substrates for the anti-CD3 and anti-BCMA antibodies are provided. The host cell line used for production of both antibodies and plasmid maps for the expression vectors are provided. A common two-tiered cell banking system consisting of a master cell bank (MCB) and WCB were individually used for both anti-BCMA and anti-CD3 MAb. MCBs and WCBs

were characterised and tested according to ICH guidelines Q5A, Q5B and Q5D. The identity of the cell line was confirmed to be of hamster origin. Cell banks were tested for viability, identity, purity e.g. mycoplasma, viruses, and microbial contamination following the appropriate Ph. Eur. guidelines. Genotypic and phenotypic characterisation of cell banks is sufficiently described. MCB and WCB were prepared individually for anti-BCMA MAb and anti-CD3 MAb in accordance with ICH Q5D. Protocols for the preparation and testing of new WCBs are provided and found acceptable.

Control of critical steps and intermediates

The process controls include a combination of CPPs, non-CPPs, CMAs, and IPTs. Acceptable ranges for input process controls (CPP, non-CPP and CMA) are stated.

Adequate in-process controls (IPCs) for process steps are defined during manufacture of elranatamab to ensure that process performance and product quality are maintained. Overall, the presented process controls for elranatamab active substance manufacturing is appropriate.

Process validation

The validation of the elranatamab active substance manufacturing process included independent, consecutive thaws of both the anti-BCMA MAb and anti-CD3 MAb WCBs. The genealogy of each of the elranatamab active substance batches from the process validation campaign was provided. Process validation was successful as the results demonstrate consistent and robust manufacture of elranatamab active substance.

Pre-defined acceptance criteria during the upstream process were met. It is noted that for numerous operating parameter during the bioreactor production stage the results indicate "within limits" as the parameter was determined to be within process validation control limits based on continuous on-line data collection from measurement probes and/or the absence of alarms as set by batch record control limits, which, is acceptable.

Regarding the purification process, pre-defined acceptance criteria were met in particular for parameters defined as CPPs. Only few deviations were observed, which have been adequately discussed and either concerned parameters were defined as non-CPPs or resulted in minor adaptions. Overall the results demonstrate that the purification process is robust can be consistently performed.

In-process pool hold times were validated to demonstrate biochemical stability of anti-BCMA MAb, anti-CD3 MAb, and elranatamab over a defined period of time. The validation studies were conducted at small scale under conditions and in containers representative of the full-scale manufacturing process. Each in-process pool was tested for stability using representative commercial scale manufacturing batches, which is acknowledged. The provided data support the proposed hold times from a biochemical perspective. No significant trends can be observed in protein content, monomer/HMMS, fragments, and charged variant composition. The proposed maximum in-process hold times are supported by small scale studies to demonstrate biochemical stability and manufacturing scale in-process pool hold times to demonstrate microbial control. Reprocessing was validated by refiltration of filtered virus retentive filtration (VRF) pool. IPC and release acceptance criteria were met and support one refiltration.

A monitoring programme was initiated to provide assurance that the performance of the chromatography resins in the manufacturing process is within established parameters. Recovery and impurity clearance is maintained over the currently proposed cycle numbers. The monitoring programme will be continued to provide assurance that the resins perform within the expected control ranges for the life of the resin.

The performance of the UF membranes used in the elranatamab manufacturing process indicates no adverse trends over membrane lifetimes. Following a formal risk assessment of all elranatamab

process contact materials, there were no extractables of concern identified. The manufacturing components were classified into categories of lower or higher risk. Higher risk components were further assessed to determine acceptability, including evaluation of extractables study data to identify potential target leachables. There were no extractables of concern identified that would warrant targeted leachable studies. For higher risk components vendor performed extractable studies were examined and total daily intake (TDIs) were calculated for extractables identified in the studies. Extractables with TDIs above 1.5 µg/day TDI (0.1 µg/day for elements) were submitted for a toxicological risk assessment which concluded that all identified extractables pose negligible risk to patients up to their respective TDIs. All components were deemed acceptable for use in the elranatamab manufacturing process.

The impurities considered in the studies addressing the ability of the elranatamab manufacturing process to remove process-related impurities to acceptable safety levels include residual HCPs and nucleic acids (DNA), media derived and purification process-derived Protein A. The media-derived impurities that were evaluated in the process validation studies include a range of size and chemical properties such that these components are representative of other media components. Calculations related to patient safety are based on a 75 kg patient and a worst-case dosing regimen. The listed impurities were tested using direct measurements. The data show that manufacturing process results in low levels of impurities not to be expected to impact patient safety.

The methods used to study other impurities were qualified for their intended use. Descriptions of the assays and summaries of the validation/qualification were provided in the dossier. No concerns regarding the methodology are raised. The presented data demonstrate that the active substance manufacturing process consistently clears process-related impurities to acceptable safety levels. The impurity removal studies are further supported by the levels of impurities measured in the elranatamab active substance.

The presented shipping validation studies cover the shipping process of elranatamab active substance Multiple routes for the global supply chain are covered by providing an assessment of shipping validation data. The shipping qualification test results with duration of the study were summarised in the dossier. The provided information is considered sufficient as transport validation is covered by EU GMP. The qualification strategy considered both thermal and mechanical aspects of shipping in thermal conveyances and included operational qualification (OQ) and performance qualification (PQ) testing. All EVA flexible containers passed visual inspection with no damage noted. The recommended temperature during shelf life for the elranatamab active substance is -20°C in EVA bags. This temperature was not exceeded during the shipping qualification under worst-case shipment conditions. The OQ and PQ demonstrated that the shipping container and configuration provided physical protection to the elranatamab active substance EVA flexible containers while maintaining the shipping temperature.

Manufacturing process development

Principles outlined in ICH Q8-ICH Q11 were applied to the development of the elranatamab manufacturing process. A science- and risk-based approach was used to develop the understanding of elranatamab critical quality attributes (CQAs) and a robust manufacturing process to consistently deliver the desired quality for this product. Scoring of elranatamab active substance and finished product quality attributes was performed taking into consideration the relation to the quality target product profile (QTPP) for elranatamab finished product and the potential clinically relevant impact of the quality attributes on potency, safety/immunogenicity, and pharmacokinetics (PK) of the finished product. Based on prior knowledge certain attributes were not formally scored but were identified as obligatory CQAs. The identification and classification of CQA is considered appropriately justified.

The elranatamab active substance manufacturing process has evolved over the course of development using two main processes at two manufacturing sites and at two different scales. During manufacturing process development, changes were made to both the cell culture and purification processes to accommodate the differences between the two manufacturing facilities and to optimise the process for commercial manufacture. In addition, a WCB was established and implemented. The changes introduced to the manufacturing process during development have been adequately described and sufficient details and rationale for each step has been provided. In clinical studies, active substance batches derived with both processes were used. Process performance was comparable between Process 1 and Process 2. A comparability assessment to support the introduction of Process 2 active substance was conducted by evaluating representative batches of Process 1 and Process 2 active substance. The data show that Process 1 and Process 2 derived material can be considered comparable. Overall, the comparability of the material from Process 1 and Process 2 has been appropriately addressed.

Characterisation

The characterisation of elranatamab included primary structure, posttranslational modifications, charge and size heterogeneity, purity, high order structure, and biological activity. Analysis of the primary structure and posttranslational modifications of elranatamab was accomplished by peptide mapping. LC/MS – subunit analysis provides 100% sequence coverage of the bispecific antibody L and H chains. Molecular Mass determination confirmed the molecular masses, primary structure, posttranslational modifications, and the multi-chain architecture of intact elranatamab, as well as identify the major and minor product isoforms. Elranatamab contains 34 cysteine residues in the four-chain molecule, and these cysteines are predicted to form 17 disulfide bonds. The N-linked glycan profile observed for elranatamab displays N-linked glycans, core-fucosylated, complex-type biantennary structures. Analysis of elranatamab by imaged capillary electrophoresis (iCE) reveals a main peak and additional acidic and basic peaks migrate before and after the main peak. Charge isoform species were isolated using cation exchange high performance liquid chromatography (CEX-HPLC) and the isolated CEX-HPLC fractions were individually analysed using iCE and identified. In addition, the binding of the elranatamab charge isoforms to both of the target antigens, human BCMA and human CD3 was investigated. CEX-HPLC fractions were analysed using both the binding ELISA and the cell-based bioassay. The relative potency of acidic-, main, and basic CEX-HPLC fractions revealed no differences. The level of HMMS in elranatamab was analysed size exclusion HPLC (SE-HPLC) and confirmed only low levels of aggregation and fragmentation. A species is referred to as "anti-BCMA/anti-CD3 bispecific clip impurity was identified but the content seems to be low and does not increase upon thermal stress. Similarly residual homodimer impurities are also low.

For biological activity two binding ELISA toward human BCMA and CD3 were employed and in addition a cell-based gene reporter assay was developed. Biological activity of elranatamab is appropriately demonstrated. Elranatamab is a modified hIgG2Δa bispecific antibody that is designed to have diminished Fc effector function. This was confirmed by investigating binding of elranatamab to Fcg receptors using (SPR) and binding to C1q in an ELISA binding assay. Forced degradation experiments provided an understanding of potential elranatamab degradation pathways and products. Data indicate that elranatamab is a stable antibody showing only moderate degradation under harsh conditions.

Typical process-related impurities originate from the manufacturing process and may be derived from cell substrates (e.g. HCP, host cell DNA), cell culture process reagents, media components. Sufficient clearance of process-related impurities was demonstrated during validation. The purification process has a robust capacity for consistent removal of HCP. However, HCP content will continue to be performed as a routine active substance release test for future batches. Identified product-related impurities in elranatamab include high molecular mass species (HMMS), fragments, anti-CD3 mAb, anti-BCMA MAb and anti-BCMA/anti- CD3 bispecific clip. The content of these impurities is well

controlled during release of the active substance. The characterisation data show consistent low levels of active substance product-related impurities in all studied active substance batches : HMMS, fragments, anti-CD3 MAb, anti-BCMA MAb, and anti-BCMA/anti-CD3 bispecific clip. Observed levels of product-related impurities did not have effect on biological activity of elranatamab. Information provided regarding impurities is considered sufficient.

2.4.2.3. Specification

Specifications

Specifications are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests. Release limits were defined, which are valid until end-of-shelf life.

The approach to setting acceptance criteria for each quality attribute in the elranatamab active substance specification is based on multiple factors including manufacturing experience, batch release data sets, stability data, compendial requirements, and statistical analysis. The potency assay for active substance release is a cell-based gene reporter assay reflecting the mode of action. Elranatamab binds simultaneously to BCMA cell surface receptor of malignant plasma cells and CD3 T-cell co-receptor on the surface of cytotoxic T-cells, to enable targeted T-cell mediated lysis of malignant plasma cells. T-cell activation is initiated by the engagement of the T-cell antigen receptor (TCR/CD3) complex which leads to intracellular signalling events and the activation of the nuclear transcription factor, nuclear factor of activated T cells (NFAT). The active substance (and finished product) release limits for the potency assay are justified based on statistical analysis. The acceptance criteria was tightened during the assessment and the new limits proposed for the specification is considered acceptable. For product-related impurities anti-CD3, anti-BCMA and anti-BCMA/anti-CD3 Bispecific Clip the limits are, among others, justified with safety assessments consisting of human in vitro cytokine release assays with spiked materials. The proposed endotoxin acceptance criterion for elranatamab active substance was tightened and the new limit proposed is acceptable.

Overall, the active substance specifications are considered acceptable.

Analytical procedures

Analytical methods represent state-of-the-art methodologies and are sufficiently detailed. Except the specific potency assay, the methods are widely used on routine basis. Sufficient analytical method descriptions including e.g. a high-level listing of reagents, materials and equipment for the assays, system suitability criteria, and information on data calculation and reporting, have been provided.

Analytical procedures were confirmed to be suitable for their intended use by validation of non-compendial methods according to ICH Q2 (R1.). Compendial analytical procedures were verified, which is acceptable. Compendial analytical procedures are appearance (clarity, colouration), pH, bioburden and endotoxin. Overall, the data indicate the analytical methods are suitable for their intended use. Performance of the HCP ELISA was investigated and from the documentation it can be concluded that the HCP ELISA is process specific. The test for HCP is performed in line with recommendations from Ph. Eur. 2.6.34. The in vitro assay for the detection of viral contaminants has been validated too, as the results drive decision about batch release. In addition to the validation, product-specific qualifications to evaluate method specificity were performed using representative batches of anti-BCMA MAb and anti-CD3 MAb pre-harvest (unprocessed bulk) samples. Spiked medium and test articles were evaluated. No interference was detected.

Batch analysis

Batch data for Process 1 and Process 2 are provided indicating that the acceptance criteria in place at the time of testing were met.

Reference material

A two-tiered system for elranatamab reference material has been prepared to support the commercial product. A Primary reference material (PRM) and working reference material (WRM) was established from a representative production lot and appropriately characterised. The qualification approach for future WRMs is considered acceptable, e.g. the relative potency of the future WRM will be assigned by calibrating against the PRM. Documentation for the qualification, storage conditions and stability programme of the primary and working reference materials was provided.

Container closure system

Elranatamab active substance is stored in EVA bags which is suitable material for freezing and storage of the active substance and widely used for this purpose. Suitability is further supported by extractable and leachable studies. An overview about these studies has been provided. Representative supplier's Certificates of Release/COAs for EVA bags are provided describing the specifications, Ph. Eur., USP and ISO guidelines, and batch testing results, which is considered appropriate. Results to date for elranatamab active substance have not detected any unidentified leachable compounds at or above the safety concern threshold (SCT). The compatibility of the elranatamab active substance with the EVA containers has been adequately evaluated through stability studies. Overall, the selected container closure system for the active substance is considered acceptable with negligible risk to patients.

2.4.2.4. Stability

The applicant provided a sufficient dataset to support the currently claimed elranatamab active substance shelf-life claim of 24 months when stored at the recommended temperature of -20°±5°C in EVA bags.

No significant trends or changes in in any of the investigated parameters were observed. The shelf-life claim is further substantiated by data sets generated under accelerated conditions, thermal cycling conditions and thermal stress. The applicant is reminded that any out-of-specification (OOS) results obtained at the recommended storage condition need to be reported to the Health Authority.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Elranatamab is provided at pH 5.8 with a strength of 40 mg/mL as two vial presentations 44 mg/1.1 mL and 76 mg/1.9 mL. For both presentation there is an overfill to ensures that the respective nominal volumes can be withdrawn. The solution is clear to slightly opalescent, and colourless to pale brownish. The finished product contains 40 mg/mL elranatamab, L-histidine, L-histidine hydrochloride monohydrate, edetate disodium dihydrate, polysorbate 80, sucrose, and water for injection. The finished product is for single dose only.

The excipients except EDTA are widely used in commercial biologic products and were chosen based on experience with formulation of monoclonal antibody finished products. EDTA is used to stabilise the protein and to protect elranatamab during storage. EDTA is used in the formulation of some other approved protein products. There is no manufacturing overage for elranatamab finished product but an overfill is implemented.

The pharmaceutical development of elranatamab finished product utilised principles described in the ICH Q8 Pharmaceutical Development and was based on scientific knowledge and prior experience with similar protein products, as well as risk assessments and development studies. A QTPP was established to form the basis for development of the elranatamab finished product. Process development and characterisation studies represent a combined experience derived both from laboratory scale studies using scale-down models as well as from full-scale studies and manufacturing conducted within the commercial production environment. The finished product control strategy is in general adequately described. The control strategy of the finished product is linked to the active substance. CQAs, non-CQAs, IPC/IPTs, CPPs, non-CPPs and CMAs are defined and justifications are provided. The ranges characterised in development, process validation, and commercial manufacturing studies are set (as acceptable ranges), if studied (mostly are). Final product mixing time (lower end mainly), speed and amount of formulation buffer (which may or may not be added) are critical factors affecting homogeneity and concentration of the final finished product.

Compatibility with product contact materials used in the finished product manufacturing process was performed with elranatamab representative active substance to evaluate any impacts or material contact to protein quality attributes. Results indicate that elranatamab is stable when held in prolonged contact with materials used in the finished product manufacturing process.

Process characterisation studies led to a comprehensive approach to control strategy for the elranatamab manufacturing process by definition and classification of process parameters and the proposed limits/ranges. Further controls in place for the quality attributes are on active substance and finished product release level. Low Endotoxin Recovery (LER) describes the masking or reduction of endotoxin recoverability over a course of time and was assessed. A formal risk assessment was performed at the manufacturing site to evaluate all in-process components with contact surface materials whose liquid contact may introduce leachable compounds into the finished product stream. All elranatamab finished product process contact materials were identified, systematically assigned relative risk values, and categorised with respect to risks for potential extractables and/or leachable compounds by a manufacturing site risk assessment team. With regard to extractables and leachables of process materials with elranatamab contact the only higher risk component that was identified by a risk assessment process is the Celsius Pak bag used for active substance thaw and storage which was thoroughly investigated in detailed extractables and leachables evaluations.

Clinical finished product supplies were initially manufactured at a site on the Liquid Dose Manufacturing (LDM) filling line and then manufactured on the Small-Scale Fill Finish (S2F2) line at another site. Comparability has been demonstrated during clinical development for finished product lots manufactured at both sites on the Liquid Dose Manufacturing (LDM) filling line and on the Small-Scale Fill Finish (S2F2) line.

A comparability study was conducted to demonstrate comparability of lots derived from the commercial process to lots of elranatamab from the other site used in clinical trials. Of note, also the 76 mg vial finished product has also been introduced as clinical material. Based on the analytical release testing results, including quantitative data and overlays of chromatographic or electrophoretic profiles, the finished product lots manufactured at both sites can be considered comparable. The stability comparison demonstrated comparable stability profiles and trends. Forced degradation studies showed similar profiles. Overall, the material manufactured with the commercial process, which also was used in clinical trials, is considered comparable to clinical trial material manufactured at the other site.

The container closure system is a commonly used, consisting of 5 mL type I borosilicate glass vial, a chlorobutyl rubber serum stopper and a flip-off overseal. The glass meets the Ph. Eur. 3.2.1 compendial requirements. The container closure system was investigated in extractable and leachable

studies. For the time being (after 7 months) the potential leachable compounds were below the detection limit. Amounts of residual solvents were well below permissible daily exposure. The applicant committed to notify the authority immediately in case unexpected results/trends will be observed.

Vials are washed and depyrogenated using dry heat sterilisation prior to aseptic filling.

2.4.3.2. Manufacture of the product and process controls

The elranatamab finished product is a single dose sterile solution which contains no preservatives. During manufacturing, the formulated bulk finished product is 0.2µm sterile filtered prior to being aseptically filled. The sterilising filter is tested for integrity as part of the manufacturing process. The elranatamab finished product has been shown to be compatible with commercially available administration components that are common: polypropylene syringes, polycarbonate syringes and stainless steel needles. Once the elranatamab finished product vial is punctured, it is intended to be administered immediately, or within 24 hours when stored between 2 to 30°C.

Description of the process

All sites involved in manufacture, control and storage of the finished product operate in accordance with EU GMP.

The target finished product batch size varies between a minimum and maximum volume for each of the finished product presentations. The manufacturing process consists of preparation and filtration of formulation buffer, thawing (including a validated alternative process without agitation and longer thawing time), pooling and optional dilution of the active substance, mixing of bulk finished product, pre-filtration for bioburden reduction, sterile filtration, aseptic filling, stoppering and capping, visual inspection, labelling and packing. In case batches are split (to create a 44 mg presentation), line clearance, aseptic filling and stoppering and capping will take place. A split-batch process is described. It is indicated that one or more active substance lots may be used to achieve the finished product target batch size. The active substance in EVA bags is thawed using controlled thaw equipment or at controlled room temperature between 15-25°C. Thawed active substance may be refrozen in EVA bags a single time using controlled freezing equipment and then stored at frozen condition. Process parameters, their classification and acceptance ranges (control limits) are provided. All process parameters are categorised as non-CPP except for the aseptic filling step. Fill weight setting for both presentations are defined as CPP. Output process controls (IPCs) with their respective acceptable ranges/control limits are provided and considered sufficient to ensure product quality.

The holding times are validated and can be used in case of technical issues but should not be part of the usual manufacturing process. Critical steps are considered protein concentration at active substance pooling, pH and osmolality of the formulation buffer, dilution of pooled active substance - in case needed, sterile filtration and aseptic filling. In-process controls and test methods are defined and limits are set. These are agreed.

Process Validation

The validation includes nine process performance qualification (PPQ) lots manufactured in two elranatamab finished product process validation campaigns. PPQ lots were manufactured at commercial scale to validate the active substance thaw, formulation of bulk finished product, sterile filtration, aseptic filling, and inspection of the filled vials. The applicant indicates that active substance thaw in EVA bags using controlled freeze/thaw equipment and at controlled room temperature was validated. The sterile filtration was performed using sterilising grade filters and established process parameters. The filter pressure was measured throughout the sterile filtration process to evaluate the filling process, and the maximum pressure is reported. Regarding the aseptic filling process results for

the in-process fill weight checks for each validation lot are presented and the process capability analysis indicates that the that the process is robust and able to meet the intended specifications. Stoppered vials were transferred to the capper where they were capped with flip-off aluminum crimp seals under laminar airflow. 100% inspection of the process validation elranatamab finished product lots were performed, followed by Acceptable Quality Level (AQL) sampling of the inspected vials. All process validation lots met the 100% inspection and the AQL acceptance criteria.

During bioburden reduction filtration (pre-filtration) or storage, in the event of a technical issue that compromises the integrity of the system, the finished product could be re-filtered into a holding vessel using a new bioburden reduction filter. Release testing confirms that a single re-filtration does not impact finished product quality and is an acceptable reprocessing step. Media fills are performed in accordance with aseptic processing guidelines and are performed semi-annually or as required as part of routine requalification of the facility. Overall, the validation has demonstrated control, effectiveness, and consistency of the finished product manufacturing process. All final finished product testing met the proposed commercial specifications. The selected shipping methods consist of active temperature-controlled vehicles (TCVs), active temperature-controlled compressor-driven unit load devices (ULDs), and passive thermal container. The temperature control units are designed to maintain the contents within the recommended storage temperature range of 2 to 8°C during transit with allowable limits range of 0 to 30°C justified by the stability data. Adequate results on thermal cycling study are presented in the stability section of the dossier. Transport arrangements are relevant and have been justified and/or validated.

Overall, the finished product manufacturing process is considered validated.

Control of excipients

All the excipients are widely used and of Ph. Eur quality. Analytical methods are Ph. Eur methods, and therefore need no validation nor additional justification. TSE/BSE certificates are provided - no human or animal origin excipients are used. No novel excipients are used in the elranatamab finished product.

2.4.3.3. Product specification

Specifications

Specifications are set in accordance with ICH Q6B principles and cover all relevant characteristics of elranatamab finished product. A comprehensive test panel for elranatamab finished product includes tests for identity, purity and impurities, potency and other general tests. Method references to in house methods and Ph. Eur. monographs/chapters are included where applicable. Justification for specifications is provided (statistical tolerances are included). It is noteworthy that stability conditions are limited to long-term conditions at 5 ± 3°C, and therefore, accelerated stability results can be considered as confirmatory.

The approach to setting acceptance criteria for each quality attribute in the elranatamab finished product specification included manufacturing experience and knowledge of process capability and consistency, experience with the analytical procedures and knowledge of the method capabilities and dataset consisting of analytical test results.

The charge heterogeneity of the elranatamab finished product is monitored at release and for stability assessment. The release data and the stability data were subjected to tolerance interval statistical analyses. The three components of the charge heterogeneity quality attribute are all one sided: acidic species (upper), main species (lower) and basic species (upper). The acceptance criteria for endotoxin was defined considering the dose given to the patients, which, in general, is acceptable. As correctly indicated by the applicant the endotoxin test results for elranatamab finished product at release were

consistently below the limit of quantitation indicating the potent capability of the manufacturing process to consistently minimise the introduction of endotoxin. Container closure integrity (CCIT) is a pass/fail test used during stability studies. The test procedure relies on the assessment of the integrity of the vial container closure system by the exclusion of dye while under vacuum. All testing carried out to date on clinical and process validation lots resulted in "pass", in which no dye ingress into the vial was evident under the appropriate test conditions.

Analytical procedures

Analytical procedures common to finished product and active substance are described and discussed in the active substance section. The analytical procedures performed on finished product only are conducted according to Ph. Eur. except the determination of polysorbate 80 and container closure integrity. Polysorbate 80 is measured by mixed mode HPLC with evaporative light scattering detection. For polysorbate 80 determination, a calibration curve is established from the measured peak areas of the polysorbate 80 calibration standards. Container closure integrity is not performed at release but only performed annually on stability. For release elranatamab finished product is tested for sterility.

Analytical procedures were confirmed suitable for their intended use by assessing all relevant validation elements described in (ICH) Q2 (R1) Validation of Analytical Procedures: Text and Methodology. Compendial analytical procedures were verified. The non-compendial analytical procedures that are specific to finished product include polysorbate 80 concentration and container closure integrity. The procedures were validated and confirmed to be suitable for their intended use.

Batch analysis

Elranatamab finished product lot data are provided. Data presented were evaluated against the acceptance criteria at the time of release which were met for all batches.

Reference material

The reference standard used for analysis of finished product is the same as that used for active substance.

Characterisation of impurities

No additional impurities are introduced by the finished product manufacturing process. An elemental impurities risk assessment was performed in accordance with ICH Q3D and all identified elements are found to be below the control threshold. With the exception of trace levels of essential elements that are added to cell culture media in the form of soluble inorganic salts, elements are not used as catalysts or reagents in the elranatamab finished product manufacturing process. Thus, the method accuracy assessment was limited to the Class 1, 2a, and Class 3 elements with permitted daily exposures (PDEs) < 500 µg/day (Cu, Sb, Li). All elemental impurities measured as TDI were detected clearly below Quantitation Limits.

Nitrosamine risk assessment is provided and no risk is detected. The applicant has conducted a risk assessment for the elranatamab active substance, finished product and finished product packaging for the potential presence of N-nitrosamines identifying no potential risk factors for nitrosamine formation. The assessment identified no risk for small molecule nitrosamine (cohort of concern) formation. Additionally, from a toxicological perspective, there is no risk of the elranatamab molecule itself forming a nitrosamine. No risk of N-nitrosamines introduced from incoming materials have been identified. No nitrosating agents are used as reagents during the manufacturing of elranatamab active substance including the excipients. There is no pathway to the formation of a nitrosamine. Therefore, no risks have been identified from either the materials used or the excipients of the finished product

manufacturing process. Regarding the container closure system, neither the glass vial nor the stopper are at risk of nitrosamine presence.

Container closure system

The primary packaging components and materials of construction for the container closure system consist of a Type I borosilicate glass vial and chlorobutyl rubber vial stopper. The container closure system is a commonly used container closure system consisting of 5 mL type I borosilicate glass vial, a chlorobutyl rubber serum stopper and a flip-off overseal. The glass meets the Ph. Eur. 3.2.1 compendial requirements. The container closure system part in contact with the finished product, namely the elastomeric closure material, was investigated in extractable and leachable studies. For the time being (after 7 months) the potential leachable compounds were below the detection limit. Amounts of residual solvents were well below permissible daily exposure.

2.4.3.4. Stability of the product

An elranatamab finished product shelf life of 18 months when stored at the recommended temperature of 5 ± 3°C for the 76 mg/1.9 mL presentation and the 44 mg/1.1 mL presentation was initially proposed based on primary stability data, supportive data and comparability. In accordance with ICH Guideline ICH Q5C it would be acceptable to claim a shelf life of 24 months based on real time stability data for the primary stability lots. Supportive data for both presentations are provided. Additional updated stability data form all ongoing studies were provided during the review period and the shelf life to be granted will be based on real time/real condition data obtained for the primary stability lots if also supported by data from the supportive studies. Based on available 24 months real-time data, a shelf-life of 24 months when stored at 5 ± 3°C storage in the outer carton to protected from light is approvable.

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C. From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

2.4.3.5. Adventitious agents

The general strategy of viral safety of the elranatamab manufacturing process follows the requirements of ICH Q5A. This includes the selection of raw materials devoid of animal or human origin, the testing of the cell banks and the bioreactor harvest for a suitable panel of viruses, the design of the purification process to include two dedicated virus inactivation/removal steps and the validation of selected steps of the manufacturing process to reduce a broad panel of viruses including retrovirus-like particles, a contaminant present in the cell line.

With regard to TSE, the manufacturing process of elranatamab was shown to be in compliance with the TSE guideline EMA/410/01 rev3, because of the avoidance of any material of animal or human origin except the production cell line. CHO cells are hamster-derived and as such not derived from a TSE-relevant species. No human and animal origin material are used in elranatamab manufacture, cell bank preparation and cell line development, except the two CHO-derived production cell lines.

The anti-BCMA and anti-CD3 cell banks have been tested sufficiently for endogenous and adventitious viruses. In addition, the host cell bank was also comprehensively tested including assays for the detection of bovine and porcine viruses The testing panel and strategy is in line with ICH Q5A requirements. No viruses have been found in all tested cell banks (host cell bank, MCBs, WCBs, LIVCA cells) with the exception of A-type and C-type retrovirus-like particles which is acceptable, because

CHO cells are known to produce such particles and the elranatamab manufacturing process provides sufficient capacity to remove / inactivate enveloped viruses. Therefore, there is no concern for the use of the anti-BCMA and anti-CD3 cell bank in the manufacture of elranatamab. The testing strategy of future WCBs is also described and the same tests and acceptance criteria that as has been done on the current WCBs will be performed. This strategy is acceptable.

The unprocessed bulk harvests from both cell banks (anti-BCMA and anti-CD3) are routinely tested for adventitious viruses in accordance with ICH Q5A. It is appreciated that an assay for specific and sensitive detection of minute virus of mice (MVM) is included, because MVM has been found to be a contaminant in bio-fermenters in the past for other biotechnological products and cannot be well detected by the in vitro assay for adventitious viruses due to lower sensitivity of the assay. Several bulk harvests have further been investigated for the amount of retrovirus-like particles to enable a calculation of residual such particles in the final finished product.

The steps in the manufacturing process that have been validated for virus reduction have been described in sufficient detail. Reprocessing is not part of the manufacturing process steps that are involved in virus reduction with the exception of the VRF step This strategy is acceptable The AEX and VRF step were performed in down-scaled experimental runs. Relevant parameters of the down scale have been shown in the IMPD and the down scaling has been performed adequately.

Data on down-scale qualification demonstrate a proper downscaling for the AEX and virus filtration step as shown by MAb quality and impurity data. Suitable controls have been included in the validation studies Non-cytotoxic and non-interfering materials were spiked with the model viruses. Xenotropic murine leukaemia virus (X-MuLV), MVM and reovirus type 3 (Reo 3) were used as model viruses. The choice of viruses is acceptable, because they are either specific model virus (X-MuLV for retrovirus-like particles from the CHO cells) or unspecific (MVM and Reo 3) with different physicochemical properties and resistance to physicochemical agents. Viral clearance studies were also done with PrV (Pseudorabies virus, enveloped DNA virus). The AEX and virus retentive filtration step were validated. Process intermediates used in the down scale studies are obtained from representative manufacturing-scale batches from non-clinical toxicology and commercial scale clinical campaigns.

In summary, the provided justification is deemed sufficient. The retrovirus-like particle (RVLP) load in the elranatamab finished product has been calculated. This safety factor exceeds the expected 6 log10 margin and is thus acceptable. Furthermore, the overall clearance for all three model viruses is considered sufficient.

Overall, adventitious agents safety is considered sufficiently assured.

2.4.4. Discussion on the chemical, pharmaceutical and biological aspects

The dossier presented in support of the marketing authorisation application (MAA) for Elrexfio is of acceptable quality. No major objection was identified during the review. The other concerns were adequately addressed.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Elrexfio is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the MAA for Elrexfio is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

The binding kinetics and affinities of elranatamab were determined for human, cynomolgus monkey, rat, and mouse BCMA, human and cynomolgus monkey CD3δε, human and cynomolgus monkey FcRn, and a panel of human FcγRs. In addition, binding of elranatamab to human BCMA-expressing CHO cells, human myeloma cell lines, and human, cynomolgus monkey, mouse, and rat CD3+ T cells was measured. *In vivo* pharmacology of elranatamab to redirect human T cells against tumour cells was also evaluated.

The nonclinical PK strategy supported the nonclinical safety evaluation of elranatamab. The PK of elranatamab was characterised in cynomolgus monkeys following single IV dosing of elranatamab. Validated assays were used to support the TK and ADA evaluations in the GLP repeat-dose SC and IV toxicity studies in cynomolgus monkeys. Since elranatamab is a biotechnology-derived pharmaceutical developed with the intent to treat multiple myeloma, the nonclinical safety evaluation was designed in accordance with ICH S6(R1) and ICH S9 guidelines. The evaluation includes exploratory and pivotal toxicity studies up to 3 months in duration in cynomolgus monkeys, and tissue cross-reactivity studies in monkey and human tissues.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro binding studies

Binding affinity by surface plasmon resonance and biolayer interferometry [021407]

The binding affinity of elranatamab to human, cynomolgus, mouse and rat BCMA and to human and cynomolgus CD3εδ was determined by surface plasmon resonance (SPR) (Table 1. Binding affinity to human and cynomolgus FcRn (Table 2) by SPR. No binding of elranatamab to a range of human Fcγ receptors was detected (at elranatamab concentrations up to 1 µM for FcγRI and up to 5 µM for FcγR II and III, data not shown).

In addition, binding to N-terminal CD3ε peptides was measured by biolayer interferometry; elranatamab showed no binding to N-terminal mouse and rat CD3ε peptides at 1 µM (data not shown).

Table 1.Summary of key binding properties of elranatamab against human, monkey, mouse and rat BCMA by SPR at 37°C

Antibody	Antigen	k_a x 10^6 $M^{-1}s^{-1}$ (SD)	k_d x $10^{-3}s^{-1}$ (SD)	K_D in nM (SD)
PF-06863135	Human BCMA-Fc	5.3 (0.51)	0.20 (0.035)	0.038 (0.0075)
PF-06863135	Monkey BCMA-Fc	4.0 (0.26)	0.23 (0.037)	0.057 (0.0099)
PF-06863135	Mouse BCMA-Fc	2.9 (0.13)	4.3 (0.26)	1.5 (0.11)
PF-06863135	Rat BCMA-Fc	1.6 (0.038)	8.4 (0.30)	5.4 (0.23)
Kinetics and Affinities of PF-06863135 Against Human and Monkey CD3 εδ by SPR at 37°C[a]				
Antibody	**Antigen**	**k_a x 10^5 $M^{-1}s^{-1}$ (SD)**	**k_d x $10^{-3}s^{-1}$ (SD)**	**K_D in nM (SD)**
PF-06863135	Human CD3δε	18 (0.12)	31 (0.32)	17 (0.21)
PF-06863135	Monkey CD3δε	22 (2.4)	30 (1.2)	14 (1.6)

Reported KD values are the ratio of the means of the kinetic rate constants, KD = kd/ka.
N = 4 for human BCMA and monkey BCMA and N = 3 for moue BCMA, rat BCMA, human CD3εδ, and monkey CD3εδ. The standard deviations of the replicate experiments are shown in parentheses.

Table 2. Binding affinity of elranatamab to FcRn (top panel) by SPR at 37°C

Antigen	Sample	K_D (SD)
hFcRn	PF-06863135	800 nM (25)
	Ab19_hIgG2ΔA-D265A	800 nM (38)
cyFcRn	PF-06863135	400 nM (62)
	Ab19_hIgG2ΔA-D265A	700 nM (47)

Reported KD values are the ratio of the means of the kinetic rate constants, KD = kd/ka; N=3 for each receptor

Binding of elranatamab to cell-surface expressed BCMA and CD3 by flow cytometry [012102]

Binding of elranatamab to a panel of (luciferase-transduced) human myeloma cell lines was evaluated by flow cytometry. Using an anti-BCMA control antibody, the number of BCMA receptors per cell was determined. A broad range of BCMA receptors per cell (1,960 to 16,291) was detected across the different myeloma cell lines. Binding by elranatamab to these cell lines was then assessed by flow cytometry, and saturation binding was demonstrated at elranatamab concentrations ranging from 0.02 to 0.1 µM. Levels of elranatamab binding (mean fluorescence intensity) correlated with relative cell surface BCMA expression (data not shown).

In addition, binding of elranatamab to CD3 on purified T cells from human, cynomolgus, mouse and rat was evaluated by flow cytometry. Binding of elranatamab was evaluated for the CD8+ T cell subpopulation. Elranatamab bound to human and cynomolgus CD3+/CD8+ T cells in a dose-dependent manner (at 0.003 to 0.3 µM) but not to mouse and rat T cells (data not shown).

In vitro functional studies

Blockade of the BCMA/ligand interaction by elranatamab [021407]

BCMA binds 2 biological ligands, B cell activation factor (BAFF) and a proliferation-inducing ligand (APRIL). Blockade of the BCMA/ligand interaction by elranatamab was evaluated by biolayer interferometry. When human BCMA was captured by elranatamab, no binding of human APRIL or human BAFF to BCMA was detectable. This indicates that elranatamab blocks the interaction of BCMA with its ligands.

Elranatamab-induced cytotoxic activity and T cell activation [012102]

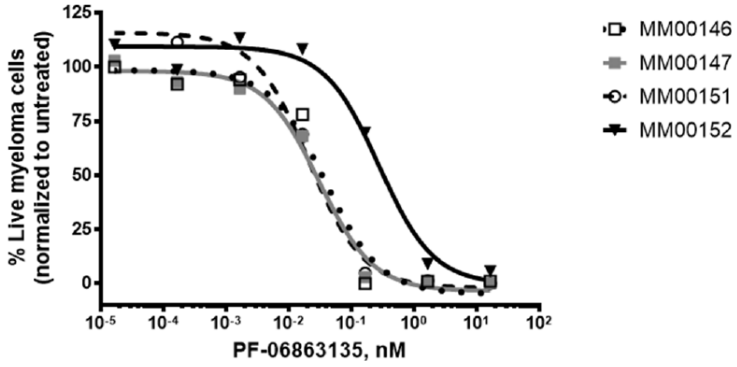
Elranatamab-mediated cell killing was assessed in a Cytotoxic T lymphocyte (CTL) assay. To demonstrate that cytotoxic activity of elranatamab is BCMA-dependent, CD3+ human T cells were incubated with BCMA-positive and negative CHO cells together with increasing concentrations of elranatamab. Target cell viability was measured after 48 hours and a half-maximal effective concentration (EC50) of activity was calculated (N = 2). Elranatamab demonstrated potent killing of the BCMA+ cell line (EC50 = 1.23 pM) but did not show detectable activity against the parental CHO cell line.

To measure cytotoxic activity of elranatamab against myeloma cells that express endogenous BCMA, human CD3+ T cells from 3 separate donors were incubated with a panel of myeloma cell lines in the presence of increasing concentrations of elranatamab. Myeloma cell viability was measured after 48 hours, and the EC50 for each myeloma cell line was determined. Elranatamab induced cytotoxicity against all multiple myeloma cell lines tested, with average EC50 values ranging from 2.1 to 748.2 pM. By linear regression analysis, there appeared to be a correlation between lower EC50 and increased binding of anti-BCMA mAb to the myeloma cell surface (although not statistically significant).

During the cytotoxicity assays, elranatamab-dependent T cell activation was evaluated, based on expression of CD69 and CD25. Both CD69 and CD25 were upregulated in CD8+ human T cells from 3 separate donors, with average EC50 values ranging from 2.8 to 43.2 pM for CD69 and from 9.4 to 115.3 pM for CD25. In addition, cytokine release (TNF-α, IFN-γ, IL-2, IL-6, IL-8 and IL-10) was determined in these assays as a measure of T cell activation. Dose-dependent elranatamab-induced cytokine production was observed (data not shown).

In addition, elranatamab-induced cytotoxic activity was assessed using T cells and myeloma cells from relapsed/refractory or progressive disease patients (from bone marrow aspirates). The number of myeloma target cells (CD38+/CD138+) and effector T cells (CD3+) in the bone marrow samples was determined by flow cytometry. Patient bone marrow cells were incubated with increasing concentrations of elranatamab; cell viability was determined after 5-7 days of cultures and the EC50 for each patient sample was determined. Elranatamab induced cytotoxicity in all patient samples with EC50 values ranging from 20.8 to 276.3 pM Figure 1).

Figure 1. Elranatamab-mediated cytotoxic activity with patient T and myeloma cells



Patient	EC50(pM)	E:T
MM00146	38.9	1:1
MM00147	30.52	2:1
MM00151	20.8	3:1
MM00152	276.3	1:2

Killing of primary myeloma cells in bone marrow aspirates ex vivo induced by elranatamab in the presence of autologous T cells. EC50 value and effector (T cell) to target (myeloma cell) ratio for each patient sample is listed. EC50 = Half maximal effective concentration; E:T = Effector to target ratio.

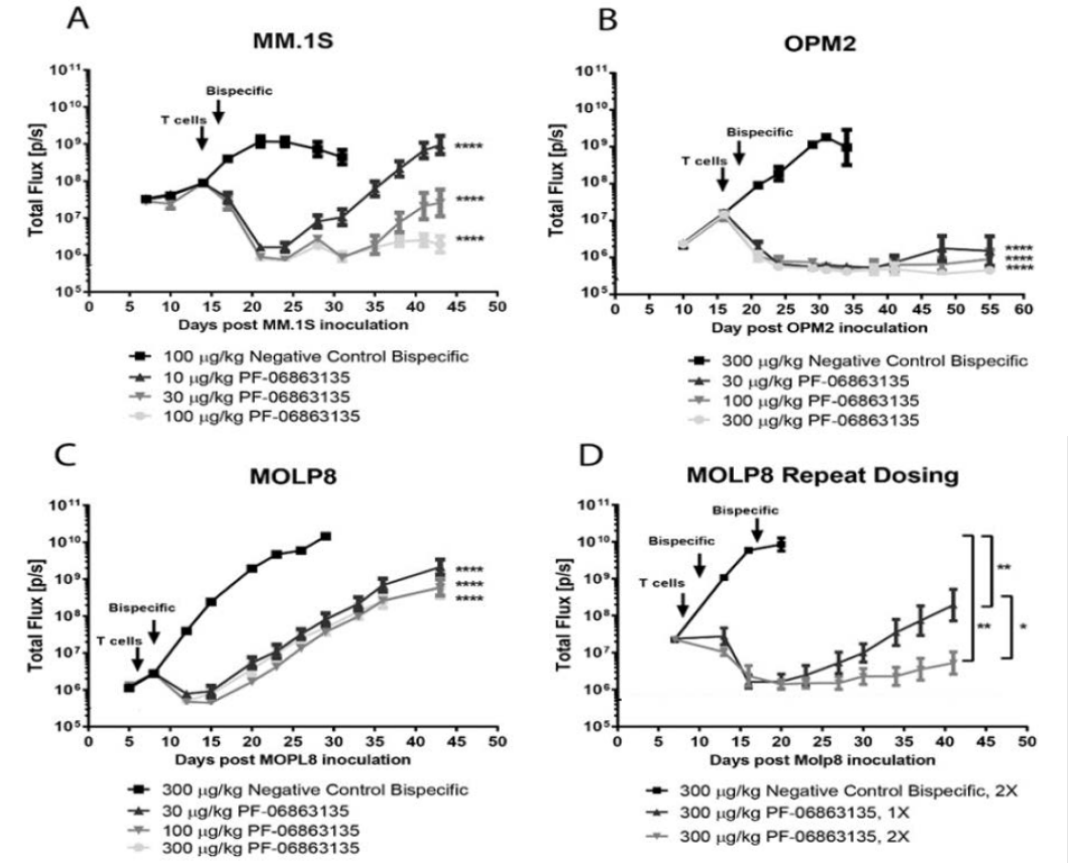
In vivo studies

Pharmacodynamic activity of elranatamab single agent in xenograft tumour models [013801]

The *in vivo* anti-tumour activity of elranatamab when used as monotherapy was evaluated in xenograft models of multiple myeloma. To this end, female NOD.Cg-Prkdc^{scid} IL2rg^{tm1Wjl}/SzJ (NSG) mice were inoculated IV with myeloma cells expressing different levels of BCMA (MM.1S, BCMA high; OPM2, BCMA mid; or MOLP8, BCMA low) and engineered to express luciferase. Upon tumour establishment, animals were administered *in vitro*-expanded human T cells and two days later a single IV dose of elranatamab or negative control bispecific mAb; animals in the MOLP8 study were administered a second dose of elranatamab or control mAb one week after the initial dose. Tumour growth was monitored via imaging measurements collected twice weekly. The statistical study analysis endpoint was reached when the first animal of the control group exhibited end-stage disease at which point the animal was sacrificed as per protocol.

In all 3 myeloma models (see Figure 2), a single IV dose of elranatamab (at all dose levels tested, ranging from 10 to 300 µg/kg) resulted in initial tumour regression, which was in some cases followed by tumour outgrowth. In all experiments, the negative control bispecific Ab did not mediate tumour growth inhibition.

Figure 2 . Elranatamab single agent activity in established myeloma models with engrafted human T cells



In vivo efficacy of elranatamab (PF-06863135) in 3 established orthotopic myeloma xenograft tumour models. Plot depicts mean logarithmic luminescence (± SEM). N = 10 animals/group for MM.1S and MOLP8 models. N = 7 animals/group for the OPM2 model. Statistics represent RMANOVA with Dunnett's post-hoc test, all groups were

*compared to negative control (**** P < 0.001, **P <0.01), and Wilcoxon signed-rank test, single dose compared to double dose (*P = 0.0117).*

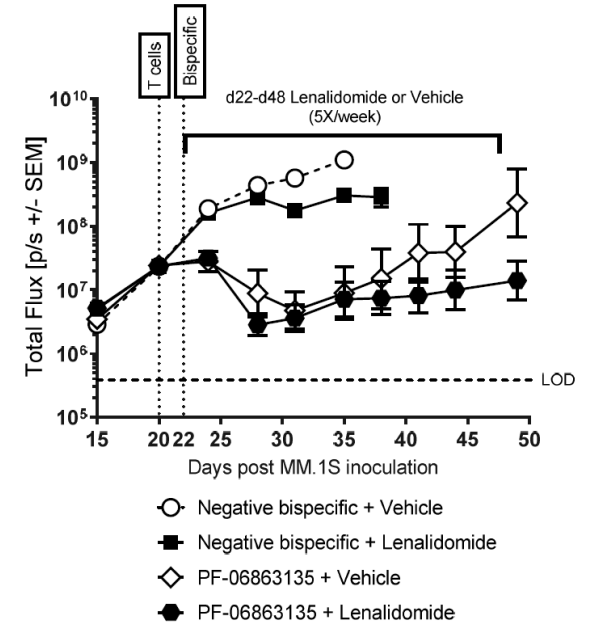
In vivo anti-tumour activity of elranatamab in combination with lenalidomide [093404]

The combined effect of elranatamab and lenalidomide in controlling tumour growth was evaluated in the MM.1S and MOLP8 xenograft models of human myeloma with adoptively transferred human T cells.

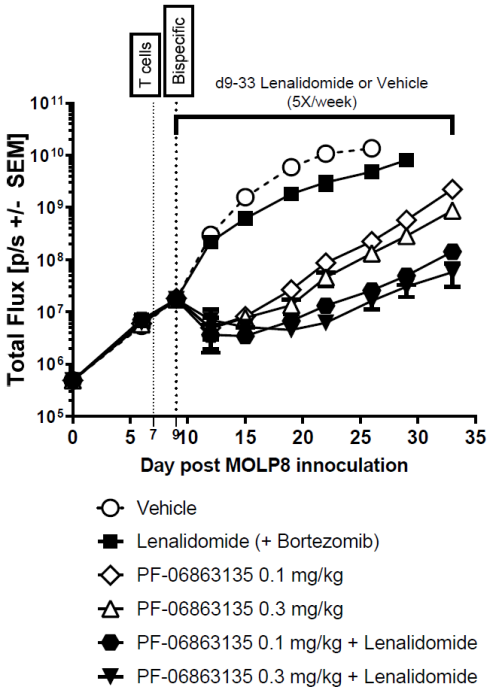
Female NSG mice were inoculated IV with myeloma cells (MM.1S, BCMA high; MOLP8, BCMA low) engineered to express luciferase. Upon tumour establishment, animals were administered in vitro-expanded human T cells and treatment was initiated two days later. In the MM.1S model, animals were administered a single IV dose of elranatamab (10 µg/kg) or negative control bispecific mAb (7 µg/kg), lenalidomide was dosed PO at 15 mg/kg and 5x/week until Day 48 of the study. In the MOLP8 tumour model, animals were administered a single IV dose of elranatamab at either 0.1 or 0.3 mg/kg, lenalidomide was dosed PO at 50 mg/kg and 5x/week thereafter until Day 33 of the study; the proteasome-inhibitor bortezomib was dosed at 1 mg/kg IP, 2x/week. In both myeloma models, tumour growth was monitored via imaging measurements collected twice weekly. Animals were euthanised upon 20% loss of initial body weight, or appearance of distress such as general inactivity, hunched posture, failure to groom, or hindleg paralysis. The study was terminated at Day 49 (MM.1S) or Day 33 (MOLP8) after tumour inoculation. Results are shown in Figure 3.

Figure 3. Elranatamab activity in combination with lenalidomide in established myeloma models with engrafted human T cells

A. MM.1S



B. MOLP8



***A**. Pre-activated and expanded T cells were administered on Day 20 after MM.1S-Luc tumour cell injection IV. Single dose elranatamab (PF-06863135) (10 ug/kg) or negative bispecific (7 µg/kg) was administered IV on Day 22 after tumour cell inoculation. Lenalidomide was administered at 15 mg/kg PO 5x/week starting on Day 22 after tumour cell injection. N = 9 to 10 animals per group. Horizontal dashed line represents limit of detection.*
***B**. Pre-activated and expanded T cells were administered on Day 7 after MOLP8-luc tumour cell injection IV. Single dose elranatamab (PF-06863135) (0.1 or 0.3 mg/kg) was administered IV on Day 9 after tumour cell injection. Lenalidomide was administered at 50 mg/kg PO 5x/week and bortezomib was administered at 1 mg/kg IP 2x/week starting on Day 9 after tumour injection. N = 6 to 7 animals per group.*

Tumour cell bioluminescence captured as Total Flux serves as a measure of tumour burden and was measured 2x a week. Plot depicts mean logarithmic luminescence (p/s ± SEM).

In vivo anti-tumour activity of elranatamab in combination with the gamma-secretase inhibitor nirogacestat [015756]

Cell surface expression of BCMA is subject to regulation by gamma-secretase, which can cleave off the extracellular portion of BCMA and create a pool of soluble BCMA that can act as decoy receptor [Laurent et al. 2015]. Thus, gamma secretase can reduce BCMA expression on multiple myeloma cells, and thereby reduce the ability of BCMA-targeting therapies to bind and induce killing of MM cells. Therapeutic use of a gamma-secretase inhibitor (GSI) which can reduce cleavage of BCMA from MM cells may increase the efficacy of BCMA-targeting therapies.

Nirogacestat (PF-03084014) is a small molecule, reversible and non-competitive GSI that was initially developed for the treatment of Alzheimer's disease. It has also been explored as both a standalone and combination agent for the treatment of certain cancers that rely on gamma-secretase activity to activate Notch signalling. The present study evaluated the effect of different doses of nirogacestat either alone or in combination with a suboptimal dose of elranatamab in a MOLP8 orthotopic xenograft model in NSG MHC I/II double knockout mice engrafted with human PBMCs.

NSG MHCI/II double knock-out mice were inoculated IV with MOLP8 myeloma cells engineered to express luciferase (Day 0). Upon tumour establishment, animals were administered human PBMC (Day 6). Mice were administered elranatamab (0.1 mg/kg) or control bispecific mAb SC Q1W for 3 weeks (on Days 14, 21 and 28). Nirogacestat was administered PO at 15, 50 or 150 mg/kg BID beginning on Day 13 and continuing through to termination on Day 34. Tumour growth was monitored by bioluminescence imaging, 2x per week starting on Day 7 after tumour cell injection. Animals were euthanised upon 20% loss of initial body weight, or appearance of distress such as general inactivity, hunched posture, failure to groom, or hindleg paralysis. A final imaging session was performed on all remaining live mice on Day 34, after which the study was terminated.

The effect of nirogacestat (with a control antibody) on tumour progression was minimal at any of the tested dose levels. The high dose (150 mg/kg BID) approached the MTD for nirogacestat. Elranatamab alone at 0.1 mg/kg produced a tumour growth inhibitory effect (87% on day 18 and 93% on Day 21) which was statistically significant. When combining elranatamab with nirogacestat tumour growth inhibition on Day 21 was significantly enhanced compared to elranatamab alone. This enhanced combination effect was observed at all 3 doses levels of nirogacestat, with maximal efficacy obtained by the 50 mg/kg dose.

With regards to survival, elranatamab alone did not achieve a survival benefit at the time of study termination. Treatment with 15 or 50 mg/kg nirogacestat alone failed to provide any survival benefit over vehicle/control bsAb; while the combination with elranatamab led to significantly enhanced survival at Day 34 compared to control groups. Treatment with 150 mg/kg nirogacestat alone did significantly delay mortality ($p < 0.05$), however, the combination of elranatamab and nirogacestat at 150 mg/kg did not provide a survival benefit over the control treatment group. Several animals in this combination group had > 20% body weight loss and had to be removed from the study.

2.5.2.2. Secondary pharmacodynamic studies

No specific secondary pharmacology studies were conducted with elranatamab.

2.5.2.3. Safety pharmacology programme

No stand-alone safety pharmacology studies were conducted with elranatamab. However, cardiovascular assessment was made as part of the pivotal toxicity studies in Cynomolgus monkeys (see Toxicology section of this report

2.5.2.4. Pharmacodynamic drug interactions

Anti-tumour activity of elranatamab in combination with an IMiD or a gamma-secretase-inhibitor was evaluated in myeloma xenograft models (See section on *in vivo* studies)

2.5.3. Pharmacokinetics

Absorption

Single-dose PK of elranatamab in Cynomolgus monkeys [022648]

Cynomolgus monkeys (1/sex/group) were administered a single IV dose of elranatamab. Serum concentrations of elranatamab were determined using a non-validated method ELC method with a range of quantitation from 2 to 800 ng/ml (Table 3).

***Table 3*. Mean PK parameters of elranatamab after single IV dosing in cynomolgus monkey**

Dose (mg/kg)[a]	AUC_{last} (µg•h/mL)	AUC_{inf} (µg•h/mL)	CL (mL/min/kg)	V_{ss} (L/kg)	$t_{½}$ (Days)
0.001	0.848	1.39	0.0126	0.134	~6
0.01	12.5	13.7	0.0124	0.0982	~4

One-month repeat-dose IV toxicity study in cynomolgus monkeys [16GR380]

Cynomolgus monkeys (3/sex/group) were administered elranatamab at 0, 0.01, 0.05 and 0.3 mg/kg IV Q1W. Toxicokinetics were determined based on blood samples collected on Day 1 and Day 22, pre-dose and up to 7 days post-dose (168 hrs). After once-weekly IV dosing (for a total of 5 doses), the systemic exposure increased with increasing dose in an approximately dose-proportional manner, and exposure (AUC168) was higher on Day 22 compared to Day 1 (Table 4)). Quantifiable concentrations of elranatamab were observed in most animals until Day 29 (last samples collected). In general, exposure on Day 22 was lower in ADA-positive animals compared to ADA-negative animals.

Table 4. Mean TK parameters of elranatamab after once weekly repeat IV dosing in cynomolgus monkeys

Study	Dose (mg/kg/dose)[a]	Study Day	C_{max} (µg/mL)	AUC_{168} (µg•h/mL)	Incidence of ADA Induction
16GR380	0.01	1	0.236	10.4	67%
		22	0.219	18.0	
	0.05	1	1.27	58.0	17%
		22	1.42	118	
	0.3	1	9.34	453	0%
		22	10.4	715	

1-month repeat-dose SC toxicity study in cynomolgus monkeys [17GR290]

Cynomolgus monkeys (3/sex/group) were administered elranatamab at 0, and 0.3 mg/kg SC Q1W for 5 doses. Toxicokinetics were determined based on blood samples collected on Day 1 and Day 22, pre-dose and up to 7 days post-dose (168 hrs). After SC dosing, mean Tmax was 56 hrs on Day 1 and 25 hrs on Day 22. After once-weekly SC dosing at 0.3 mg/kg, there was no marked accumulation in exposure (AUC168; Day 22/Day 1 was <1.4). Quantifiable concentrations of elranatamab were observed in all animals until Day 29 (last samples collected) except for one animal that was positive for ADA. On Day 22, the exposure in the ADA-positive animal was lower compared to exposure in the ADA-negative animals.

3-month repeat-dose SC toxicity study in cynomolgus monkeys [20GR302]

Cynomolgus monkeys (3/sex/group) were administered elranatamab at 0, 0.3, 3 and 6 mg/kg SC, Q1W for 14 doses. Toxicokinetics were determined based on blood samples collected on Days 1, 43 and 85, pre-dose and up to 7 days post-dose (168 hrs).

After SC dosing, mean Tmax ranged from 64 to 100 hours postdose on Day 1, from 33 to 72 hours postdose on Day 43, and from 32 to 72 hours postdose on Day 85. Following once-weekly SC dosing, systemic exposure increased with increasing dose in an approximately dose-proportional manner (Table 5. Exposure (AUC168) was higher on Days 43 and 85 compared to Day 1, with mean accumulation ratios (AUC168; Day 85 or 43/ Day 1) ranging from 3.2x to 7.3x. Quantifiable concentrations of elranatamab were observed until Day 85 in the 0.3 and 3 mg/kg dose groups. The presence of ADA was only detected in 2 animals from the 0.3 mg/kg dose group; exposures were similar in ADA-positive compared to ADA-negative animals.

Table 5. Mean TK parameters of elranatamab after once weekly repeat SC dosing (14 doses)

Study	Dose (mg/kg/dose)	Study Day	C_{max} (µg/mL)	T_{max} (h)	AUC_{168} (µg•h/mL)	Incidence of ADA Induction
20GR302[a]	0.3	1	1.52	100	208	33%
		43	6.31	33	826	
		85	4.97	32	647	
	3.0	1	15.9	64	2100	0%
		43	83.4	72	12200	
		85	101	72	15300	
	6.0[b]	1	40.9	80	5630	0%
		43	185	60	26900	

Note: SC Bioavailability (~50%) was calculated using Day 1 AUC168 values from the 0.3 mg/kg dose groups ([208 µg•h/mL, SC 20GR302/ 453 µg•h/mL, IV 16GR380] •100).
a. Animals were dosed at N = 3 /sex/dose group.
b. Due to early animal deaths, TK analysis wasn't performed on Day 85.

Distribution

Protein binding and tissue distribution studies were not conducted for elranatamab in nonclinical species. The Vss of elranatamab in monkeys was approximately 0.1 L/kg after single IV dosing, consistent with the limited distribution expected for an IgG (Lin et al, 1999; Mascelli et al, 2007).

Metabolism

Metabolism studies were not conducted with elranatamab as these are not considered necessary or relevant for biologics such as elranatamab (ICH S6). Similar to other therapeutic proteins with molecular weights above the glomerular filtration cut-off, elranatamab is expected to be metabolised primarily by catabolic degradation (Lobo et al, 2004; Mascelli et al, 2007; Vugmeyster et al, 2012).

Excretion

Standard elimination studies routinely conducted for small molecule drugs are not considered necessary or relevant to biotechnology-derived pharmaceuticals such as elranatamab (ICH S6); therefore, an excretion study was not conducted in nonclinical species for elranatamab.

Pharmacokinetic drug interactions

No specific non-clinical PK drug interaction studies were conducted with elranatamab.

2.5.4. Toxicology

The non-clinical safety evaluation for elranatamab was designed in accordance with ICH S6(R1) and ICH S9 guidelines for a biotechnology-derived pharmaceutical developed with the intent to treat advanced cancer. These studies are summarised in Table 6.

Table 6. Overview elranatamab toxicology studies

Study Type or Duration/Study Number(s)	Route(s) of Administration	Species	GLP Compliance
Single-dose Toxicity			
2 weeks/20GR260	SC	Cynomolgus Monkey	No
Repeat-dose Toxicity			
10 days/15GR126	IV	Cynomolgus Monkey	No
1 month/16GR380/17GR290	IV/SC	Cynomolgus Monkey	Yes
3 months/20GR302	SC	Cynomolgus Monkey	Yes
Local Tolerance			
1 month/16GR380/17GR290	IV/SC	Cynomolgus Monkey	Yes
Other Toxicity Studies			
Immunotoxicity/17GR008	In Vitro	Human	No
Impurities/22LJ023	In Vitro	Human	No
BCMA Expression/22LJ024	In Vitro	Monkey/Human	No
Tissue Cross-Reactivity/20104929/20105532	In Vitro	Monkey/Human	No/Yes

2.5.4.1. Single dose toxicity

Escalating, single-dose SC injection tolerability and TK study of elranatamab in cynomolgus monkeys [20GR260]

This exploratory single-dose study was a dose range-finding study for the 3-month toxicity study using the SC route of administration. Sexually mature cynomolgus monkeys (6-8 years old, 1 M/group for low and mid dose; 2/sex/group for high dose) were administered elranatamab at 3, 6, and 15 mg/kg SC on Day 1 and followed for a period of 2 weeks. Animals were returned to the colony on Day 15.

The study revealed that at higher dose levels ≥ 6 mg/kg), a single dose of elranatamab given SC is less well tolerated and associated with emesis. At the high-dose (15 mg/kg), elranatamab induced also faecal changes, and skin discolorations at various sites, as well as decreased activity. In addition, there were elranatamab-related changes (at ≥ 6 mg/kg) in haematology (increases in neutrophils, monocytes, basophils, eosinophils and/LUC), and clinical pathology (increases in fibrinogen, increases in CRPHS) which are consistent with an acute phase response.

As observed in previous studies, there was an almost complete depletion of peripheral blood B cells (< 0.09x compared with baseline) across all dose groups on Day 3 which persisted to the end of the

observation period (Day 15) as well as a depletion of Ab-secreting cells from peripheral blood. Elranatamab-related effects on T cells and NK cells were transient.

Based on the clinical findings observed at the high-dose, the 6 mg/kg was considered the maximal tolerated dose and selected as high-dose for the 3-months study.

2.5.4.2. Repeat dose toxicity

10-Day IV exploratory toxicity study of elranatamab in cynomolgus monkeys [15GR126]

Cynomolgus monkeys (2F/group) were administered elranatamab at 0, 0.1 and 0.3 mg/kg IV or a control bi-specific Ab at 0.1 mg/kg IV on Days 1 and 8. All animals survived until scheduled necropsy which was performed on Day 10. Elranatamab was tolerated with transient clinical signs of emesis and transient decreases in food consumption. The main test article-related effects were in the secondary lymphoid tissues (tonsil, spleen, and lymph nodes), bone marrow, peripheral blood lymphocyte subsets, and IgG-secreting plasma cells.

At 0.3 mg/kg/dose, the mean Cmax and AUC48 for elranatamab were 6.73 µg/mL and 208 µg*h/mL, respectively, on Day 8.

1-month IV toxicity study of elranatamab in cynomolgus monkeys [16GR380, GLP]

Cynomolgus monkeys (3/sex/group, 3-4 years old, Mauritius origin) were administered elranatamab at 0, 0.01, 0.05 and 0.3 mg/kg IV Q1W for 5 doses. Necropsy was performed on Day 30. A recovery period was not included.

There was no mortality and clinical signs were limited to emesis at all doses levels, generally associated with the 1st dose administration. These clinical signs may be a consequence of the elranatamab-related cytokine release, that was most prominent on dosing Day 1 at 6 hrs post-dose.

Elranatamab treatment was associated with a marked and progressive decrease in peripheral blood B lymphocytes, with nadir levels of <0.01x baseline at 0.3 mg/kg dose. In addition, a nearly complete depletion of Ab-secreting cells from peripheral blood, spleen and bone marrow was observed at ≥ 0.1 mg/kg in the exploratory study, but not in the 4-wk study. The latter finding was unexpected; however the issue is not pursued further, since depletion of Ab-secreting cells was demonstrated again in the subsequent toxicity studies. Nevertheless, decreased cellularity of the germinal centre was observed microscopically, in spleen and the lymph nodes analysed (axillary, mesenteric LN, and GALT) at all dose levels, with the exception of individual animals at 0.01 or 0.05 mg/kg/ dose with increased cellularity of the germinal centres, that may be reflective of an ADA response.

Following elranatamab administration, there was also a transient decline in the number of peripheral blood T cells, consistent with T cell margination, and an increase in the number of activated T cells, both CD8 and CD4 T cells, evidenced by the increase in activation markers CD69 and CD25. Elranatamab-related clinical chemistry findings consisted of decreases in globulin and an associated increase in the albumin/globulin ratio at all dose levels.

By Day 22 of treatment, skin discoloration was observed at ≥ 0.05 mg/kg/dose. Microscopic skin findings consisted of epidermal hyperplasia, perivascular inflammation, erosion and ulcer.

1-month SC toxicity study of elranatamab in cynomolgus monkeys [17GR290, GLP]

Cynomolgus monkeys (3/sex/group, 3-4 years old, Mauritius origin) were administered elranatamab at 0, and 0.3 mg/kg SC Q1W for 5 doses. Necropsy was performed on Day 30. A recovery period was not included.

At the tested dose level (0.3 mg/kg), elranatamab administered SC was tolerated better than given IV. In the present study no emesis occurred, and there were no treatment-related effects on body weight or food consumption although elranatamab induced release of pro-inflammatory cytokines. After the 1st SC administration of elranatamab, cytokine concentrations were highest at 6 hrs post-dose, although maximum elranatamab serum concentrations were reached later (Tmax at 56 hrs). At the SC injection sites minimal inflammatory reactions were observed.

3-month SC toxicity study of elranatamab in cynomolgus monkeys [20GR302, GLP]

Cynomolgus monkeys (3/sex/group, 5-8 years of age, sexually mature, Mauritius origin) were administered elranatamab at 0, 0.3, 3 and 6 mg/kg SC, Q1W for 14 doses. Scheduled necropsy was performed on Day 93; one day after the last dose. A recovery period was not included.

Unlike the previous toxicity studies (with a shorter treatment duration and/or lower elranatamab doses), treatment in this pivotal 3-months study was associated with elranatamab-related mortality. Unscheduled euthanasia occurred at all dose levels, in all high-dose animals and the majority of the mid-dose animals (between Day 58 and Day 82), and in 1 low-dose animal (Day 91). The moribundity was attributed to bacterial and/or viral infections that were likely secondary to the immunosuppressive effects of elranatamab.

The immunosuppression was evident based on a complete and persistent depletion of B lymphocytes and of Ab-secreting cells and associated decreases in globulin (IgA, IGM and IgG). Microscopically, decreased cellularity of lymphoid follicles in the spleen, and decreased lymphocyte cellularity in lymph nodes and gut-associated lymphoid tissue were evident.

Microscopic findings attributed to infection included inflammation and infiltration of the gastrointestinal system and kidneys; cellular infiltration, inflammation, thrombus, necrosis, intra-lesional bacterial colonies and/or vial inclusion bodies in multiple organs.

Decreases in red blood cell mass and decreased HGB levels at ≥ 0.3 mg/kg (considered adverse at 6 mg/kg) were attributed to an erythrocyte-destructive process in some animals likely due to secondary infections or sepsis. Red cell mass decreases were accompanied by increases in MCV, RDW, and/or reticulocytes, indicating a regenerative process. Other clinical pathology changes were non-adverse and were considered secondary to multisystemic or tissue-specific inflammation, secondary infection, inanition, and/or gastrointestinal/renal loss.

As observed in the previous studies, there were additional effects on T and NK cell populations at all dose levels. These included a transient decrease in T cells, fluctuations in NK cell numbers and increases in the percentage of activated (CD69+) and proliferating (Ki-67+) T cells, both CD4+ and CD8+ cells. In addition, increases in cytokines were observed, at all dose levels, which were most prominent on Day 1 at 7 hrs post-dose.

Given the mortality at all dose levels, a NOAEL was not identified in this study. The 0.3 mg/kg dose level is a LOEL associated with a mean Cmax of 4.97 µg/mL and AUClast of 647 µg*h/mL on Day 85.

- **Interspecies comparison**

The serum concentrations of elranatamab after SC administration in cynomolgus monkeys and associated with key responses are shown in Table 7. Clinical exposures are based on population PK steady-state exposure metrics for a typical patient receiving 76 mg QW elranatamab after a priming dose.

Table 7. Concentrations of elranatamab associated with key responses

Key Response(s)	Dose (mg/kg/week)	C_{max}[a] (ng/mL)	AUC_{last}[a] (ng•h/mL)	Exposure Margin[b]	
				C_{max}	AUC_{last}
1-Month Subcutaneous Toxicity Study in Cynomolgus Monkeys (3/sex/dose) 17GR290					
Clinical pathology/pharmacology: ↑ cytokines Histopathology: Injection site inflammation	0.3 NOAEL	2840	378000	0.1x	0.1x
3-Month Subcutaneous Toxicity Study in Cynomolgus Monkeys (3/sex/dose) 20GR302					
Moribundity (1/6 animals) Clinical observations: ↓ activity, emesis, soft feces; ↓ body weight and/or food consumption Clinical pathology/pharmacology: ↓ immunoglobulins, ↓ total B cells, ↑ cytokines; ↓ RBC mass, total protein, globulin Histopathology: Secondary infection - ↓ cellularity of spleen, lymph node, GALT Inflammation and/or infiltration of kidney and gastrointestinal system	0.3 LOAEL	4970	647000	0.2x	0.2x
Same as above, plus: ↑ Incidence of moribundity (4/6 animals);	3	101000	15300000	3.9x	3.7x
Same as above, plus: ↑ Incidence of moribundity (6/6 animals)	6	185000[c]	26900000[c]	7.2x	6.5x

a. AUC168 and Cmax values indicate mean serum concentrations. Reported values were obtained near termination, or as specified.

b. Exposure margins (i.e., safety margins) are calculated from human population PK modelling exposure estimates for elranatamab (Section 2.7.2). Steady-state total exposure estimates for a typical patient receiving 6 cycles of 76 mg QW after a priming dose are Cmax = 25,784 ng/mL and AUCtau = 4157189 ng•h/mL (173,216 ng•day/mL).

c. Day 43 values due to early moribundity.

2.5.4.3. Genotoxicity

Genotoxicity studies with elranatamab have not been conducted since they are generally not required for protein-based biotherapeutics per ICH S6(R1).

2.5.4.4. Carcinogenicity

Carcinogenicity studies with elranatamab have not been conducted since they are generally not required for advanced cancer and protein-based biotherapeutics per ICH S9 and ICH S6(R1), respectively.

2.5.4.5. Reproductive and developmental toxicity

Stand-alone reproductive and development toxicity studies have not been conducted with elranatamab. Effects on reproductive organs were assessed as part of the repeat-dose toxicity studies. In the 3-months toxicity study in sexually mature cynomolgus monkeys no effects on male and female reproductive organs were observed.

The potential for elranatamab to elicit developmental effects was assessed based on an integrated weight-of-evidence approach. Such approach is in line with ICH S6(R1). The assessment takes into account non-clinical and clinical data for elranatamab and considers published literature about the role of BCMA, CD3 and of cytokines in reproduction and development. Elranatamab induces depletion of B lymphocytes. Based on experience with other B cell-targeting medicinal products (e.g. rituximab or belimumab), depletion of B cells does not affect normal pregnancy but the treatment causes lymphopenia in the off-spring, which is reversible upon cessation of exposure. Furthermore, elranatamab activates T cells and induces production of pro-inflammatory cytokines. A pro-inflammatory immune response can disturb the immunological balance required throughout pregnancy, e.g. for implantation, tolerance to the allogeneic fetus and parturition. In humans, a pro-inflammatory immune response has been associated with pregnancy loss, pre-eclampsia and pre-term labour. Thus, the pro-inflammatory response induced by elranatamab may adversely affect pregnancy outcome.

2.5.4.6. Toxicokinetic data

TK results from the pivotal toxicity studies are presented in the PK section of this report.

2.5.4.7. Local tolerance

Stand-alone local tolerance studies have not been conducted with elranatamab; however, injections sites were evaluated microscopically as part of the repeat-dose toxicity studies.

In the 1-month SC study [17GR290] elranatamab-related minimal or moderate inflammation was present at the SC injection sites. The finding was not considered adverse since epidermis and adnexa were not compromised and there were no associated clinical signs or macroscopic findings.

In the 3-month SC study [20GR302], injection site findings, including minimal mixed cell infiltration and minimal degeneration/ necrosis of skeletal muscle were not considered test article-related, but considered procedure-related, because of lack of dose-response.

2.5.4.8. Other toxicity studies

Immunotoxicity

In vitro, elranatamab-mediated, BCMA-dependent cytotoxicity was demonstrated in human cells as part of the primary pharmacology [study 012102].

In vivo, administration of elranatamab to cynomolgus monkeys induced depletion of B cells and a reduction of immunoglobulins leading to the loss of humoral immunity and an increased observation of infections over 3 months. Redistribution of T cells and NK cells was also observed and characterised by transient decreases in these cell populations in blood and tissues.

In vitro cytokine release assay in human whole blood [17GR008]

The study evaluated the capacity of elranatamab to induce cytokine release in a soluble phase human whole blood in vitro assay. Cells expressing the target antigens are present in human whole blood, i.e. CD3+ T cells and BCMA-positive plasma cells, which are present in blood at frequencies of < 0.5% in most individuals.

Whole blood from healthy donors was incubated with elranatamab (at 0.005, 0.5 and 50 µg/ml), IgG2 isotype control Ab or positive control reagents (anti-CD3 at 5 or 50 µg/ml or LPS at 1 ng/ml). After 24 hrs incubation, concentrations of TNF-α, IL-6 and IFN-γ were determined in plasma samples. Elranatamab (at 0.5 and 50 µg/ml) induced production of IFN-γ from all donor samples, TNF-α in a

majority of the donors, and IL-6 in approx. half of the donors. Generally, the levels of cytokines induced by elranatamab were lower than those induced by the positive control anti-CD3.

2.5.4.9. Other studies

Tissue cross-reactivity studies [16LJ087, non-GLP; 16LJ088, GLP]

Cross-reactivity of elranatamab with human and cynomolgus tissue was assessed by immunohistochemistry staining. Based on the reactivity of elranatamab with positive control material and lack of reactivity with negative control samples, the method is considered suitable.

In human and cynomolgus tissues, elranatamab stained membrane and cytoplasm of bone marrow cells and of mononuclear cells in most tissues observed. This staining was as expected considering the known expression profiles of BCMA and CD3. In addition, elranatamab produced cytoplasmic staining in selected epithelia in humans and cynomolgus. This staining is considered unexpected, but of low toxicological concern, since cytoplasmic binding sites generally are not accessible to an antibody *in vivo*.

2.5.5. Ecotoxicity/environmental risk assessment

Elranatamab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no studies as part of the Environmental Risk Assessment for elranatamab are required.

2.5.6. Discussion on non-clinical aspects

The applicant has presented non-clinical *in vitro* data to describe the pharmacological mode of action of elranatamab. The studies provide information on binding affinity of elranatamab to its target antigens. It is noted that the affinity of elranatamab to the tumour antigen BCMA is higher than to CD3, which should ensure preferential binding to tumour cells.

In vitro functional studies have adequately shown that elranatamab mediates cytotoxic activity against BCMA+ tumour cells in the presence of CD3+ effector T cells. Most importantly, this activity was also demonstrated in patient-derived bone marrow samples, even though effector:target cell ratios were less than optimal. The BCMA ligands APRIL and BAFF at concentrations reported in multiple myeloma patients did not significantly impair the cytotoxic activity of elranatamab, while soluble BCMA did interfere with the elranatamab activity. The mode of action of elranatamab is associated with T cell activation and induction of cytokine release. Cytokine release syndrome is an identified risk for elranatamab and adequately addressed in the SmPC and the RMP.

The lack of Fc functionality was sufficiently demonstrated.

In vivo anti-tumour activity of elranatamab was demonstrated in mouse xenograft models of human multiple myeloma in the presence of human effector T cells. Elranatamab induced tumour growth inhibition as monotherapy; in combination with an IMiD (lenalidomide) or a gamma-secretase inhibitor the anti-tumour activity was enhanced. These in vivo studies provide sufficient proof-of-concept for the use of elranatamab in treatment of Multiple Myeloma.

The pharmacokinetic and toxicokinetic studies performed for the present application are considered sufficient and support the subcutaneous route of administration.

To support the safety of elranatamab the applicant has presented a toxicology programme which is in line with current guidance (ICH S6(R1), ICH S9) and takes into account scientific advice received from CHMP. The GLP principles were followed in the repeat-dose toxicity testing programme as well as when investigating local tolerance. Selection of cynomolgus as relevant species appears adequate, based on comparable binding affinity of elranatamab to cynomolgus and human BCMA and CD3, and a comparable frequency and phenotype of cynomolgus and human BCMA+ cells.

Elranatamab-related findings in the toxicity studies were related to its pharmacology. Increases in cytokines were observed, most prominently after the first administration and were associated with clinical signs such as emesis and reduced food consumption. In line with the CD3-dependent T cell activation, transient reductions in T cell (and NK cell) numbers were observed likely due to margination or migration into tissues. As expected, decreases in BCMA+ Ab-secreting cells and associated decreases in globulins were observed as well as decreases in cellularity in germinal centres in spleen and lymph nodes. In addition, depletion of peripheral B cells was observed.

At doses up to 0.3 mg/kg or when administered for a limited time (up to 1 month), elranatamab was tolerated; however, at higher doses or with longer duration, elranatamab treatment resulted in immunosuppression, leading to secondary bacterial or viral infections and ultimately moribundity. This occurred at exposure levels of ≥ 3.9x the human exposure (at steady state) based on Cmax and ≥ 3.7x based on AUC. At the NOAEL/LOEL of 0.3 mg/kg, exposure in cynomolgus was well below the human exposure (0.1x or 0.2x).

Reproductive and developmental toxicity studies have not been conducted with elranatamab. No effects on reproductive organs were observed in the 3-months toxicity study in sexually mature monkeys. Human immunoglobulin (IgG) is known to cross the placenta after the first trimester of pregnancy. Based on the mechanism of action, elranatamab may cause foetal harm when administered to a pregnant woman and therefore it is not recommended for use during pregnancy.

Women of child-bearing potential should use effective contraception during treatment with elranatamab and for 6 months after the last dose.

Elranatamab is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with elranatamab should be considered.

The justification not to provide ERA studies for the medicinal product due to its nature as an amino acid unlikely to result in significant risk is accepted.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view elranatamab has been adequately characterised and is recommended for marketing authorisation.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Protocol # Cutoff Date	Number of participants with PK/PD/ADA Data	Treatments	Study Design Primary Objective	Analyses
C1071001 Cutoff dates Clinical cutoff date: 22 June 2022 PK/PD cutoff date: 17 May 2022 N = 101	Elranatamab PK Total PK (n=100) Free PK (n= 100) sBCMA Total sBCMA (n= 88) Free sBCMA (n= 73) ADA (n=100)	Part 1: Dose Escalation IV: (0.1-50 µg/kg) QW SC: (80-1000 µg/kg) QW Part 1.1: Priming Cohorts 600 µg/kg priming dose; 1000 µg/kg full dose either QW or Q2W Part 2: Dose Expansion 44 mg priming dose; 76 mg full dose QW Participants treated with elranatamab QW for ≥6 months and with stable disease assessments for ≥2 months could switch to Q2W dosing if allowed by sponsor.	Phase 1, open label, multiple-dose, multicenter, dose escalation, safety, PK and PD trial of elranatamab in adult patients with RRMM advanced multiple myeloma. Assess safety and tolerability at increasing dose levels of elranatamab as monotherapy and in combination with lenalidomide, pomalidomide, or dexamethasone in successive cohorts of patients with MM in order to estimate the MTD or MAD and select the RP2D. All elranatamab monotherapy cohorts (IV and SC) are included in the SCP analyses. The part of this study to evaluate elranatamab in combination with dexamethasone was not enrolled.	NCA PopPK ER-efficacy ER-safety Cytokines PD (sBCMA)
C1071002 Cutoff dates Clinical cutoff date: 27 May 2022 PK/PD cutoff date: 27 May 2022 N = 4	Elranatamab PK Total PK (n=4) Free PK (n= 4) sBCMA Total sBCMA (n=0) Free sBCMA (n= 4) ADA (n= 4)	Elranatamab 600 µg/kg priming dose; 1000 µg/kg QW as full dose Participants treated QW for ≥6 months and with stable disease assessments for ≥2 months could switch to Q2W dosing if allowed by sponsor.	Phase 1, open label study to evaluate safety and PK of elranatamab as a single agent in Japanese participants with RR advanced MM. Assess safety and tolerability at RP2D with a priming dose approach of single-agent elranatamab administered to Japanese participants.	NCA PopPK ER-efficacy ER-safety Cytokines PD (sBCMA)

C

C1071003 Cutoff dates Clinical cutoff date: 14 October 2022 PK/PD cutoff date: 17 Jun 2022 N = 187	Elranatamab PK Total PK (n =187) Free PK (n = 168) sBCMA Total sBCMA (n=187) Free sBCMA (n= 157) ADA (n= 187)	Elranatamab Step-up priming dose (12 mg/32 mg); 76 mg QW as full dose; 76 mg Q2W starting C7+ for participants with ≥ PR.	Phase 2 open-label, multicenter, non-randomized study of elranatamab monotherapy in participants with MM who are refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody. Determine efficacy (ie, ORR) of elranatamab as assessed by BICR as defined by IMWG for each of 2 independent cohorts: participants naïve to BCMA-directed therapies (Cohort A) and participants who have been previously exposed to BCMA-directed therapy (Cohort B).	PopPK ER-efficacy ER-safety Cytokines PD (sBCMA)
C1071009 Locations: Cutoff dates Clinical cutoff date: 29 July 2022 PK/PD cutoff date: 17 June 2022 N = 43	Elranatamab PK Total PK (n= 43) Free PK (n= 43) sBCMA Total sBCMA (n= 42) Free sBCMA (n= 39) ADA (n= 43)	Part 1: Elranatamab Step-up priming dose (4 mg/20 mg); 76 mg QW as full dose; 76 mg Q2W starting C7+ for participants with ≥ PR and/or RP2D (116 mg or 152 mg) Q4W starting C7+ for participants with ≥ PR (RP2D identified in part 2A) Part 2A: DL1: Elranatamab Step-up priming dose (4 mg/20 mg); 76 mg QW for C1; 116 mg Q2W C2-C6; 116 mg Q4W starting C7+ for participants with ≥ PR DL2: Elranatamab Step-up priming dose (4 mg/20 mg); 76 mg QW for C1; 152 mg Q2W C2-C6; 152 mg Q4W starting C7+ for participants with ≥ PR	Phase 1/2, open-label, multicenter study to evaluate a dosing regimen with two step-up priming doses and longer dosing intervals and higher doses of elranatamab monotherapy in participants with RRMM. Assess rate of Grade ≥2 CRS when elranatamab is administered with a dosing regimen of 2 step-up priming doses and premedication in participants with RRMM.	PopPK ER-efficacy ER-safety PD (sBCMA)

2.6.2. Clinical pharmacology

Population PK (PopPK) analysis

A population PK analysis of elranatamab was performed using pooled data from 321 participants who received elranatamab monotherapy in Studies 1001, 1002, 1003, and 1009.

Elranatamab total and free PK were adequately characterised by a semi-mechanistic target-mediated drug disposition (TMDD) model with first order absorption (Hayashi et al, 2007). The model was parameterised in terms of the three entities, free elranatamab, free sBCMA, and the elranatamab-sBCMA complex, each with separate clearance and volume of distribution. The model assumes that the free drug, the target (i.e., free sBCMA), and the elranatamab-sBCMA complex are in equilibrium meaning that the binding rate is balanced by the dissociation rate on the time scale of other disposition processes. In total, there were 13,233 observations; 3,739 total elranatamab PK observations, 2,947 free elranatamab observations, 3,812 total sBCMA observations, and 2,735 free sBCMA observations.

The semi-mechanistic model structure described the observed concentration-time profiles of free and total elranatamab and sBCMA reasonably well. The final parameter estimates are presented in Table 8.

Table 8. Final model parameter estimates

Parameter	Estimate (CV%)[a]	RSE	95% CI
$\theta_{CL\ elranatamab}$(L/day)	0.324 (100%)	9.114	(0.266; 0.382)
$\theta_{Vc\ elranatamab}$(L)	4.777 (69%)	5.745	(4.239; 5.315)
$\theta_{Vc\ sBCMA}$(L)	15.418 (136%)	10.904	(12.123; 18.713)
$\theta_{CL\ sBCMA}$(L/day)	0.273 (448%)	21.030	(0.161; 0.386)
$\theta_{CL\ complex}$(L/day)	0.164 (79%)	9.201	(0.134; 0.193)
$\theta_{Vc\ complex}$(L)	3.802 (70%)	4.848	(3.441; 4.164)
$\theta_{BL\ sBCMA}$(nM)	6.914 (135%)	7.793	(5.858; 7.970
$\theta_{Vp\ elranatamab}$ (L)[b]	2.830	1.766	(2.732; 2.928)
θ_{Q}(L/day)[b]	0.225	1.933	(0.217; 0.234)
$\theta_{CL\ elranatamab}$(L/day)	0.324 (100%)	9.114	(0.266; 0.382)
$\theta_{Vc\ elranatamab}$(L)	4.777 (69%)	5.745	(4.239; 5.315)
$\theta_{Vc\ sBCMA}$(L)	15.418 (136%)	10.904	(12.123; 18.713)
$\theta_{CL\ sBCMA}$(L/day)	0.273 (448%)	21.030	(0.161; 0.386)
$\theta_{CL\ complex}$(L/day)	0.164 (79%)	9.201	(0.134; 0.193)
$\theta_{Vc\ complex}$(L)	3.802 (70%)	4.848	(3.441; 4.164)
$\theta_{BL\ sBCMA}$(nM)	6.914 (135%)	7.793	(5.858; 7.970
$\theta_{Vp\ elranatamab}$ (L)[b]	2.830	1.766	(2.732; 2.928)
θ_{Q}(L/day)[b]	0.225	1.933	(0.217; 0.234)
θ_{F}[b]	0.562	0.564	(0.556; 0.568)
θ_{ka} (day^{-1})	0.287 (68%)	4.432	(0.262; 0.311)
θ_{Kd} (nM)[b]	3.138	3.312	(2.934; 3.342)
$\theta_{Residual\ error\ total\ elranatamab}$	0.422	3.038	(0.397; 0.447)
$\theta_{Residual\ error\ total\ sBCMA}$	0.347	4.028	(0.320; 0.375)
$\theta_{Residual\ error\ free\ elranatamab}$	0.347	2.610	(0.330; 0.365)
$\theta_{Residual\ error\ free\ sBCMA}$	0.518	3.503	(0.482; 0.553)
$\theta_{Sex\ on\ CL\ elranatamab}$	-0.492	12.533	(-0.613; -0.371)
$\theta_{Bwt\ on\ Vc\ elranatamab}$	1.017	22.351	(0.571; 1.462)
$\theta_{Age\ on\ ka}$	-1.459	20.025	(-2.031; -0.886)
OFV	52404.246	-	-

a. Parameters in which IIV was added in the model have associated CV%. RSEs for IIVs included in the final model were < 60% and shrinkage for these IIV values were all < 35%. Refer to Module 5.3.3.5 PMAR-1353 - Study Report Table 8 for additional information.
b. IIV for parameter fixed to 14.83%
Table abbreviations: CI=confidence interval; CL=clearance; CV=coefficient of variation; F=bioavailability; Prop=proportional; ka=first-order absorption rate constant; IIV=inter-individual variability; OFV=objective function value; Q=inter-compartmental clearance; RSE=relative standard error; sBCMA=soluble B-cell Maturation Antigen; Complex=elranatamab-sBCMA; Vc=central volume of distribution; Vp=peripheral volume of distribution; kd=dissociation constant of elranatamab:sBCMA.

Various covariates were tested on the elranatamab PopPK model, and the statistically significant covariates that improved model fit were retained in the final model. The equations describing the final model estimation of typical values of elranatamab CLelranatamab, Vc,elranatamab, and Ka for the typical subject before IIV are shown below:

$$CLelranatamab = 0.324L/d \times(1-0.492 \times CLcovSEXF)$$

$$Vc,elranatamab = 4.777L \times (BWT/71.45)\ 1.017$$

$$Ka = 0.287d\text{-}1 \times (AGE/66)\text{-}1.459$$

In the above equations, CLelranatamab is the clearance of free elranatamab concentrations, Vc,elranatamab is the free elranatamab central volume of distribution, and Ka is the first-order absorption rate constant. The CLcovSEXF covariate is in reference to patients who are male and is equal to 1 if the patient is female and 0 otherwise. BWT is the baseline body weight (kg), and AGE is age in years. In order to evaluate the effects of sex on CLelranatamab, body weight on Vc,elranatamab, and age on Ka, relevant exposure metrics were simulated and compared to exposure for the reference group (eg, exposure for female vs male, and exposure at the 10th and 90th percentiles of body weight and age ranges compared to exposure at the median body weight and age, respectively). Only the covariates that reduced inter-individual variability (IIV) on their respective parameter and had an effect that did not include zero were selected for the subsequent analyses.

Comparison of base vs final popPK model

The OFV estimates for the base popPK model dropped only marginally, by introducing three covariates (Sex on CL_e (-0.492, (-0.613;-0.371)), BW on Vc_e (1.017, (0.571;1.462)) and AGE on ka (-1.459, (-2.031; -0.886))). Of note, there is still a large IIV identified on in total twelve parameters on which IIV was estimated (ETA shrinkage up to 31.3%) and partly fixed in addition to covariate testing. ETA distribution of the base model was observed to be skewed, in particular for IIV on CL_e and n CL_sBCMA.

Thus, the applicant was asked to further investigate covariate selection and in particular weight effect on PK. A sensitivity analysis comparing model estimates assuming fix allometry (0.75, 1) for scaling CL and V, respectively, was also requested. The estimated allometric exponent (weight on Vc) was included in the model and almost the same as the theoretical exponent (1.017 vs 1.00). Regarding investigation of weight effect on CL, it was argued that the objective function value (OFV) of the final model (52404.246) was 75.281 lower than the OFV of the allometric model (52479.527) indicating the final model resulted in a much better fit to the observations. In addition, the definite comparison in terms of covariates that has been provided as response to the requested sensitivity analysis cannot followed in detail. It seems that the gender effect seems to outweigh the expected weight effect on CL. As noted by the applicant, the individual level EBEs for CL from the submitted model (PMAR model) versus allometry model were highly similar (R-squared 0.8569). Major difference in individual EBEs for CL could be observed for ~10 subjects (~0.3% of population). As expected, median weight was higher in men than in women, and gender was included in the submitted model as a covariate for CL (women

had ~49% lower CL). The observed free elranatamab Ctrough levels from Study C1071003 appeared to overlap in subjects with weight < 10th percentile, 10th to 90th percentile, and > 90th percentile. A trend for slightly lower median Ctrough in subjects with weight > 90th percentile might be present at the last time point (Cycle 7 Day 1).

Forrest plots for total and free elranatamab AUCtau,ss and Cmax,ss for significant covariates in the final PopPK model were provided (data not shown). As expected, low BW is expected to have the highest impact on PK (over 3-fold (free elranatamab) and over 2.5 fold (total mab) of Cmax_ss, AUC_ss, respectively) compared to the typical subject.

Model diagnostics -Goodness of Fit (Final model)

Predication-based and residual-based Goodness-of-Fit plots indicate a high variability in the data and some deviation from the line of identity (trend of overpredicting total antibody, trend of underpredicting free antibody), and the horizontal line, in particular at later time points.

Overall, the final PopPK model described the mean observed data reasonably well until about 35 days (total antibody) and until day 50 (free antibody). Beyond this time points, the median concentrations are underpredicted, and overall, the variability is overpredicted (all data), in particular for total antibody, as the lower 5th percentile is not covered.

A simulations-based approach was utilised to predict free and total SC elranatamab PK parameters after multiple doses for the 2-dose step-up priming regimen of 12 mg / 32 mg / 76 mg. Table 9 presents PopPK model predictions of AUC_{tau}, C_{max}, and C_{trough} after multiple doses up to the end of Week 24 (i.e., max elranatamab exposure as the dosing intensity is reduced to Q2W for responding participants thereafter).

***Table 9*. Summary of exposure metrics after 24 weeks of 76 mg weekly dosing of elranatamab with 12/32 mg priming dose[a]**

Elranatamab PK	Statistic	C_{max} (µg/mL)	AUC_{tau} (µg*day/mL)	C_{trough} (µg/mL)
Free	Geometric mean (CV%)	15.99 (137%)	105.24 (146%)	14.17 (158%)
Total	Geometric mean (CV%)	25.78 (67%)	173.22 (69%)	23.86 (72%)

[a] Multiple doses of 76 mg QW following 2 step-up priming regimen in the first week up to Week 24 where max elranatamab exposure as the dosing intensity starting Week 25 is reduced to Q2W for responding participants.

2.6.1.1. Pharmacokinetics

Absorption

Following elranatamab SC administration, T_{max} ranged from 3 to 7 days after single or multiple SC administration. The SC absolute bioavailability (BA) of elranatamab is estimated to be 56.2% using the pooled PopPK analysis.

Three formulation strengths have been used in the clinical study 1001; 2 mg/ml or 10 mg/ml for IV cohorts, 2 mg/ml for 80 µg/kg SC cohort, and 10 mg/ml for other SC cohorts except Part 2A 44 mg/76 mg QW SC, which was administered with 40 mg/ml strength. The 2 mg/ml and 10 mg/ml product strengths have been used in Part I dose escalation/dose finding of the study 1001 to characterise dose proportionality of free and total elranatamab. The 40 mg/ml strength is the intended commercial product strength used in the Part 1-2A of study 1001, and in the studies 1002, 1003 and 1009 (249

patients). The PK data included in the population PK modelling was obtained including all the three formulations.

Non-compartmental analysis of total and free elranatamab PK exposure did not indicate any difference in exposure between participants that were treated with the 10 mg/mL formulation strength or the 40 mg/mL formulation strength. This was supported by the PopPK model as formulation strength was not a significant covariate on elranatamab PK.

Distribution

The population PK model-estimated typical volume of distribution for the central compartment was 4.78 L (CV% 69%) for free elranatamab and 3.80 L (CV% 70%) for the elranatamab-sBCMA-complex. The slightly lower Vc for elranatamab-sBCMA-complex is understandable based on its larger molecular size. Volume of distribution increased with body weight. The typical peripheral volume was estimated to be 2.83. The volume of distribution is typical of monoclonal antibodies.

Elimination

Based on population PK analysis, the population median free elranatamab clearance (CLelranatamab) and volume of distribution (Vc,elranatamab) were 0.324 L/day (100% CV) and 4.78 L, respectively. sBCMA clearance was 0.273 L/d (448% CV) and the clearance of the elranatamab:sBCMA complex was 0.164 L/d (79%CV). Apparent clearance of total elranatamab (CL/F) was 0.44 L/d (69%) calculated as dose/simulated AUC_{tau} after multiple weekly doses on week 24. Model-predicted absolute bioavailability from SC route is ~ 56.2%. Median T_{max} after the first dose across dose levels for the SC route ranged from 3 to 7 days.

Dose proportionality and time dependencies

Results of Study 1001 indicate that observed total elranatamab serum exposure is dose-proportional across the dose range of 0.1 to 50 µg/kg IV and 80 to 1000 µg/kg SC. This suggests linear PK for total elranatamab PK. Total elranatamab exposure is not significantly affected by baseline sBCMA levels. More than dose-proportional increase of exposure at steady state was observed for a group of the baseline sBCMA 90th percentile level of 214.81 ng/ml which is relatively high compared to 100 ng/ml used as cut point in exposure-response analyses.

Based on model simulated results, total and free elranatamab exposure for the overall population increased with dose in approximately dose-proportional manner over the dose range evaluated via SC route (fixed doses of 6 to 76 mg) (slope value for the linear regression analysis = 0.98 to 1.2). Across different baseline sBCMA levels, total PK increased in approximately dose proportional manner over the clinical dose range (slope = 0.98 to 1.1). Free PK is linear over the clinical dose range (slope value = 1 to 1.2) except for patients with high baseline sBCMA (> 90th percentile) where more than dose proportional increase in exposure with dose was observed reflecting a potential impact of high baseline sBCMA on free elranatamab exposure (slope = 1.5 to 1.6). A trend for lower free elranatamab exposure was observed in participants with high baseline sBCMA.

Maximum elranatamab exposure is expected on week 24 as the dosing intensity is reduced to Q2W for responding patients thereafter. The mean accumulation ratio after 24 weeks of weekly dosing relative to the first subcutaneous dose of elranatamab 76 mg for free and total elranatamab AUC_{tau} was 11.2 and 8.0, respectively, and for free and total elranatamab C_{max} was 6.6 and 4.8, respectively.

The theoretical accumulation factor assuming weekly dosing and a half-life of 25 days (as suggested by popPK modelling) is expected to be about 5.7, suggesting maybe a longer half-life observed for free and total elranatamab.

Intra- and inter-individual variability

The model features inter-individual variabilities about 69% for central volume of distribution, 15% for peripheral volume of distribution, 100% for elranatamab clearance, 448% for sBMCA clearance and 79% for elranatamab:sBCMA complex clearance. Thus, variability is indicated to be moderate to high by the data and model-based approach.

Special populations

No dedicated studies to investigate the pharmacokinetics of elranatamab in special populations have been conducted. The effect of intrinsic factors on pharmacokinetics was investigated by population pharmacokinetic approach.

Baseline eGFR (range: 22.5-125 mL/min/1.73 m^2) was not a significant covariate on total or free elranatamab exposure in the final PopPK model. The population PK model included 123 and 70 participants with mild and moderate renal impairment, respectively, which is considered sufficient to detect a clinically relevant change in clearance.

For the assessment of hepatic function, the results of the PopPK model indicated that none of the baseline associated safety laboratory measurements (albumin, AST, or bilirubin), were found to be statistically significant covariates in the final model.

The effect of gender on exposure is not clinically meaningful. Dose adjustment based on gender is not indicated. Overall, 167 (52%) of participants were male, thus male and female subjects were balanced.

The number of elderly subjects for whom PK data were available is shown in Table 10.

Table 10. Summary of elderly subjects in the pivotal studies of elranatamab

Variable	Category	C1071001	C1071002	C1071003	C1071009	Total
N (%)		87	4	187	43	321
Age Group	Group 1: <65	42 (48%)	1 (25%)	71 (38%)	24 (56%)	138 (43%)
	Group 2: 65 to <75	34 (39%)	3 (75%)	80 (43%)	16 (37%)	133 (41%)
	Group 3: 75 to <85	11 (13%)	0 (0%)	33 (18%)	3 (7%)	47 (15%)
	Group 4: 85+	0 (0%)	0 (0%)	3 (2%)	0 (0%)	3 (1%)

Pharmacokinetic interaction studies

No studies that examine the interaction between elranatamab and other products were submitted.

2.6.1.2. Pharmacodynamics

Mechanism of action

Elranatamab is a bispecific B-cell maturation antigen (BCMA)-directed T-cell engaging antibody that binds BCMA on plasma cells, plasma blasts, and multiple myeloma cells and CD3-epsilon on T cells leading to selective cytolysis of the BCMA-expressing cells. The anticancer activity of elranatamab

involves selective therapeutic targeting and activation of T cells re-directed against BCMA-expressing malignant plasma cells.

Primary pharmacology

Decline in free sBCMA concentrations after elranatamab administration were observed for the majority of responding participants within 2-3 cycles. In contrast, free sBCMA in non-responding participants remained largely unchanged or increased in some participants.

Peak cytokine concentrations (IL-2, IL-6, IL-8, IL-10, TNF-α, and IFN-γ) within the first 7 days of treatment appear to be higher within the efficacious dose range (doses 215 to 1000 µg/kg compared to lower dose). Increases with some cytokines were lower with the addition of pre-medications.

Data from the pivotal study (1003) indicated that median levels for peak cytokines appeared to be higher in participants experiencing CRS. Time of the maximum cytokine concentration generally occurred during the 2-dose step-up priming regimen and concentrations continue to decrease over the course of the first cycle.

The overall incidence of ADA across studies, dose levels, route of administration, and formulation strengths was characterised to be of low incidence, low titre with a relatively early onset, and transient. At the proposed full dose of 76 mg elranatamab administered SC, the ADA and Nab incidence was 8.3% (20/240) and 4.2% (10/239) respectively and the median ADA and Nab onset was 56.5 and 53 days respectively. The median titre was low (≤ 300) across all time points and there were no trends in ADA titre over time.

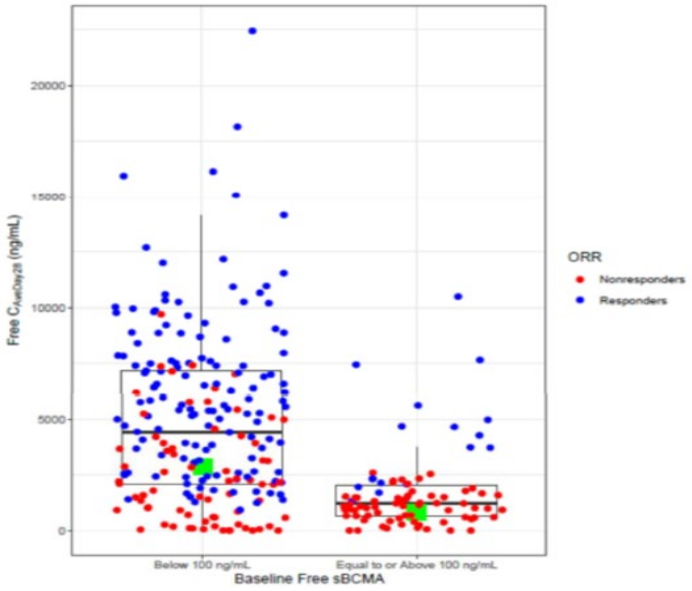
ADA (overall and baseline ADA status) was not found to be a significant covariate for elranatamab clearance (free and total), ORR, CRS, neutropenia, and infections. Sub-group analysis of safety data for ADA-positive participants also indicated no meaningful differences in the safety profile between participants with or without treatment emergent ADA to elranatamab.

It was noted that in IG Pool 3, 14.2% and 3.3% of study participants were ADA or NAb positive at baseline. The Applicant was therefore asked to provide an analysis as to whether there was a correlation to prior BCMA directed therapy. Incidence of NAb at baseline was comparable (1.4% (1/72) and 4.2% (7/167) for participants with or without prior BCMA-directed therapy, respectively). The incidence of treatment-induced NAb also followed similar trends (2.8% (2/72) and 4.8% (8/168) with or without prior BCMA-directed therapy, respectively). Though both ADA and NAb incidences comparison between the two groups are limited by sample size, there appeared to be no clear impact of prior BCMA-directed therapy on the overall immunogenicity risk.

Relationship between plasma concentration and effect

In the total PK logistic regression analysis, baseline sBCMA level was inversely associated with ORR (higher sBCMA associated with lower probability of objective response). Free elranatamab exposure was lower in participants with high sBCMA (>100 ng/mL) which suggests that sBCMA acts as a sink that reduces free drug exposure Figure 4.

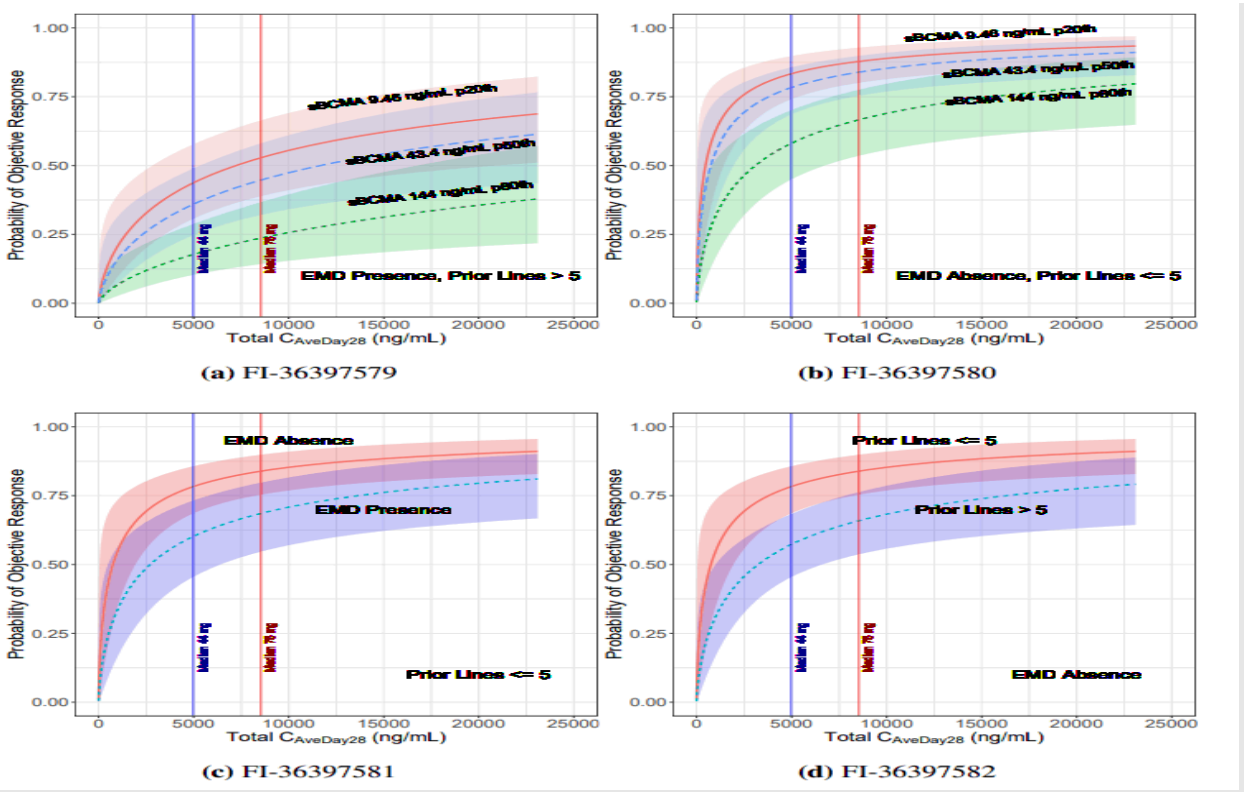
Figure 4. Free elranatamab $C_{ave,\ Day28}$ by baseline free sBCMA level and ORR status



Source: Module 5.3.3.5 PMAR-1354 - Study Report Figure 15. Green squares represent the geometric mean of the corresponding group. Figure abbreviations: Cave=average concentration.

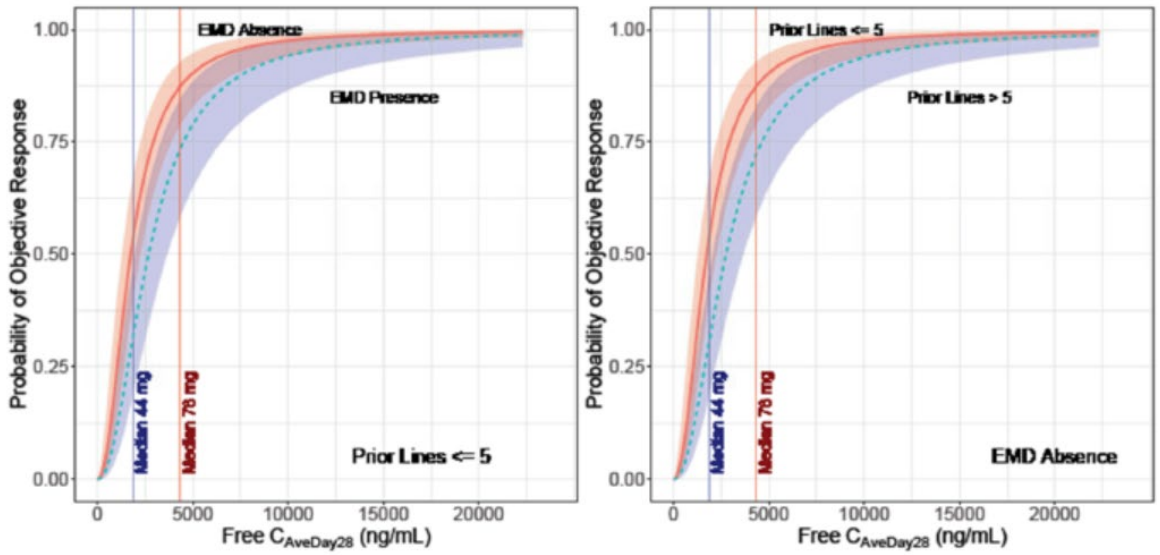
Predicted probabilities of ORR as a function of $C_{ave,\ Day28}$, baseline sBCMA (low: 20th, intermediate: 50th, and high: 80th percentiles), number of prior lines of therapy, and EMD status are shown in Figure 5 (total) and Figure 6 (free)).

Figure 5. Final model for ORR illustrating the association of elranatamab total exposure ($C_{ave,\ Day\ 28}$), baseline sBCMA, number of prior lines of therapy, and EMD status



Source: Module 5.3.3.5 PMAR-1354 - Study Report Figure 16. In figures (a) and (b), red, blue, and green curved lines and shaded regions represent median and 95% CI predicted probability of objective Response for patients with 20th, 50th, and 80th percentiles of sBCMA, respectively. In figures (c) and (d), simulations utilizing 50th percentile of sBCMA are displayed.

Figure 6. Final model for ORR illustrating the association of elranatamab free exposure (Cave, Day 28), and number of prior lines of therapy, and EMD status



The 76 mg QW regimen results in higher probability of achieving an objective response vs lower dose with no expected impact on safety.

Exposure-Response Analyses for Safety

Exposure-safety relationship for AEs of CRS: higher early elranatamab exposure ($C_{max, 24}$ after first dose (both free and total) was associated with higher probability of any Grade CRS and Grade ≥2 CRS. For the analysis using free elranatamab exposure, no other covariates than exposure were significant. For the analysis using total elranatamab exposure, baseline sBCMA was also inversely associated with any Grade CRS but was not a predictor for Grade ≥2 CRS.

No clinically meaningful relationship was observed between elranatamab exposure (free or total) and the incidence of Grade ≥ 2 PN AEs.

No statistically significant relationship was observed between elranatamab exposure (free or total average exposure up to event time) and the incidence of Grade ≥ 3 AEs of neutropenia in the final model.

No statistically significant relationship was observed between elranatamab exposure (free or total) and the incidence of Grade ≥ 3 infections in the final model.

Total and free elranatamab concentrations had no clinically meaningful effect on the QT interval corrected for heart rate over a range of serum concentrations observed across all 4 clinical studies.

2.6.2. Discussion on clinical pharmacology

The C_{max} and AUC_{tau} of elranatamab after the first subcutaneous dose increased in a dose proportional manner over the evaluated dose range via subcutaneous administration (~ 6 to 76 mg). The median accumulation ratio after 24 weeks of weekly dosing relative to the first subcutaneous dose of elranatamab 76 mg for C_{max} and AUC_{tau} was 6.6-fold and 11.2-fold, respectively.

The population PK model predictions for total and free elranatamab at steady state on week 24 are lower than the actual C_{trough} concentrations observed in study C1071003, as also identified by VPC plots. The applicant noted that the median treatment duration in non-responders was considerably shorter vs responders. Therefore, the predicted exposures at later cycles (i.e., at steady state) is predominantly relevant for responders only. A summary of steady state PK parameters by response status was provided, indicating ~ 5-6-fold higher exposure in responders at the start of treatment than the concentrations that would be predicted by a time-constant PK model. Pooling PK parameters from responders and non-responders result in a lower average steady-state exposure and exaggerate the variability.

A comparison of elranatamab C_{trough} in Study 1003 in responders vs non-responders was also provided by the applicant. Even though, the observed C_{trough} in Study 1003 was higher than the PopPK predictions based on all participants, the model predicted C_{trough} for the responders consistent with the observed C_{trough} at Cycle 7 in Study 1003. This also supports the inclusion of PK parameters in the section 5.2 of the SmPC for the responders subgroup only as it is consistent with Study 1003 and represent the more clinically relevant exposure at steady state.

The shorter treatment duration period and the lower exposure for non-responders is also considered to be the main cause of the underprediction of elranatamab exposure in the VPCs beyond Day 50.

The predicted mean bioavailability of elranatamab was 56.2% when administered subcutaneously. The median T_{max} after elranatamab SC administration across all dose levels ranged from 3 to 7 days.

The preferred injection site for elranatamab is the abdomen as in the pivotal clinical study (C1071003), the subcutaneous injections of elranatamab were generally given in abdomen. A small number of subjects contributed PK data after administration to the thigh. Considering the observed trough concentrations and variability of the PK data, the thigh can be used as an alternative administration site when injections in the abdomen are not possible.

Based on the population pharmacokinetic model, the predicted mean volume of distribution of unbound elranatamab was 4.78 L, 69% (CV) for the central compartment, and 2.83 L for the peripheral compartment.

The predicted geometric mean half-life of elranatamab is 22, 64% (CV) days at week 24 following dose of 76 mg weekly. Based on the population pharmacokinetic model, the predicted mean elranatamab clearance was 0.324 L/day, 69% (CV).

ADA and baseline ADA status was not a statistically significant or clinically meaningful covariate for elranatamab exposure, efficacy or safety in the population PK modelling and exposure-response analyses.

The CHMP noted that long-term stability data for free elranatamab from study 1001 and from study 1002 for total and free sBCMA were not available at the time of evaluation and it is recommended that these are submitted when available. In addition, the applicant should provide the final PK incurred sample reanalysis data in an updated bioanalytical report from study 1009.

No clinically relevant differences in the pharmacokinetics of elranatamab were observed based on age (36 to 89 years), sex (167 male, 154 female), race (193 White, 49 Asian, 29 Black), and body weight

(37 to 160 kg). The observed free elranatamab C_{trough} levels from Study C1071003 appeared to overlap in subjects with weight < 10th percentile, 10th to 90th percentile, and > 90th percentile. A trend for slightly lower median C_{trough} in subjects with weight > 90th percentile might be present at the last time point (Cycle 7 Day 1), but this should be interpreted with caution because of small number of subjects with observations at Cycle 7.

No studies of elranatamab in patients with renal impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild renal impairment (60 mL/min/1.73 m2 ≤estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m2) or moderate renal impairment (30 mL/min/1.73 m2 ≤ eGFR < 60 mL/min/1.73 m2) did not significantly influence the pharmacokinetics of elranatamab. Limited data are available from patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2).

No studies of elranatamab in patients with hepatic impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin > 1 to 1.5 times ULN and AST, or total bilirubin ≤ ULN and AST > ULN) did not significantly influence the pharmacokinetics of elranatamab. No data are available in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN and any AST) or severe (total bilirubin > 3.0 × ULN and any AST) hepatic impairment.

In conclusion, no dose adjustments are required based on the body weight or for the elderly or patients with mild to moderate renal impairment or mild hepatic impairment and this is reflected in the SmPC.

Elranatamab is not metabolised via CYP enzymes and is not expected to directly affect CYP enzymes. Therefore, the absence of specific clinical DDI studies is acceptable.

The exposure-efficacy analysis revealed that higher elranatamab exposure, both total and free PK, were associated with higher probability of achieving ORR (investigator assessment). The model predicts that participants with higher total exposure and lower baseline sBCMA are more likely to achieve objective responses. Participants with prior lines of therapy≤5 and no EMD status at baseline have a higher likelihood of achieving objective responses at a given elranatamab total exposure and baseline sBCMA levels.

The association between higher baseline sBCMA and CRS rate appears to be congruent with the model of ORR. Participants who do not respond to elranatamab would likely have less T cell engager-mediated cell killing and thus less release of cytokines.

2.6.3. Conclusions on clinical pharmacology

The applicant has adequately characterised the pharmacokinetic and pharmacodynamic properties of elranatamab which therefore can be recommended for (conditional) marketing authorisation.

2.6.4. Clinical efficacy

2.6.4.1. Dose response study

First step-up priming dose

The 2 step-up priming dose regimen of 12 mg/32 mg was selected and implemented in the registrational Study 1003 based on the totality of safety, efficacy, PK, PD, and exposure-response analyses including:

a) the observed incidence of All Grades CRS and Grade ≥ 2 CRS,

b) sufficient stimulation of cytokines with an initial dose of 12 mg, and

c) the predictable timing and manageable profile of CRS with this regimen.

Data from SC cohorts of Study 1001 Part 1 (dose escalation 80 – 1000 µg/kg) showed an overall incidence of All Grades CRS of 73.3% (22/30) and all events were limited to Grade 1 or 2 according to ASTCT criteria. Incidence of CRS generally increased with dose. CRS was observed in all participants in the 600 and 1000 µg/kg cohorts (n = 6 each). Two participants in 1000 µg/kg cohort experienced prolonged CRS (10 days each). Grade ≥2 CRS was observed in 1/6 (16.7%) and 2/6 (33.3%) in the 600 and 1000 µg/kg. Collectively, this data supported the need for priming regimens to mitigate the risk of CRS, in particular the rate of Grade ≥2 CRS.

Second step-up priming dose

Predictions based on the logistic regression analyses of Cmax, 24h indicated a considerably lower incidence of any grade and Grade ≥2 CRS with 2 step-up priming dose regimens (12 mg/32 mg + pre-medications Study 1003, or 4 mg/20 mg + pre-medications regimen) compared to a 1 step-up priming dose regimen (44 mg) with or without pre-medications.

Selection of 12/32 priming doses

Based on safety of diverse step-up priming regimens, the selected one 12/32 has shown the lowest CRS incidence.

Table 11. Summary of CRS incidence across different priming regimens (Studies C1071001, C107002, C107003 and C1071009)

	44/76 mg priming dose without premedication	44/76 mg priming dose with premedication	12/32/76	4/20/76
Studies	1001	1001, 1002, 1003	1003	1009
Cohorts	1001: Part 1.1	1001: Part 1.1, Part 2A; 1002: All participants; 1003: First 4 participants.	1003: All but first 4 participants	1009: All participants
N	20	23	183	45
With Adverse Event of CRS	20 (100.0%)	18 (78.3%)	106 (57.9%)	29 (64.4%)
Grade 1	10 (50.0%)	7 (30.4%)	80 (43.7%)	23 (51.1%)
Grade 2	10 (50.0%)	10 (43.5%)	25 (13.7%)	6 (13.3%)
Grade 3	0	1 (4.3%)	1 (0.5%)	0
Grade 4/5	0	0	0	0
More than 1 CRS AE	2 (10.0%)	0	24 (13.1%)	10 (22.2%)
CRS after 1st dose	20 (100.0%)	18 (78.3%)	79 (43.2%)	14 (31.1%)
Grade 1	10 (50.0%)	7 (30.4%)	60 (32.8%)	12 (26.7%)
Grade 2	10 (50.0%)	10 (43.5%)	18 (9.8%)	2 (4.4%)
Grade 3	0	1 (4.3%)	1 (0.5%)	0
CRS after 2nd dose	2 (10.0%)	0	35 (19.1%)	12 (26.7%)
Grade 1	2 (10.0%)	0	30 (16.4%)	11 (24.4%)
Grade 2	0	0	5 (2.7%)	1 (2.2%)
Grade 3	0	0	0	0
CRS after 3rd dose	0	0	13 (7.1%)	8 (17.8%)
Grade 1	0	0	9 (4.9%)	6 (13.3%)
Grade 2	0	0	4 (2.2%)	2 (4.4%)
Grade 3	0	0	0	0
CRS after >3rd dose	0	0	3 (1.6%)	7 (15.6%)
Grade 1	0	0	3 (1.6%)	6 (13.3%)
Grade 2	0	0	0	1 (2.2%)
Grade 3	0	0	0	0

Participants in Study C1071001 Part 1.1 and Study C1071002 received single priming dose regimen 600/1000 µg/kg which is the body weight-based equivalent of 44/76 mg for a 75 kg patient.

Full dose 76 mg

The recommended full treatment dose of elranatamab (76 mg QW), initiated following the 2 step-up priming dose regimen, is supported by exposure-efficacy and exposure-safety analysis.

Exposure-efficacy analysis showed that elranatamab exposure both free (sBCMA-unbound) and total (sBCMA-bound and unbound), are associated with ORR. In the total PK logistic regression analysis, baseline sBCMA level was inversely associated with ORR (higher sBCMA associated with lower probability of objective response-See Clinical Pharmacology Section of this report). Free elranatamab exposure was lower in participants with high baseline sBCMA which suggests that sBCMA acts as a sink that reduces free drug exposure.

The 76 mg QW regimen is the highest tested full treatment dose/dosing intensity and achieves the highest free elranatamab exposure at a given baseline sBCMA level in the dose range evaluated. This regimen results in higher probability of achieving an objective response vs lower doses with no expected impact on safety.

Switching to Q2W

In Study 1003, the dosing interval was switched after 6 cycles of weekly dosing to Q2W for participants with responses ≥ PR for at least 2 months. Several responding participants in Study 1001 also switched to Q2W regimen at later treatment cycles. In addition to the maintained/deepening clinical benefit observed in Studies 1003 and 1001 with the Q2W dosing interval, longitudinal sBCMA data were observed with rapid and deep decline in free sBCMA concentrations in the majority of responding participants. The rapid decrease in free sBCMA level in responders could be an indication of a reduced disease burden in responding participants with declines maintained over time. It also suggests saturation of sBCMA in responding participants. Therefore, less dosing intensity (i.e., Q2W) would be needed to maintain the responses achieved during initial treatment phases (after 24 weeks of initial QW dosing).

The lack of association between exposure and/or the Q2W switch and DOR supports reducing the dosing interval in responders after at least 24 weeks.

2.6.4.2. Main study

Study C107003 (MAGNETISMM-3): An Open-Label, Multicenter, Non-Randomized Phase 2 Study of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One Proteasome Inhibitor, One Immunomodulatory Drug and One Anti-CD38 Antibody.

Methods

- **Study Participants**

Inclusion Criteria (Main)

1. Male or female participants age ≥18 years.
2. Prior diagnosis of MM as defined according to IMWG criteria (Rajkumar et al, 2014).
3. Measurable disease based on IMWG criteria as defined by at least 1 of the following:
    a) Serum M-protein ≥0.5 g/dL by SPEP
    b) Urinary M-protein excretion ≥200 mg/24 hours by UPEP
    c) Serum immunoglobulin FLC ≥10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65)
4. Refractory to at least one IMiD
5. Refractory to at least one PI
6. Refractory to at least one anti-CD38 antibody
7. Relapsed or refractory to last anti-MM regimen.

    Note: Refractory is defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response.

8. Cohort A: Has not received prior BCMA-directed therapy. Cohort B: Has received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy, either approved or investigational.
9. ECOG performance status ≤2.

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

11. Adequate hepatic function characterised 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

12. 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).

13. Adequate BM function characterised by the following:

a) ANC ≥1.0 × 109/L (use of granulocyte-colony stimulating factors is permitted if completed at least 7 days prior to planned start of dosing);

b) Platelets ≥25 × 109/L (transfusion support is permitted if completed at least 7 days prior to planned start of dosing); and

c) Haemoglobin ≥8 g/dL (transfusion support is permitted if completed at least 7 days prior to planned start of dosing).

14. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1.

Exclusion Criteria (Main)

1. Smouldering MM.

2. Active plasma cell leukaemia.

3. Amyloidosis.

4. POEMS syndrome

5. Stem cell transplant within 12 weeks prior to enrolment or active GVHD.

6. Ongoing Grade ≥2 peripheral sensory or motor neuropathy.

7. History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B).

8. History of GBS or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.

9. 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 enrolment.

10.Previous treatment with an anti-BCMA bispecific antibody.

- **Treatments**

Enrolled participants received SC elranatamab with a 2 step-up priming regimen of 12 mg on C1D1 and 32 mg on C1D4 followed by the first full dose (76 mg) of elranatamab on C1D8 and QW thereafter, except for the first 4 participants that received 1 step-up priming dose of 44 mg on C1D1 followed by the first full dose (76 mg) on C1D8.

Premedication with dexamethasone, acetaminophen and diphenhydramine prior to administration of the step-up priming dose(s) and first full dose of elranatamab was required.

If a participant received QW dosing for at least 6 cycles and achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval was to be changed from QW to Q2W (e.g., beginning C7D1). If the participant subsequently began to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals were to return to weekly dosing.

Each participant received study intervention until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

- **Objectives**

The purpose of the study was to evaluate whether single-agent elranatamab can provide clinical benefit in participants with RRMM who are refractory to at least one PI, one IMiD and one anti-CD38 mAb.

The primary objective was to determine the efficacy of elranatamab in Cohort A and Cohort B. The corresponding endpoint was confirmed ORR by BICR per IMWG in Cohort A and Cohort B.

The key secondary objective was to determine additional efficacy of elranatamab.

Other efficacy objectives analysing depth of response, its duration and survival in Cohort A and B have also been implemented.

- **Outcomes/endpoints**

Primary endpoint:

- ORR by BICR per IMWG in Cohort A and Cohort B. Objective response was defined as having a best overall response (BOR) of confirmed sCR, CR, VGPR or PR per IMWG criteria.

Secondary endpoints (by BICR and Investigator per IMWG) in Cohort A and Cohort B:

- ORR by Baseline EMD status Cohort A (key secondary),
- ORR by investigator,
- CRR,
- DOR,
- DOCR,
- PFS,
- TTR,
- OS
- MRD negativity rate (central lab) per IMWG

- **Sample size**

The sample size for Cohort A and Cohort B was calculated to provide adequate power for testing the statistical hypotheses regarding the primary endpoint of ORR independently in the 2 cohorts using a 2-stage design based on exact binomial distribution. A total of 120 participants enrolled and treated in Cohort A provided approximately 98% power to reject the null hypothesis (ORR by BICR of 30%) when the alternative hypothesis that ORR by BICR of 48% is true, with a 1-sided significance level of 0.025. Similarly, a total of 60 participants enrolled and treated in Cohort B provided approximately 95% power to reject the null hypothesis (ORR by BICR of 15%) when the alternative hypothesis that ORR by BICR of 34% is true, with a 1-sided significance level of 0.025.

An interim analysis for both (non-binding) futility and efficacy was to be conducted on ORR by BICR based on the first 90 and 30 participants enrolled and treated in Cohort A and B, respectively. Each respective interim analysis was to occur no earlier than the point at which all early responders (i.e., those who respond within the first 3 post-baseline assessments) among the participants to be included have had their responses confirmed. At the time of the statistical analysis plan (SAP) amendment prior to the interim analysis, enrolment had exceeded the 120 Cohort A and 60 Cohort B participants. Enrolment closed in January 2022 with 123 Cohort A and 64 Cohort B participants enrolled and treated.

The final analysis of each cohort for the primary endpoint of ORR by BICR was to be conducted once all participants had at least 2 postbaseline response assessments or had otherwise discontinued response assessments within the first 2 months of treatment.

- **Randomisation and Blinding (masking)**

The study was uncontrolled and open-label. However, the central assessment of participants' response was done by blinded independent central review (BICR) that reviewed data from site-sourced components of response assessment (e.g., select laboratory assessments, select bone marrow pathology report data, radiologic imaging data) and provided overall response assessments at different time points using IMWG response criteria, while remaining blinded to investigator-assessed responses.

- **Statistical methods**

Estimands

Primary Estimand: the treatment effect of elranatamab on ORR as assessed by BICR per the IMWG criteria. The estimand has the following attributes:

- Population: RRMM participants, as defined by the inclusion and exclusion criteria to reflect the targeted population of the treatment, who received at least one dose of study intervention.
- Variable: OR defined as confirmed sCR, CR, VGPR and PR according to the IMWG criteria based on BICR assessment, from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy.
- Intercurrent event(s): All data collected after an intercurrent event of subsequent anticancer therapy will be excluded except if required to confirm PD. All response assessments regardless of gaps in disease assessments were planned to be considered. Participants who do not have a post-baseline disease assessment due to early confirmed PD, who receive anticancer therapies other than the study intervention prior to achieving an OR, or who die, experience confirmed PD, or stop disease assessments for any reason prior to achieving an OR were planned to be counted as non-responders.
- Population-level summary measure: ORR defined as the proportion of participants in the analysis population with an OR and 2-sided 95% CI for ORR.

The key secondary estimand for ORR by BICR baseline EMD status per IMWG for Cohort A is the same as the primary estimand except performed separately for participants with and without EMD at baseline per BICR.

Statistical Hypotheses

This study has two cohorts: Cohort A was planned to enrol participants who are naïve to BCMA directed therapies, and Cohort B will enrol participants who have prior exposure to BCMA directed therapies. The primary objective of this study is to determine the efficacy in Cohort A and Cohort B with respect to ORR by BICR, as defined by IMWG.

In Cohort A, the study was planned to test the null hypothesis that the ORR by BICR as defined by IMWG is ≤30% versus the alternative hypothesis that the ORR by BICR as defined by MWG is >30%. The null hypothesis ORR for this cohort is based on the results of the DREAMM-2 study (Lonial et al, 2020b) and the STORM study (Chari et al, 2019), which were conducted in similar multiple myeloma populations with respect to prior treatments.

In Cohort B, the study will test the null hypothesis that the ORR by BICR as defined by IMWG is ≤15% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >15%. There were limited data available on the response rate after retreatment with a BCMA antibody drug conjugate or CAR-T therapy, but it is expected that the ORR would likely be notably lower than the BCMA naïve population. Thus, a null ORR of 15% was anticipated to be a reasonable estimate.

Analysis of the primary endpoint and multiplicity

The primary endpoint of ORR by BICR was defined as the proportion of participants with an OR by BICR per IMWG criteria and was planned to be analysed in the Safety Analysis Set. Point estimates of ORR by BICR in each of Cohort A and Cohort B was planned to be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method. The null hypothesis was planned to be tested at 1-sided alpha of 0.025. independently in the two cohorts using the exact binomial test, and the corresponding 1-sided p-value will be provided separately for Cohort A and Cohort B.

Interim Analysis for Futility and Efficacy

An IA for both (non-binding) futility and efficacy was planned to be conducted on ORR by BICR for Cohort A based on the first 90 participants enrolled and treated in that cohort. At the IA for Cohort A, if there are ≤31 (34.4%) objective responders by BICR observed, accrual was planned to be stopped for further evaluation due to futility; if there are ≥38 (42.2%) objective responders by BICR observed, the efficacy boundary was planned to be considered crossed; if the IA crosses neither the futility boundary nor the efficacy boundary, Cohort A was planned to proceed as planned to the final analysis. If the efficacy boundary is crossed, enrolment to the study was planned to continue up to the specified number of participants for the final analysis, and all ongoing participants were planned to continue with scheduled visits.

An IA for (non-binding) futility and efficacy was planned to be conducted on ORR by BICR for Cohort B based on the first 30 participants enrolled and treated in that cohort. At the IA for Cohort B, if there are ≤3 (10.0%) objective responders by BICR observed, accrual was planned to be stopped for further evaluation due to futility; if there are ≥11 (36.7%) objective responders by BICR observed, the efficacy boundary was planned to be considered crossed; if the IA crosses neither the futility boundary nor the efficacy boundary, Cohort B was planned to proceed as planned to the final analysis. If the efficacy boundary is crossed, enrolment to the study was planned to continue up to the specified number of participants for the final analysis, and all ongoing participants will continue with scheduled visits.

Each respective interim analysis was planned to occur no earlier than the point at which all early responders (i.e., those who respond within the first 3 post-baseline assessments) among the participants to be included have had their responses confirmed. At the time of the interim analysis, the testing rule was planned to depend on the actual number of participants included in the analysis for each cohort with sufficient follow-up.

At the time of the SAP amendment prior to the interim analysis, 94 Cohort A participants were initially dosed at least 4 months prior to the data cutoff and were to be included in the interim analysis. The updated boundaries were ≤33 (35.1%) objective responders by BICR for futility and ≥41 (43.6%) objective responders by BICR for efficacy. It was determined no interim analysis would be performed for Cohort B participants as not enough participants had adequate follow-up since Cohort B had a

higher incidence of EMD at baseline compared to Cohort A. The boundaries at the final analysis for Cohort B do not change if no interim analysis is performed.

Operating characteristics (Type I and Type II error) were calculated using the exact binomial distribution and were detailed in the SAP. It can be noted that the futility stopping boundary for both cohorts at the interim and final analyses use the rho family beta-spending boundary with parameter = 3 and that the efficacy stopping boundary for both cohorts at the interim and final analyses use the rho family alpha-spending boundary with parameter = 5.

Results

- **Participant flow**

In total 237 subjects were screened for inclusion in the study and 187 participants (123 in Cohort A and 64 in Cohort B) were assigned to and received at least one dose of study treatment. 45 participants failed screening. .The most common screen failure reasons were:

- not meeting bone marrow function criteria (ANC ≥1.0 x 109/L, platelets ≥25 x 109/L, haemoglobin ≥8 g/dL) (n=13);
- not meeting measurable disease per IMWG criteria (n=9);
- having surgical/medical/psychiatric condition that per investigator's judgment makes participation inappropriate (n=5);
- not meeting renal function criteria (estimated CrCl >=30 mL/min) (n=4);
- not meeting LVEF criterion (≥40%) (n=4); and
- not meeting inclusion criterion requiring that participants be refractory to at least one anti-CD38 antibody (n=3).
- Other screen fail reasons were reported for ≤ 2 individuals.

5 individuals were not enrolled but were not summarised as screen failures are as follows:

- not enrolled due to US FDA partial clinical hold (n=2),
- withdraw consent (n=1),
- immediate multiple myeloma treatment required (n=1),
- prostate cancer (n=1).

- **Recruitment**

First subject enrolled: 09 February 2021.

The study is ongoing.

- **Conduct of the study**

All changes in the conduct of the study were implemented in a total of 9 protocol amendments.

Per Amendment 1 from 07 January 2021 patients below the age of 18 years old were removed, standardisation of switching between QW and Q2W was introduced, threshold for MRD negativity 10E-5 has been added, end of study criterion was introduced, which specified that the study will be completed when all participants will be followed for at least 2 years, rationale for hypothesis has been introduced and power changed from 80% to 90% to detect ORR 48% in Cohort A and 34% in Cohort B.

Protocol modifications made per Amendment 2 from 14 February 2021, Amendment 3 from 24 March 2021 and Amendment 4 from 09 April 2021 were relevant only from a safety perspective.

Per Amendment 5 from 2 May 2023 interim analysis set populations for Cohort A and B were further defined.

Per Amendment 6 from 30 May 2021 imaging schedule was made mandatory to be repeated every 12 weeks for subjects with EMD.

Per Amendment 7 from 11 November 2021 the total number of planned participants was elevated from 150 to 180 subjects to allow for more robust dataset. Power and sample size calculations were updated to be based on normal distribution from exact method. Also, interim analysis was revised to include more robust data and the FU period was revised. Also, a statement that IA may be used for decision making has been added. Sampling for disease monitoring was amended for some situations.

Per Amendment 8, from 23 December 2021 it was clarified that all participants would be enrolled for the final analysis if the interim efficacy boundary is crossed. It was clarified that the operating characteristics for the design are in the SAP. Also, posterior probability threshold for some safety AEs was adjusted.

Per Amendment 9 from 29 July 2022 key efficacy endpoint ORR by BICR on baseline EMD status for Cohort A has been added. Also, the protocol was further aligned with SAP including IA plans for Cohort B.

All protocol deviations were systematically reviewed by the study team to identify potentially important protocol deviations (IPDs).

At least 1 IPD was reported in 148 (79.1%) of participants. None of these deviations led to exclusion of data from the efficacy or safety analyses.

The protocol deviation categories with the highest frequency (≥ 20%) were Procedures/Tests (30.5%), Safety Reporting (29.9%), Informed Consent (29.4%), Investigational Product (28.3%), and Visit Schedule (27.8%). Of all enrolled participants, a total of 9 participants (4 in Cohort A and 5 in Cohort B) did not meet study eligibility criteria, including 6 participants (Cohort A: 4; Cohort B: 2) due to inclusion criteria and 3 participants (all in Cohort B) due to an exclusion criterion.

- **Baseline data**

Demographics, disease characteristics and prior multiple myeloma therapies are summarised separately for Cohorts A and B and for all patients in this section.

Table 12. Demographic characteristics (Safety Analysis Set) (Protocol C1071003)

	Cohort A (N=123)	Cohort B (N=64)	Total (N=187)
Age (Years), n (%)			
18 -< 65	43 (35.0)	28 (43.8)	71 (38.0)
≥ 65	80 (65.0)	36 (56.3)	116 (62.0)
≥ 65 -< 75	56 (45.5)	24 (37.5)	80 (42.8)
< 75	99 (80.5)	52 (81.3)	151 (80.7)
≥ 75	24 (19.5)	12 (18.8)	36 (19.3)
Mean (SD)	67.1 (9.45)	65.7 (9.42)	66.6 (9.43)
Q1	63.0	60.5	61.0

	Cohort A (N=123)	Cohort B (N=64)	Total (N=187)
Median	68.0	67.0	68.0
Q3	73.0	71.5	73.0
Range	(36, 89)	(41, 84)	(36, 89)
Gender, n (%)			
Male	68 (55.3)	30 (46.9)	98 (52.4)
Female	55 (44.7)	34 (53.1)	89 (47.6)
Race, n (%)			
White	72 (58.5)	44 (68.8)	116 (62.0)
Black or African American	9 (7.3)	2 (3.1)	11 (5.9)
Asian	16 (13.0)	1 (1.6)	17 (9.1)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Multiracial	0	0	0
Unknown	2 (1.6)	1 (1.6)	3 (1.6)
Not reported	24 (19.5)	16 (25.0)	40 (21.4)
Ethnicity, n (%)			
Hispanic or Latino	11 (8.9)	7 (10.9)	18 (9.6)
Not Hispanic or Latino	85 (69.1)	34 (53.1)	119 (63.6)
Not reported	26 (21.1)	22 (34.4)	48 (25.7)
Missing	1 (0.8)	1 (1.6)	2 (1.1)
Geographic Region, n (%)			
North America	58 (47.2)	37 (57.8)	95 (50.8)
Europe	45 (36.6)	26 (40.6)	71 (38.0)
Asia	12 (9.8)	0	12 (6.4)
Other	8 (6.5)	1 (1.6)	9 (4.8)

Cutoff date is 14 October 2022 for all participants.

Table 13. Baseline characteristics (Safety Analysis Set) (Protocol C1071003)

	Cohort A (N=123)	Cohort B (N=64)	Total (N=187)
ECOG Performance Status, n(%)			
0	45 (36.6)	20 (31.3)	65 (34.8)
1	71 (57.7)	40 (62.5)	111 (59.4)
2	7 (5.7)	4 (6.3)	11 (5.9)
3	0	0	0
Missing	0	0	0
Disease Stage (R-ISS), n(%)			
I	28 (22.8)	11 (17.2)	39 (20.9)
II	68 (55.3)	36 (56.3)	104 (55.6)
III	19 (15.4)	15 (23.4)	34 (18.2)
UNKNOWN	8 (6.5)	2 (3.1)	10 (5.3)
Missing	0	0	0

	Cohort A (N=123)	Cohort B (N=64)	Total (N=187)
Cytogenetic Risk, n(%)			
Standard Risk	83 (67.5)	42 (65.6)	125 (66.8)
High-Risk	31 (25.2)	13 (20.3)	44 (23.5)
Missing	9 (7.3)	9 (14.1)	18 (9.6)
Extramedullary Disease by INV, n(%)			
Yes	38 (30.9)	36 (56.3)	74 (39.6)
Target EMD	25 (20.3)	25 (39.1)	50 (26.7)
non-Target EMD only	13 (10.6)	11 (17.2)	24 (12.8)
Missing	0	0	0
No	85 (69.1)	28 (43.8)	113 (60.4)
Non-target Bone Lesions Only	34 (27.6)	14 (21.9)	48 (25.7)
No Lesion	51 (41.5)	14 (21.9)	65 (34.8)
Missing	0	0	0
Extramedullary Disease by BICR, n(%)			
Yes	39 (31.7)	37 (57.8)	76 (40.6)
Target EMD	37 (30.1)	36 (56.3)	73 (39.0)
non-Target EMD only	2 (1.6)	1 (1.6)	3 (1.6)
Missing	0	0	0
No	84 (68.3)	27 (42.2)	111 (59.4)
Non-target Bone Lesions Only	43 (35.0)	21 (32.8)	64 (34.2)
No Lesion	41 (33.3)	6 (9.4)	47 (25.1)
Missing	0	0	0
Participants with non-target bone lesions only by INV, n(%)			
1-4	25 (20.3)	12 (18.8)	37 (19.8)
5-10	9 (7.3)	2 (3.1)	11 (5.9)
>10	0	0	0
Participants with non-target bone lesions only by BICR, n(%)			
1-4	42 (34.1)	21 (32.8)	63 (33.7)
5-10	1 (0.8)	0	1 (0.5)
>10	0	0	0
Type of Myeloma, n(%)			
IgG	65 (52.8)	41 (64.1)	106 (56.7)
Non-IgG	21 (17.1)	8 (12.5)	29 (15.5)
IgA	20 (16.3)	7 (10.9)	27 (14.4)
IgD	1 (0.8)	1 (1.6)	2 (1.1)
IgE	0	0	0
IgM	0	0	0
Light chain only	24 (19.5)	10 (15.6)	34 (18.2)
Unknown	13 (10.6)	5 (7.8)	18 (9.6)
Measurable Disease at Baseline, n(%)			
Yes	123 (100.0)	63 (98.4)	186 (99.5)
Type			
Serum M-protein	78 (63.4)	37 (57.8)	115 (61.5)
Urine M-protein	32 (26.0)	17 (26.6)	49 (26.2)
Serum free light chain*	24 (19.5)	16 (25.0)	40 (21.4)
No	0	1 (1.6)	1 (0.5)

	Cohort A (N=123)	Cohort B (N=64)	Total (N=187)
Missing	0	0	0
Baseline bone marrow plasma cells, n(%)			
<50%	89 (72.4)	44 (68.8)	133 (71.1)
>=50%	26 (21.1)	11 (17.2)	37 (19.8)
Missing	8 (6.5)	9 (14.1)	17 (9.1)
Renal Function, n(%)			
CrCl <= 60 mL/min	42 (34.1)	23 (35.9)	65 (34.8)
CrCl > 60 mL/min	81 (65.9)	41 (64.1)	122 (65.2)
Missing	0	0	0
Liver Function, n(%)			
Normal	106 (86.2)	49 (76.6)	155 (82.9)
Impaired	17 (13.8)	15 (23.4)	32 (17.1)
Missing	0	0	0
Participants with at least one poor prognosis feature**, n(%)	81 (65.9)	48 (75.0)	129 (69.0)

Chromosomal abnormalities by FISH and/or Karyotyping.
"High-Risk" if any of the following 3 chromosomal abnormalities in interest is "YES": T(4;14), T(14;16), DEL (17P).
Liver function: Normal = AST and total bilirubin ≤ ULN, Impaired = AST or total bilirubin > ULN (including both AST and total bilirubin >ULN).
Chromosomal abnormalities by FISH and Karyotyping.
* Includes measurable FLC only patients.
Extramedullary disease (EMD) was defined as presence of any plasmacytoma (extramedullary and/or paramedullary) with a soft-tissue component.
** Includes participants who have at least one of the following: ECOG of 2, R-ISS of 3, EMD at baseline by BICR, high cytogenetic risk or bone marrow plasma cell involvement >=50%.

Cutoff date is 14 October 2022 for all participants.

Table 14. Prior anticancer therapy (Safety Analysis Set) (Protocol C1071003)

	Cohort A (N=123)	Cohort B (N=64)	Total (N=187)
Number of Prior Anticancer Therapy Line			
2	5 (4.1)	0	5 (2.7)
3	21 (17.1)	1 (1.6)	22 (11.8)
4	33 (26.8)	5 (7.8)	38 (20.3)
5	22 (17.9)	9 (14.1)	31 (16.6)
6	16 (13.0)	7 (10.9)	23 (12.3)
7	10 (8.1)	10 (15.6)	20 (10.7)
8	4 (3.3)	12 (18.8)	16 (8.6)
9	4 (3.3)	6 (9.4)	10 (5.3)
10	5 (4.1)	4 (6.3)	9 (4.8)
> 10	3 (2.4)	10 (15.6)	13 (7.0)
1 - 3	26 (21.1)	1 (1.6)	27 (14.4)
4 - 5	55 (44.7)	14 (21.9)	69 (36.9)
> 5	42 (34.1)	49 (76.6)	91 (48.7)
Missing	0	0	0
Mean (SD)	5.2 (2.58)	7.9 (3.03)	6.1 (3.01)
Median (range)	5.0 (2, 22)	7.5 (3, 19)	5.0 (2, 22)
Participants with Prior IMiDs	123 (100.0)	64 (100.0)	187 (100.0)

Lenalidomide	121 (98.4)	62 (96.9)	183 (97.9)
Pomalidomide	100 (81.3)	61 (95.3)	161 (86.1)
Thalidomide	36 (29.3)	18 (28.1)	54 (28.9)
Iberdomide	1 (0.8)	4 (6.3)	5 (2.7)
Other IMiDs	2 (1.6)	2 (3.1)	4 (2.1)
Participants with Prior PI	123 (100.0)	64 (100.0)	187 (100.0)
Bortezomib	119 (96.7)	62 (96.9)	181 (96.8)
Carfilzomib	93 (75.6)	56 (87.5)	149 (79.7)
Ixazomib	30 (24.4)	21 (32.8)	51 (27.3)
Other PI	1 (0.8)	1 (1.6)	2 (1.1)
Participants with Prior Anti-CD38	123 (100.0)	64 (100.0)	187 (100.0)
Daratumumab	113 (91.9)	60 (93.8)	173 (92.5)
Isatuximab	16 (13.0)	15 (23.4)	31 (16.6)
Other anti-CD38	0	1 (1.6)	1 (0.5)
Participants who are Triple-class Exposed [1]	123 (100.0)	64 (100.0)	187 (100.0)
Participants who are Triple-class Refractory [2]	119 (96.7)	62 (96.9)	181 (96.8)
Participants who are Penta-drug Exposed [3]	87 (70.7)	54 (84.4)	141 (75.4)
Participants who are Penta-drug Refractory [4]	52 (42.3)	33 (51.6)	85 (45.5)
Refractory to Last Line of Therapy	118 (95.9)	56 (87.5)	174 (93.0)
Participants with Prior Stem Cell Transplant	87 (70.7)	53 (82.8)	140 (74.9)
Autologous	84 (68.3)	53 (82.8)	137 (73.3)
Allogeneic	7 (5.7)	2 (3.1)	9 (4.8)
Syngeneic	0	0	0
Unknown	0	1 (1.6)	1 (0.5)
Participants with Prior BCMA-targeted therapy	0	64 (100.0)	64 (34.2)
ADC	0	46 (71.9)	46 (24.6)
CAR-T	0	21 (32.8)	21 (11.2)
ADC and CAR-T	0	3 (4.7)	3 (1.6)
Anti-BCMA Bi-specific	0	1 (1.6)	1 (0.5)

[1] Triple-class exposed refers to having received at least 1 PI, 1 IMID and 1 anti-CD38.
[2] Triple-class refractory refers to refractory to at least 1 PI, 1 IMID and 1 anti-CD38.
[3] Penta-drug exposed refers to having received at least 2 PIs, 2 IMIDs and 1 anti-CD38.
[4] Penta-drug refractory refers to refractory to at least 2 PIs, 2 IMIDs and 1 anti-CD38.
Cutoff date is 14 October 2022 for all participants.

- **Numbers analysed**

Table 15. Participant evaluation groups (Protocol C1071003)

	Cohort A (N=123) n (%)	Cohort B (N=64) n (%)	Total (N=187) n (%)
Treated	123 (100.0)	64 (100.0)	187 (100.0)
Not Treated	0	0	0
Safety Analysis Set	123 (100.0)	64 (100.0)	187 (100.0)
PRO Analysis Set	116 (94.3)	54 (84.4)	170 (90.9)
Immunogenicity Analysis Set	123 (100.0)	64 (100.0)	187 (100.0)
MRD Evaluable	22 (17.9)	2 (3.1)	24 (12.8)
PK Analysis Set	123 (100.0)	64 (100.0)	187 (100.0)

The PRO analysis set includes all participants in the safety analysis set who completed a baseline (last PRO assessment prior to or on the first dose of study intervention) and at least one post-baseline PRO assessment.
MRD evaluable population includes patients with CR/sCR and with at least one MRD assessment.
Cutoff date is 14Oct2022 for all data types except PK, PD. For PK, PD data cutoff date is 17Jun2022.

- **Outcomes and estimation**

The applicant provided data from two different cut-off dates: 14th of October 2022 and 16th of April 2023. Data presented in this section are from the latest data cut-off date unless otherwise specified.

Primary endpoint: Overall Response Rate

Table 16. Summary of overall best confirmed response based on blinded independent review committee (BIRC) Cohort A (Safety Analysis Set) (Protocol C1071003)

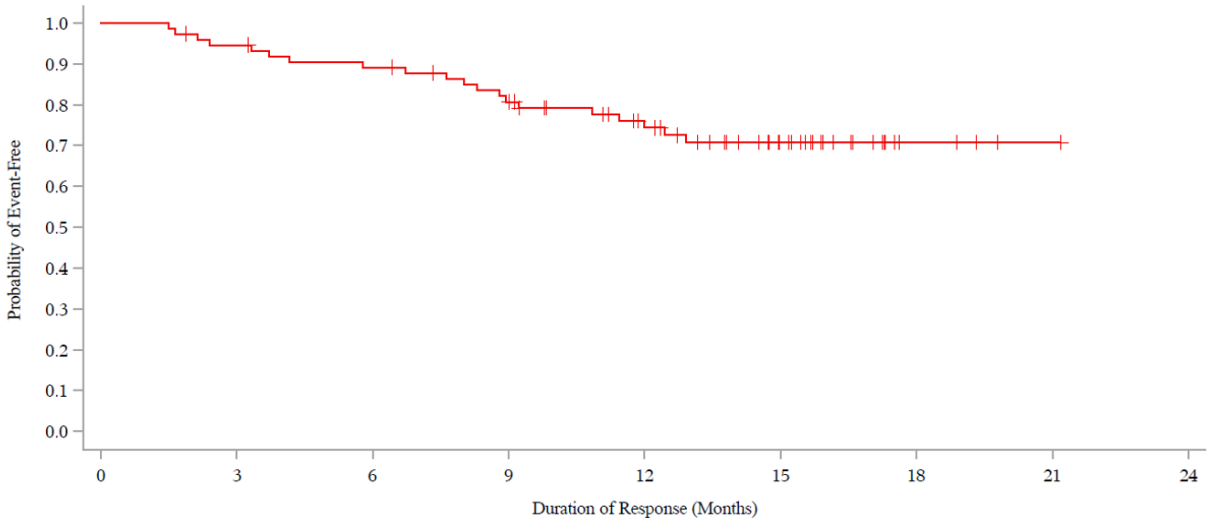
	Cohort A (N=123)
Best Overall Response, n (%)	
Stringent Complete Response (sCR)	19 (15.4)
Complete response (CR)	25 (20.3)
Very Good Partial Response (VGPR)	25 (20.3)
Partial response (PR)	6 (4.9)
Minimal Response (MR)	0
Stable disease (SD)	21 (17.1)
Progressive disease (PD)	22 (17.9)
Not evaluable (NE)	5 (4.1)
Objective Response (sCR+CR+VGPR+PR) Rate, n (%)	75 (61.0)
95% CI [1]	51.8, 69.6
p-value (exact, one-sided)	<0.0001
Complete Response (sCR+CR) Rate, n (%)	44 (35.8)
95% CI [1]	27.3, 44.9
VGPR or Better (sCR+CR+VGPR) Rate, n (%)	69 (56.1)
95% CI [1]	46.9, 65.0
Clinical Benefit (sCR+CR+VGPR+PR+MR) Rate, n (%)	75 (61.0)
95% CI [1]	51.8, 69.6
Participants still on-treatment without progression and confirmed response	0
Responders still on-treatment without progression and confirmed VGPR	1 (0.8)
Responders still on-treatment without progression and confirmed CR	8 (6.5)

[1] Clopper-Pearson method used.
For Cohort A: 1-sided efficacy boundary p-value <= 0.0202(>=48 responders) for H0: ORR<=30%

Duration of response

Among responders, after a median (range) follow-up from initial response of 15.21 (2.40, 24.21) months, the median DOR (months) was not yet reached (95% CI: NE, NE), and the Kaplan-Meier probability of maintaining response at 15 months was 70.8% (95% CI: 58.2, 80.2) (Figure 7). Based on data as of the cut-off date and assuming a model with an increased failure rate over time as a realistic estimate, the projected median DOR was >20 months.

Figure 7. Duration of response by BICR (Responders in Cohort A) – Kaplan-Meier Plot (Protocol C1071003)



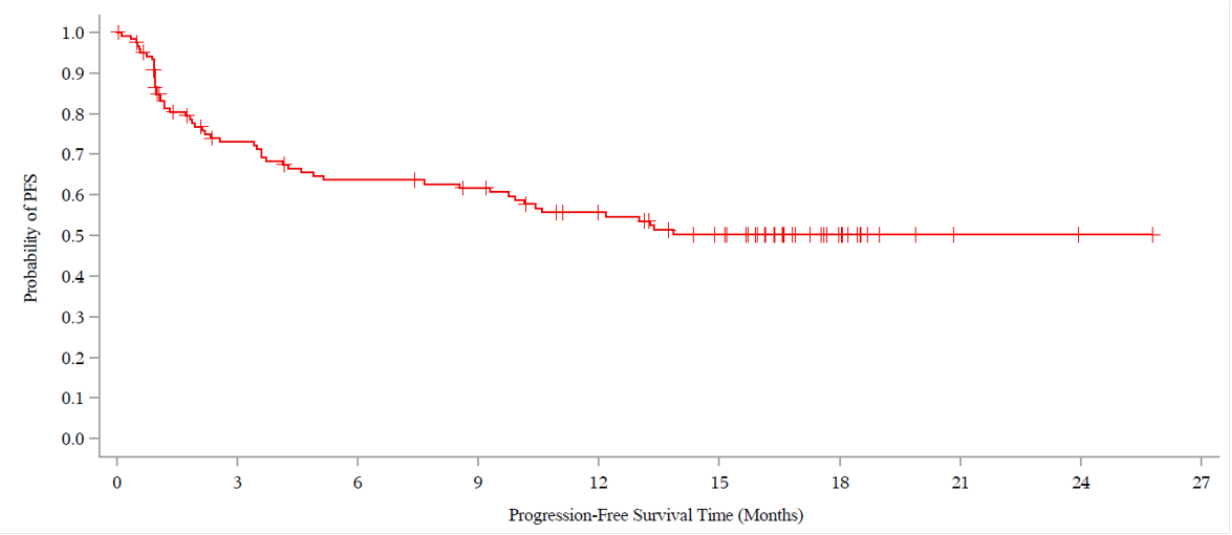
Minimal residual disease

In the overall population, there were 26 (21.1% [95% CI: 14.30, 29.42]) participants who were MRD-negative at a sensitivity of 10^{-5}. Among participants with sCR/CR (n=44), 59.1% (95% CI: 43.25, 73.66) were MRD negative and among evaluable participants (those with sCR/CR and with an evaluable sample, n=29), 89.7% (95% CI: 72.65, 97.81) were MRD negative.

Progression-free survival

The median PFS by BICR in months was not yet reached at the latest data cut-off date (95% CI: 9.8, NE), and the Kaplan-Meier probability of being event-free at 15 months was 50.2% (95% CI: 40.2, 59.3) (Figure 8).

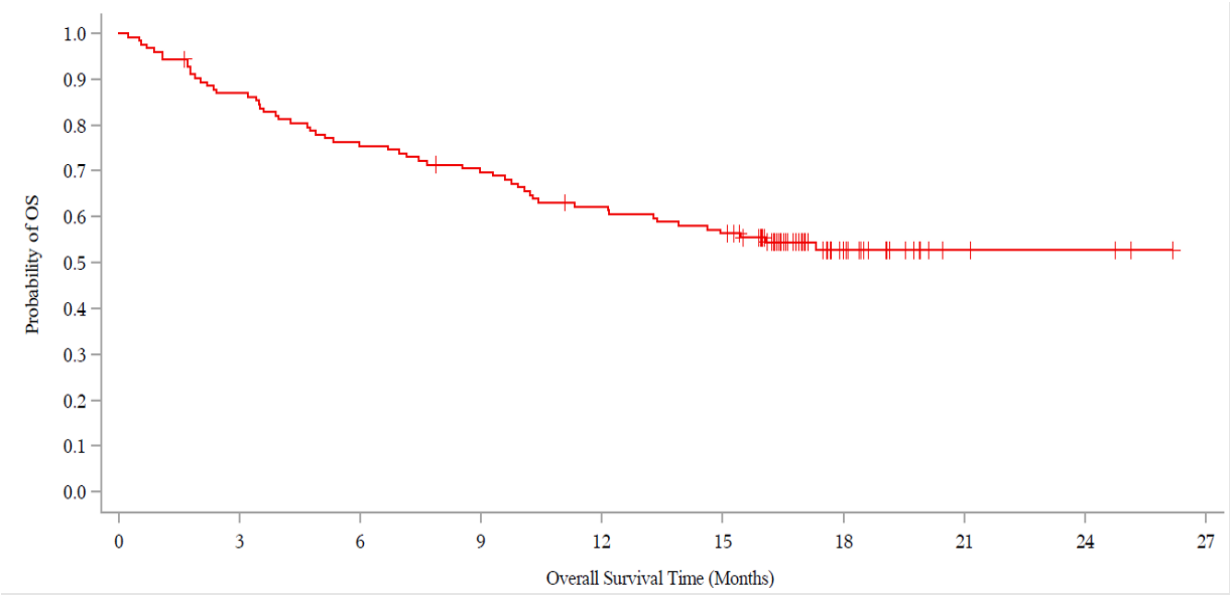
Figure 8. Progression-free survival by BICR – Kaplan-Meier plot (Cohort A Participants in Safety Analysis Set) (Protocol C1071003)



Overall survival

OS data were immature as of the data cut-off date, 56 (45.5%) participants had died (Figure 9. The median OS (months) was not yet reached (95% CI: 13.4, NE), and the Kaplan-Meier probability of being alive at 15 months was 56.3% (95% CI: 47.0, 64.6).

Figure 9. Kaplan-Meier plot of overall survival (Cohort A participants in Safety Analysis Set) (Protocol C1071003)



C1071003 Cohort B supportive – anti BCMA pre-treated

Efficacy data by BICR for Cohort B which included 64 patients treated with prior BCMA-targeted therapy are summarised as follows:

- The ORR was 34.4% (95% CI: 22.9, 47.3; null hypothesis rate of 15%). 32.8% achieved VGPR or better and 10.9% achieved CR or better. Responses deepened over time with 2 (3.1%) new patients achieving a best overall response of CR or sCR in this updated analysis. Six (9.4%) responders are still on-treatment and have not achieved CR.
- Among responders, after a median (range) follow-up from initial response of 13.42 (2.43, 16.95) months, the median DOR (months) was not yet reached (95% CI: 11.8, NE), and the Kaplan-Meier probability of maintaining response at 15 months was 67.5% (95% CI: 40.9, 84.1). Based on data as of the cut-off date and assuming a model with an increased failure rate over time as a realistic estimate, the projected median DOR was >20 months.
- Among responders, the median DOCR by BICR was not yet reached (95% CI: 9.2, NE); 5 (71.4%) of participants were ongoing without an event.
- The median PFS by BICR was 3.5 (95% CI: 1.9, 6.6) months.
- The median OS was 11.3 (95% CI: 6.5, NE) months.

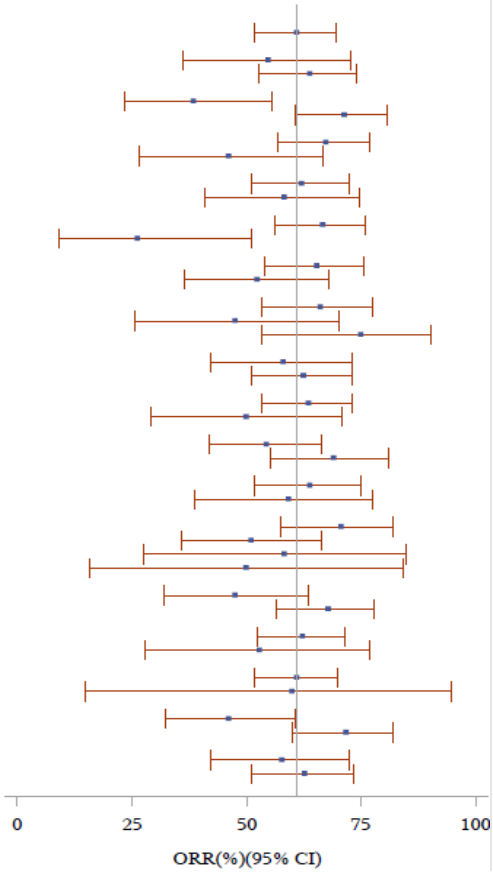
- **Ancillary analyses**

Comparison of Results in Subpopulations (original data cut-off 14 October 2022)

In Cohort A, a consistent ORR benefit as assessed by BICR was observed across prespecified subgroups. Although differences in ORR were observed in participants with poor prognostic features, including EMD at baseline, disease stage (R-ISS) III, and penta-refractory disease, the ORR in these subgroups was clinically meaningful (Figure 10. In Cohort A, an analysis by number of prior lines of treatment showed an efficacy benefit across all lines of treatment including in heavily pretreated participants; however, efficacy was higher in less pretreated participants. Among participants with 2-3 prior lines (n=26), 4-5 prior lines (n=55), and ≥6 prior lines (n=42), the confirmed ORR by BICR was 73.1% (95% CI: 52.2, 88.4), 61.8% (95% CI: 47.7, 74.6), and 52.4% (95% CI: 36.4, 68.0), respectively (Table 14.2.1.1.8). Similar results were observed in Cohort B (data not shown); a consistent ORR benefit as assessed by BICR was observed across prespecified subgroups. Although a difference in ORR was observed in participants with EMD at baseline (a poor prognostic feature), the ORR in this subgroup was considered clinically meaningful.

Figure 10. Forest plot – Objective response rate by BICR in subsets (Safety Analysis Set) (Cohort A) (Protocol C1071003)

Subgroup	Responders(n)/Participants(N)	ORR (%) (95% CI)
All Participants	75/123	61.0 (51.8, 69.6)
Baseline Cytogenetics		
High Risk	17/31	54.8 (36.0, 72.7)
Standard Risk	53/83	63.9 (52.6, 74.1)
Baseline Extramedullary Disease		
Yes	15/39	38.5 (23.4, 55.4)
No	60/84	71.4 (60.5, 80.8)
Baseline Bone Marrow Plasma Cells		
<50%	60/89	67.4 (56.7, 77.0)
>=50%	12/26	46.2 (26.6, 66.6)
Prior Stem Cell Transplant		
Yes	54/87	62.1 (51.0, 72.3)
No	21/36	58.3 (40.8, 74.5)
Disease stage		
1-2	64/96	66.7 (56.3, 76.0)
3	5/19	26.3 (9.1, 51.2)
Number of Prior Lines		
<=5	53/81	65.4 (54.0, 75.7)
>5	22/42	52.4 (36.4, 68.0)
Type of Myeloma		
IgG	43/65	66.2 (53.4, 77.4)
Non-IgG	10/21	47.6 (25.7, 70.2)
Light chain only	18/24	75.0 (53.3, 90.2)
Age (Years)		
<65	25/43	58.1 (42.1, 73.0)
>=65	50/80	62.5 (51.0, 73.1)
<75	63/99	63.6 (53.4, 73.1)
>=75	12/24	50.0 (29.1, 70.9)
Sex		
Male	37/68	54.4 (41.9, 66.5)
Female	38/55	69.1 (55.2, 80.9)
Race		
White	46/72	63.9 (51.7, 74.9)
Others	16/27	59.3 (38.8, 77.6)
Region		
North America	41/58	70.7 (57.3, 81.9)
Europe	23/45	51.1 (35.8, 66.3)
Asia	7/12	58.3 (27.7, 84.8)
Other	4/8	50.0 (15.7, 84.3)
Renal Function		
CrCl <= 60 mL/min	20/42	47.6 (32.0, 63.6)
CrCl > 60 mL/min	55/81	67.9 (56.6, 77.8)
Liver Function		
Normal	66/106	62.3 (52.3, 71.5)
Impaired	9/17	52.9 (27.8, 77.0)
Refractory to Last Therapy		
Yes	72/118	61.0 (51.6, 69.9)
No	3/5	60.0 (14.7, 94.7)
Penta Refractory		
Yes	24/52	46.2 (32.2, 60.5)
No	51/71	71.8 (59.9, 81.9)
ECOG		
0	26/45	57.8 (42.2, 72.3)
1-2	49/78	62.8 (51.1, 73.5)



- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of efficacy for trial MAGNETISMM-3 (C1071003)

Title: An Open-Label, Multicenter, Non-Randomized Phase 2 Study of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One Proteasome Inhibitor, One Immunomodulatory Drug and One Anti-CD38 Antibody		
Study identifier	C1071003, 2020-004533-21, NCT04649359	
Design	Phase 2, open-label, non-randomised, multicenter	
	Duration of main phase:	First participant first dose (FPFD) on 09 February 2021, the study is ongoing; Clinical data cut-off date 16 April 2023. Study intervention to be administered until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination.
Hypothesis	Exploratory: To evaluate whether single-agent elranatamab can provide clinical benefit in participants with RRMM who are refractory to at least one proteasome inhibitor (PI), one immunomodulatory drug (IMiD) and one anti-cluster of differentiation (CD) CD38 monoclonal antibody. • Cohort A included participants who had not received prior B-cell maturation antigen (BCMA)-directed therapy (BCMA-naïve) • Cohort B included participants who had received prior BCMA-directed antibody-drug conjugate (ADC) or BCMA-directed chimeric antigen receptor T cell (CAR T-cell) therapy, either approved or investigational (BCMA-exposed). The primary endpoint was confirmed objective response rate (ORR) by Blinded Independent Central Review (BICR) per International Myeloma Working Group (IMWG) in Cohort A and Cohort B. In Cohort A, the study tested the null hypothesis that the ORR by BICR is ⩽30% versus the alternative hypothesis that the ORR by BICR is >30%. In Cohort B, the study tested the null hypothesis that the ORR by BICR is ⩽15% versus the alternative hypothesis that the ORR by BICR is >15%. If the null hypothesis for ORR by BICR was rejected for Cohort A, the key secondary endpoint of ORR by BICR for those without extramedullary disease (EMD) at baseline would be tested in a hierarchical fashion using the gatekeeping procedure that the ORR is ⩽38% with a 1-sided significance level of 0.025. If the null hypothesis for ORR by BICR for those without EMD at baseline was rejected for Cohort A, the key secondary endpoint of ORR by BICR for those with EMD at baseline would be tested in a hierarchical fashion using the gatekeeping procedure that the ORR is ⩽12% with a 1-sided significance level of 0.025	
Treatments groups	Elranatamab monotherapy subcutaneous (SC) every week (QW) at 76 mg starting Cycle 1 Day 8 with a 2 step-up priming dose of 12 mg (Cycle 1 Day 1) and 32 mg on (Cycle 1 Day 4) • Cohort A: BCMA naïve (no prior BCMA-directed therapy): N=123 • Cohort B: BCMA exposed (prior BCMA-directed therapy [ADC and /or CAR-T]): N=64	

Endpoints and definitions	Primary endpoint	ORR by BICR per IMWG	ORR by BICR is defined as the proportion of participants with an objective response by BICR per IMWG criteria. Objective response is defined as having a best overall response (BOR) of confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) per IMWG criteria, from the date of first dose until confirmed progressive disease (PD), death or start of new anticancer therapy, whichever occurs first.
	Key Secondary	ORR by BICR EMD baseline status for Cohort A	ORR by BICR baseline extramedullary disease (EMD) status for Cohort A is defined the same as the primary endpoint except separately for participants with and without EMD at baseline per BICR.
	Secondary	CRR	Complete response rate (CRR) is defined as the proportion of participants with a BOR of confirmed sCR/CR per IMWG criteria.
	Secondary	DOR	Duration of response (DOR) is defined, for participants with an objective response per IMWG criteria, as the time from the first documentation of objective response that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, or start of new anticancer therapy, whichever occurs first, or censoring.
	Secondary	DOCR	Duration of complete response (DOCR) is defined, for participants with a sCR/CR per IMWG criteria, as the time from the first documentation of sCR/CR that is subsequently confirmed, until confirmed PD per IMWG criteria, or death due to any cause, or start of new anticancer therapy, whichever occurs first, or censoring.
	Secondary	TTR	Time to response (TTR) is defined, for participants with an objective response per IMWG criteria, as the time from the date of first dose to the first documentation of objective response that is subsequently confirmed.
	Secondary	PFS	Progression-free survival (PFS) is defined as the time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause, or start of new anticancer therapy, whichever occurs first, or censoring.
	Secondary	OS	Overall survival (OS) is defined as the time from the date of first dose until death due to any cause or censoring.
	Secondary	MRD	Minimal Residual Disease (MRD) (assessed by central lab) negativity rate is the proportion of participants with sCR/CR and with negative MRD per IMWG sequencing criteria by bone marrow aspirate (BMA) from the date of first dose until confirmed PD, death or start of new anticancer therapy, whichever occurs first.
Database lock	The clinical cutoff date for the analysis: 16 April 2023, >15 months after the last participant first dose.		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Primary efficacy data are presented for participants from Study C1071003 which includes 123 participants in Cohort A and 64 participants in Cohort B. Efficacy analyses for the primary and secondary efficacy endpoint analyses in these participants were based on a 16 April 2023 data cutoff date. The final analysis evaluation set (interchangeable with safety analysis set) for efficacy includes all enrolled participants who received at least one dose of study intervention. The median (range) follow-up since initial dose was 15.21 (2.40, 24.21) months for Cohort A and 13.42 (2.43, 16.95) months for Cohort B.	
Descriptive statistics and estimate variability	**Treatment group**	**Cohort A**
	Number of participants	123
	ORR by BICR per IMWG (%)	61.0
	95% CI (%)	51.8, 69.6
	ORR by BICR without baseline EMD (%)	71.4
	95% CI (%)	60.5, 80.8
	ORR by BICR with baseline EMD (%)	38.5
	95% CI (%)	23.4, 55.4
	CRR by BICR (%)	35.8
	95% CI (%)	27.3, 44.9
	Median DOR (months) by BICR	Not yet reached
	95% CI (%)	NE, NE
	Kaplan Meier Probability of Maintaining Response at 15 months (%)	70.8
	95% CI (%)	58.2, 80.2
	Median DOCR (months) by BICR	Not yet reached
	95% CI (%)	NE, NE
	Median (range) TTR (months) by BICR	1.22 (0.89, 7.36)
	Median PFS by BICR (months)	Not yet reached
	95% CI (%)	9.8, NE
	Kaplan Meier Probability of Being Event-Free at 15 months (%)	50.2
	95% CI (%)	40.2, 59.3
	Median OS (months)	Not yet reached
	95% CI (%)	13.4, NE
	Kaplan-Meier Probability of Being Alive at 15 months (%)	56.3
	95% CI (%)	47.0, 64.6

	MRD negativity (at a sensitivity level of 10^{-5}) (%)	**21.1 (N=26)**
	95% CI (%)	14.30, 29.42
	MRD negativity (at a sensitivity level of 10^{-5}) among the 44 participants with sCR/CR (%)	59.1 (N=26)
	95% CI (%)	43.25, 73.66
	MRD negativity (at a sensitivity level of 10^{-5}) among the 29 participants with sCR/CR and an evaluable sample (%)	89.7 (N=26)
	95% CI (%)	72.65, 97.81
Effect estimate per comparison	Not applicable, single-arm study	
Analysis Description	**Other**	
Descriptive statistics and estimate variability	Cohort B results: The primary endpoint of confirmed ORR was 34.4% (95% CI: 22.9, 47.3), 32.8% achieved VGPR or better and 10.9% achieved CR or better. Among responders, the median DOR was not yet reached (95% CI: 11.8, NE), and the 15-month Kaplan-Meier probability of maintaining response was 67.5% (95% CI: 40.9, 84.1). Among responders, the median DOCR was not yet reached (95% CI: 9.2, NE), 5 (71.4%) participants were ongoing without an event. Among responders the median (range) TTR was 1.92 (0.92, 6.74) months. The median PFS was 3.5 (95% CI: 1.9, 6.6) months. The median OS was 11.3 (95% CI: 6.5, NE) months.	
Effect estimate per comparison	Not applicable, single-arm study	

2.6.4.3. Clinical studies in special populations

Renal impairment

The majority of participants had an adequate baseline renal function, 65.2% had CrCL >60 mL/min.

Hepatic impairment

The majority of participants had an adequate baseline liver function, 82.9% had a normal liver function.

Table 18. Summary of elderly subjects in the pivotal studies of elranatamab

Variable	Category	C1071001	C1071002	C1071003	C1071009	Total
N (%)		87	4	187	43	321
Age Group	Group 1: <65	42 (48%)	1 (25%)	71 (38%)	24 (56%)	138 (43%)
	Group 2: 65 to <75	34 (39%)	3 (75%)	80 (43%)	16 (37%)	133 (41%)
	Group 3: 75 to <85	11 (13%)	0 (0%)	33 (18%)	3 (7%)	47 (15%)
	Group 4: 85+	0 (0%)	0 (0%)	3 (2%)	0 (0%)	3 (1%)

2.6.4.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.4.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

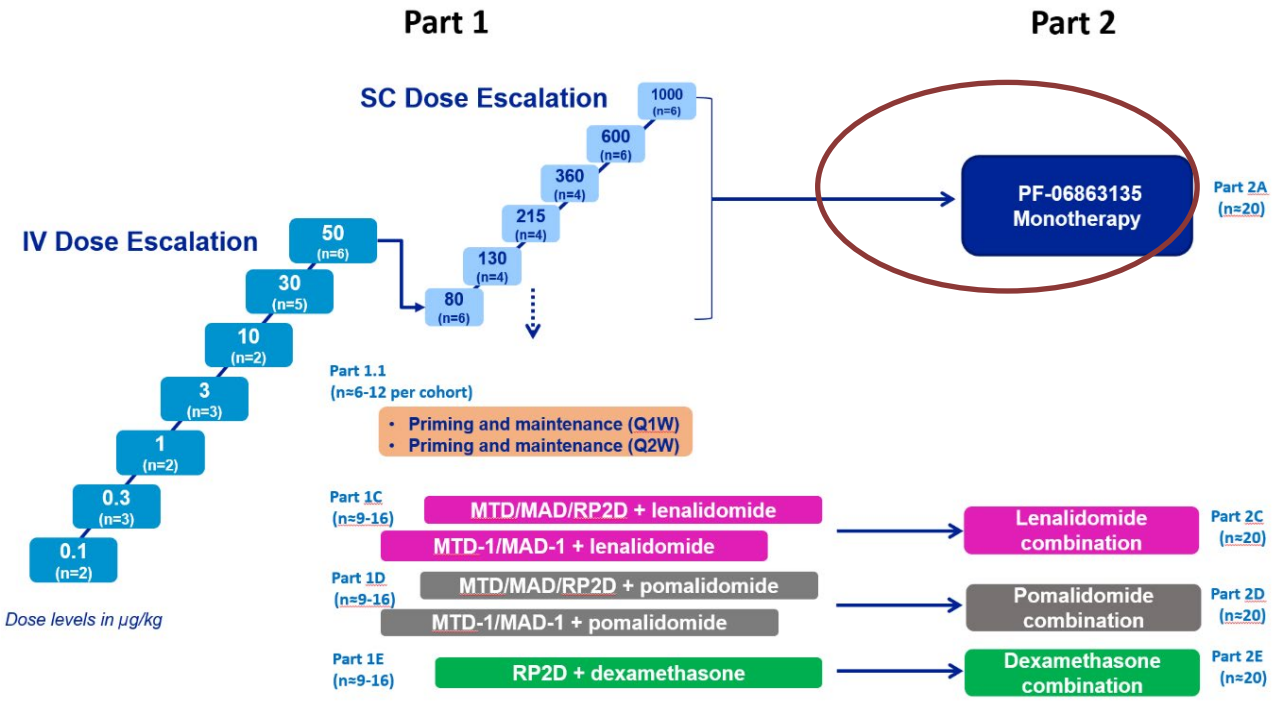
2.6.4.6. Supportive studies

C1071001 Part 2A

Study C1071001 is a Phase 1, open-label, multidose, multicenter, dose escalation/dose expansion study assessing safety/tolerability, PK, PD, immunogenicity and anti-myeloma activity of elranatamab.

The study design is depicted in **Figure 12**.

Figure 11. Design of study C1071001



The study included adult participants with advanced MM who have relapsed from or are refractory to standard therapy. Participants must had progressed on or be intolerant of established therapies known to provide clinical benefit in MM including a PI, an IMiD and an anti-CD38 mAb, either in combination or as single agents.

Results of Part 2A (BCMA Naïve)

Efficacy data by Investigator for the 12 BCMA naïve participants (out of 15 in Part 2 A) are presented below.

As of the data cutoff date (22 June 2022), 25.0% participants were still receiving elranatamab; 75.0% had discontinued study treatment, with the most common reason for treatment discontinuation being progressive disease (50.0%), followed by adverse event (16.7%). 50.0% discontinued the study, all due to death.

The median (range) age was 70 (50, 80) years, 25.0% were ≥75 years old. The majority were male (58.3%) and White (75.0%).

The majority were R-ISS disease stage II (50.0%) or III (33.3%), had an ECOG PS of 0 (16.7%) or 1 (66.7%). 16.7% had EMD at baseline and 33.3% had a high cytogenetic risk.

All participants had received at least one PI, one IMiD, and one anti-CD38 mAb. Participants had a median (range) of 5.0 (3, 9) prior lines of anticancer therapy, 75.0% were triple-class refractory and 66.7% were penta-drug refractory with 91.7% being refractory to the last line of therapy.

Outcomes

As of the data cutoff, the median (range) follow-up from first dose was 13.98 (4.17, 15.93) months, the median (range) treatment duration was 6.80 (1.64, 15.93) months, and the median (range) relative dose was 89.3% (79.1, 100.0).

As of the data cutoff, 25.0% of participants were still receiving elranatamab; 75.0% had discontinued study treatment, with the most common reason for treatment discontinuation being progressive disease (50.0%).

- The primary endpoint of confirmed ORR was clinically meaningful: ORR was 75.0% [95% CI: 46.8, 91.1]); 58.3% achieved VGPR or better and 41.7% achieved CR or better
- After a median (range) follow-up since initial response of 12.32 (6.11, 14.65) months, the median DOR was 11.6 (95% CI: 2.5, NE) months
- Among participants with a CR, 60.0% were ongoing without an event
- Among responders, the median (range) TTR was 1.31 (0.26, 8.61) months
- The median PFS was 11.8 months (95% CI: 2.2, NE)
- 50.0% of the participants had died. The median OS was 15.3 months (95% CI: 7.6, NE)
- Among 5 participants with sCR/CR, 3 participants were evaluable for MRD negativity. All 3 were MRD negative at a sensitivity level of 10^{-5}

Results of Part 2A (BCMA Exposed):

In Part 2A, there were 3/15 participants who were BCMA exposed, of these, none achieved an objective response, BOR was SD in 1 (33.3%) participant and PD in 2 (66.7%) participants.

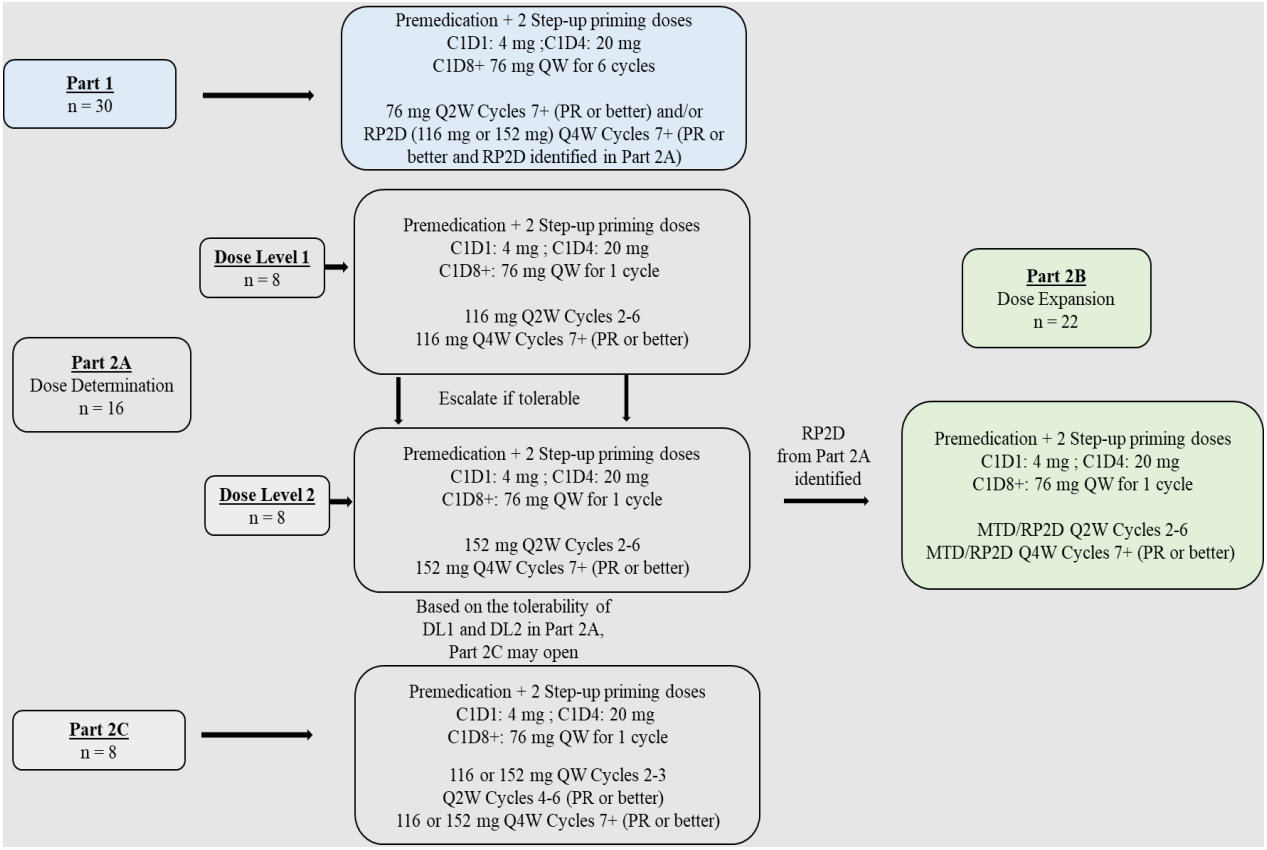
C1071009 Part 1

Design

Study 1009 is a Phase 1/2, prospective, open-label, multicenter, non-randomised study to evaluate a dosing regimen with 2 step-up priming doses and longer dosing intervals of elranatamab monotherapy in participants with RRMM who are refractory to at least one PI, one IMiD, and one anti-CD38 mAb and is depicted in **Figure *13***.

The objective of the study was to evaluate the rate of Grade ≥2 CRS using a priming regimen that involved premedication and 2 step-up priming doses as well as to evaluate safety, tolerability, PK, PD, immunogenicity, PRO, biomarker, and preliminary anti-myeloma activity of elranatamab full doses 76 mg and >76 mg with different dosing intervals.

Figure 12. C1071009 study design



Study C1071009 Supporting Part 1 (BCMA Naïve)

Efficacy data for the 24 BCMA naïve participants out of 33 enrolled and treated in Part 1 are presented in this section.

As of the data cutoff date (29 July 2022), 54.2% of participants were still receiving elranatamab; 45.8% discontinued study treatment, with the most common reason for treatment discontinuation being progressive disease (16.7%), followed by adverse event (12.5%)/ 16.7% discontinued study; all of which were due to death.

- The median (range) age of participants was 63 (36, 79) years; 4.2% were ≥75 years old. The majority were female (58.3%) and Asian (75.0%).
- The majority were R-ISS disease stage I (33.3%) or II (33.3%), had an ECOG PS of 0 (66.7%) or 1 (33.3%). 37.5% had EMD at baseline and 33.3% had a high cytogenetic risk.

- All participants had received at least one PI, one IMiD, and one anti-CD38 mAb. Participants had a median (range) of 5 (3, 10) prior lines of anticancer therapy, 87.5% were triple-class refractory and 33.3% were penta-drug refractory with 91.7% being refractory to the last line of therapy.

Outcomes

As of the data cutoff date, the median (range) follow-up from first dose was 5.06 (1.18, 7.39) months. The median (range) treatment duration was 4.21 (0.99, 6.57) months and the median (range) relative dose was 67.99% (21.0, 100.0).

As of the data cutoff date, 54.2% of participants were still receiving elranatamab; 45.8% discontinued study treatment, with the most common reason for treatment discontinuation being progressive disease (16.7%)/

- Confirmed ORR was 54.2% (95% CI: 32.8, 74.4); VGPR or better was 29.2% and CR or better was 4.2%, with VGPR and CR rates anticipated to increase with longer follow-up as responses deepen over time.
- The median DOR (months) was not yet reached (95% CI: NE, NE), the Kaplan-Meier probability of maintaining response at 3 months was 91.7% (95% CI: 53.9, 98.8).
- Among responders, the median (range) TTR was 1.02 (0.92, 5.36) months.

Study C1071009 Supporting Part 1 (BCMA exposed): In Part 1, there were 9/33 participants who were BCMA exposed, the confirmed ORR rate was 44.4% (95% CI: 13.7, 78.8), VGPR and CR were 22.2% each. At the time of data cutoff, there were 2 additional participants (22.2%) still on-treatment without progression and confirmed response. Among responders, 100% were still ongoing without an event at data cutoff.

C1071024 – comparison with RWD

Comparative Effectiveness of Elranatamab (PF-06863135) in Clinical Study C1071003 Versus Standard of Care (SOC) in Real-World (RW) External Control Arms in Patients with Triple-Class Refractory (TCR) Multiple Myeloma (MM).

Methods

2 cohorts of RW TCR MM patients were identified from 2 US-based oncology electronic health record (EHR) databases, Flatiron Health, and COTA.

The date of initiation of the first regimen after TCR MM eligibility will be defined as the index date. Only patients with an index date occurring between 16 November 2015, and 31 March 2022 will be selected (the first anti-CD38 therapy was approved by the FDA on 16 November 2015). The study period will be comprised of the baseline period (time preceding the index date) and the observational period (time following the index date). The observational period will span from the index date to the earliest of death, or the latest available patient's record, whichever comes first. Clinical outcomes of interest will be ORR, TTR, and DOR.

For the primary analyses, differences in baseline and key covariate characteristics including treatment history and disease-related characteristics at the index date between patients in Study C1071003 and each external control arm will be balanced using inverse probability of treatment weighting (IPTW).

Outcomes

Between February 2021 and June 2022, a total of 123 TCR MM participants were enrolled in Study C1071003 Cohort A and were included in the primary analysis. Using the critical eligibility criteria, 233 TCR RW patients initiating a new LOT between November 2015 and March 2022 were identified in COTA, and 152 TCR RW patients initiating a new LOT between November 2015 and August 2021were identified in Flatiron Health. A different period for the selection of TCR MM patients in COTA and Flatiron Health was used due to differences in data availability.

The median follow-up time was 10.4 months in Study C1071003 Cohort A, and the median follow-up time was 8.8 and 7.7 months in COTA, and Flatiron Health, respectively. Objective response rates and duration of responses in the 3 cohorts are summarised in Table 19. and Table 20 respectively.

Table 19. Frequencies of responses in participants in study C1071003 and RW external control arms

Response	C1071003 Cohort A (N=123)	COTA (N=233)	Flatiron Health (N=152)
Number (%) of patients with OR event	75 (61.0)	73 (31.3)	46 (30.3)
ORR (95% CI)[1]	61.0 (51.8-69.6)	31.3 (25.4-37.7)	30.3 (23.1-38.2)
Number (%) of patients with the following best response:			
sCR	16 (13.0)	0 (0.0)	-
CR	18 (14.6)	0 (0.0)	-
VGPR	34 (27.6)	2 (0.9)	14 (9.2)
PR	7 (5.7)	71 (30.5)	32 (21.1)

Abbreviations: CR=complete response; OR=objective response; ORR=objective response rate; PR=partial response; RW=real-world; sCR=stringent complete response; VGPR=very good partial response.
Note:
[1]Clopper-Pearson two-sided 95% exact confidence intervals were reported.

Table 20. Duration of responses in participants in study C1071003 and RW external control arms

	Total N of patients with OR	N (%) of patients with an event[1]	Median time (95% CI)[2], months	25th percentile (95% CI)[2], months	75th percentile (95% CI)[2], months
Study C1071003 Cohort A[3]	75	12 (16.0)	NE (11.99-NE)	11.99 (8.80-NE)	NE (NE-NE)
COTA	73	63 (86.3)	4.37 (2.86-8.05)	2.14 (1.35-2.83)	13.08 (8.57-19.55)
Flatiron Health	46	31 (67.4)	7.16 (4.99-13.60)	2.63 (1.08-5.06)	22.60 (9.69-33.38)

Abbreviations: CI=confidence interval; DOR=duration of response; NE=not estimable; OR=objective response; RW=real-world.
Notes:
[1]Events were defined as disease progression or death.
[2]DOR was defined as the time from the first documentation of OR until disease progression or death due to any cause, whichever occurs first. Censoring was applied for patients who started a new line of therapy prior to an event (on the date the new anticancer therapy was initiated for RW patients, and on the last adequate disease assessment date before the new anticancer therapy for Study C107003 Cohort A participants). For patients without an event, censoring was applied on the last record date or data cut-off date for RW patients (whichever occurred first) and was applied on the last adequate disease assessment date for Study C107003 Cohort A participants. Non-parametric Kaplan-Meier estimators were used to estimate the median, 25th and 75th percentile confidence intervals.
[3] More than half of the participants in Study C1071003 Cohort A did not have a disease progression and were still alive when the data was collected, therefore the median and 75th percentile cannot be estimated.

MAIC report - elranatamab vs approved therapies for the treatment of patients with triple-class exposed (TCE)

Matching-adjusted indirect treatment comparison (MAIC) of elranatamab vs approved therapies for the treatment of patients with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM).

Methods

The Matching-adjusted indirect treatment comparison was performed between pivotal studies. Several analyses were conducted to identify potential prognostic variables and effect modifiers with different criteria to select those, based on the p-value of modelled associations with outcome and based on systematic literature review (Table 21).

Table 21. Overview of base case settings and scenario analyses for MAIC

Scenario	Settings
Base case	Only includes statistically significant PVs ($p \leq 0.05$)
Scenario 1	Only includes statistically significant PVs ($p \leq 0.1$)
Scenario 2	Includes statistically significant PVs ($p \leq 0.05$) and EMs from SLR
Scenario 3	Includes statistically significant PVs ($p \leq 0.05$) and PVs/EMs from SLR
Scenario 4	Includes statistically significant PVs ($p \leq 0.1$) and PVs/EMs from SLR

Abbreviations: EM = effect modifier; PV = prognostic variable; SLR = systematic literature review

Results

Table 22. Relative efficacy comparison-ORR: MagnetisMM-3 vs. DREAMM-2 (Belantamab mafodotin)

Scenario	MagnetisMM-3 (Cohort A)	DREAMM-2	ESS	Rate difference [95% CI]	Odds ratio [95% CI]	p value
Naïve comparison	75 (61%)	31 (32%)	123	29.02 [16.35, 41.68]	3.33 [1.90, 5.82]	0.000
Base case & Scenario 1	48 (50%)	31 (32%)	83	17.70 [4.10, 31.30]	2.10 [1.17, 3.76]	0.019
Scenario 2	41 (51%)	31 (32%)	64	18.63 [4.31, 32.94]	2.18 [1.18, 4.01]	0.014
Scenario 3 & Scenario 4	37 (47%)	31 (32%)	60	15.47 [1.00, 29.93]	1.92 [1.04, 3.56]	0.043

Abbreviations: ESS = effective sample size; MAIC = matching adjusted indirect comparison; ORR = overall response rate.

Table 23. Relative efficacy comparison-ORR: MagnetisMM-3 vs. STORM (Selinexor)

Scenario	MagnetisMM-3 (Cohort A)	STORM	ESS	Rate difference [95% CI]	Odds ratio [95% CI]	p value
Naïve comparison	75 (61%)	32 (26%)	123	34.75 [23.12, 46.38]	4.39 [2.56, 7.56]	0.000
Base case	51 (57%)	32 (26%)	79	30.76 [17.88, 43.63]	3.73 [2.08, 6.66]	0.000
Scenario 1	51 (57%)	32 (26%)	79	30.69 [17.81, 43.57]	3.72 [2.08, 6.64]	0.000
Scenario 2	40 (56%)	32 (26%)	52	29.75 [15.88, 43.62]	3.58 [1.93, 6.62]	0.000
Scenario 3	37 (54%)	32 (26%)	49	27.97 [13.79, 42.15]	3.33 [1.78, 6.21]	0.000
Scenario 4	36 (54%)	32 (26%)	49	27.93 [13.75, 42.11]	3.32 [1.78, 6.20]	0.000

Abbreviations: ESS = effective sample size; MAIC = matching adjusted indirect comparison; ORR = overall response rate.

Table 24. Relative efficacy comparison-ORR: MagnetisMM-3 vs. MajesTEC-1 (Teclistamab)

Scenario	MagnetisMM-3 (Cohort A)	MajesTEC-1	ESS	Rate difference [95% CI]	Odds ratio [95% CI]	p value
Naïve comparison	72 (62%)	104 (63%)	116	-0.96 [-12.46, 10.54]	0.96 [0.59, 1.57]	0.901
Base case & Scenario 1	65 (70%)	104 (63%)	86	7.20 [-4.67, 19.07]	1.38 [0.80, 2.39]	0.279
Scenario 2	65 (71%)	104 (63%)	85	7.61 [-4.26, 19.48]	1.41 [0.82, 2.44]	0.273
Scenario 3 & Scenario 4	65 (70%)	104 (63%)	85	7.45 [-4.44, 19.33]	1.40 [0.81, 2.42]	0.273

Abbreviations: ESS = effective sample size; MAIC = matching adjusted indirect comparison; ORR = overall response rate

Table 25. Relative efficacy comparison-ORR: MagnetisMM-3 vs. LocoMMotion (Standard of Care)

Scenario	Magnetis MM-3 (Cohort A)	LocoMMotion	ESS	Rate difference [95% CI]	Odds ratio [95% CI]	p value
Naïve comparison	75 (61%)	74 (30%)	123	31.14 [20.80, 41.47]	3.67 [2.34, 5.78]	0.000
Base case & Scenario 1	54 (57%)	74 (30%)	84	27.61 [16.11, 39.11]	3.17 [1.94, 5.19]	0.000
Scenario 2 & Scenario 3 & Scenario 4	53 (57%)	74 (30%)	83	27.38 [15.84, 38.93]	3.15 [1.92, 5.15]	0.000

Patient consultation by patient organisation

A document by the patient Organisation Myeloma Patients Europe (MPE) entitled "final MPE comments on elranatamab for the treatment of RRMM" was submitted for consideration by the CHMP as part of the EMA's ongoing initiative of contacting patient organisations at the start of evaluation of the marketing authorisation applications. The document summarised data captured by MPE, through surveys and direct interviews with 14 European myeloma patients on their perspectives on the publicly available data on MagnetisMM-3 clinical trial data for Cohort A. Patients interviewed had a varying number of prior lines of therapy and were at different stages of the disease.

Advantages as per MPE based on survey (patients cited comments not provided here)

1. Patients value access to treatments with different targets and mechanisms of action.
2. Elranatamab elicits a good and durable response and has a strong anti-myeloma effect on a population of heavily pre-treated patients who were relapsed and refractory to the main drug classes in myeloma (triple-class and penta-refractory, with a high number of extramedullary disease – a poor prognosis). Accessing additional treatment options for this group of patients is an area of unmet need and there is good single agent action, implying it could provide significant benefit when used earlier on in the pathway. Patients interviewed highlighted that many patients in this heavily pretreated setting would consider this as a viable treatment option. The data also highlighted that 91% of patients who achieved a complete response, achieved MRD negativity, which is a very deep response in a heavily pre-treated setting.

   It was acknowledged and discussed by some patients that the data is early and further data on progression free (PFS) and overall survival (OS) and quality of life (QoL) would be helpful to help patients make a decision on whether to take the drug. Although, this was not important to all.

3. The administration of elranatamab, provided via a subcutaneous injection, is very acceptable to most patients and they are very used to this method.

Disadvantages as per MPE based on survey (Patients cited comments not provided here)

1. Currently available data highlights that the treatment works well in BCMA naïve patients. However, patients commented they would like to understand how patients who have previously received a BCMA targeting therapy would respond and, in addition, whether receiving elranatamab would prevent them from receiving a BCMA targeting bispecific or CAR-T in the future.
2. Patients reflected on the number of high-grade side-effects and the impact they might have in a heavily pre-treated population. The particular side-effects raised were the rates of grade 3 – 4 infection and the rates of grade 3 – 4 haematological side effects. They also raised concerns about the reported number of grade 5 side-effects in the clinical trial, although they acknowledged there is limited data currently available on why these occurred. However, patients also outlined that this all needs to be considered in relation to the patient population in question and that patients may have limited options. Decisions on whether patients are willing to tolerate a specific side-effect profile would come down to an individual perspective, based on a discussion with a doctor. The rates of side-effects may also have been affected by prior lines of therapy and pre-existing quality of life of the patient.

   From the perspective of MPE, there is a clear need to implement a management plan between a doctor and patient to reduce the risk of infection. Some patients felt that whilst infections were high, there were mitigation plans that could be in place for this.
3. Cytokine release syndrome and neurotoxicity, whilst lower grade compared to existing CAR-T products, are still present with elranatamab and can have a big impact on quality of life if experienced. All patients had knowledge of the potential impact CRS could have on quality of life. Some patients commented that they were positively surprised that the rates of CRS were lower than they thought they were going to be, there were no high-grade CRS. Other patients did not raise this as a concern.

2.6.5. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of this application efficacy results from the single arm trial C10071003, which is being conducted in 10 countries in Europe, North America, and Japan have been submitted. The target population of this phase 2 study represents a MM patient population with multi-refractory disease where most patients were previously treated with several (median 5) previous lines of therapies. The pivotal Cohort A in this study included 123 participants who had received at least one PI, one IMiD, and one anti-CD38 mAb and who were relapsed or refractory to the last anti-MM regimen and naïve to prior BCMA-directed therapy.

The indication initially sought by the applicant was for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy. The CHMP requested that the indication should be revised as the enrolled patient population was largely triple refractory and had demonstrated disease progression on the last therapy. The applicant acknowledged that even though participants enrolled in Study C1071003 could have relapsed on treatment with other drugs and/or received IMiDs, PIs and anti-CD38 antibodies subsequently, this represented a small sub-population (4% of patients in

Cohort A). Considering the limited number of participants in this sub-group of relapsed participants, the applicant agreed to modify the indication as follows 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 ł antibody and have demonstrated disease progression on the last therapy.

The remaining inclusion and exclusion criteria in the study are adequately reflected in section 5.1 of the SmPC including the requirement that patients must have had an adequate organ reserve and sufficient bone marrow reserve but excluded in case of clinically significant cardiovascular diseases Hypersensitivity to the active substance or to any of the excipients as required in exclusion criterion is adequately reflected in section 4.3 (Contraindications).

The type of myeloma was unknown for 18 patients (9.6%) included in the clinical trial due to missing immunofixation data at baseline. As one does not necessarily need to know the isotype to treat and assess response this missing information does not seem to have an impact on assessing the B/R of the product. It must be noted however, that not all plasma cells express BCMA. One study in heavily pretreated myeloma patients (median 7 prior lines of therapy) found that 52 of 85 patients (61%) had BCMA positive bone marrow sections by immunohistochemistry. The remaining 33 were negative. (Ali et al. Blood 2016, https://doi.org/10.1182/blood-2016-04-711903). The applicant did not examine BM in the pivotal study for BCMA expression, but instead investigated sBCMA levels. Across all elranatamab studies, out of 290 response-evaluable participants with available baseline sBCMA data, only 4 participants had baseline levels that were below the limit of the assay quantification of 1 ng/mL (4/290, 1.4%). Additionally, in Study C1071003 Cohort A, only 1 participant had baseline level < 1 ng/mL and this participant achieved objective response. CHMP considers that the limit of the assay quantification of 1 ng/mL used by the applicant is sufficient as even in healthy donor controls the average value was 71 ng/mL.[1] This observation suggests that even low levels of sBCMA may be sufficient to achieve responses to elranatamab therapy, and the applicant is encouraged to do further analyses to support this notion.

Enrolled participants received SC elranatamab with a 2 step-up priming regimen of 12 mg on C1D1 and 32 mg on C1D4 followed by the first full dose (76 mg) of elranatamab on C1D8 and QW thereafter, except for the first 4 participants that received 1 step-up priming dose of 44 mg on C1D1 followed by the first full dose (76 mg) on C1D8. If a participant received QW dosing for at least 6 cycles and achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval was to be changed from QW to Q2W (e.g., beginning C7D1). After switching to Q2W after 6 cycles longitudinal sBCMA data were observed with further rapid and deep decline in free sBCMA concentrations in the majority of responding participants. This suggests the possibility of reducing the dosing interval in responding subjects.
The primary objective of the study was to determine the efficacy of elranatamab. The corresponding endpoint was confirmed ORR by BICR per IMWG. In Cohort A, the study tested the null hypothesis that the ORR by BICR is ≤30% versus the alternative hypothesis that the ORR by BICR is >30%. The null hypothesis ORR for cohort A is based on the results of the DREAMM-2 study (Belantamab mafodotin) (Lonial et al, 2020b) and the STORM study (Selinexor) (Chari et al, 2019), which were conducted in similar MM populations.

If the null hypothesis for ORR by BICR was rejected for Cohort A, the key corresponding secondary endpoint of ORR by BICR for those without EMD in Cohort A at baseline would be tested in a hierarchical fashion using the gatekeeping procedure that the ORR is ≤38% with a 1-sided significance level of 0.025. If the null hypothesis for ORR by BICR for those without EMD at baseline was rejected

[1] Kinneer, K. et al. Preclinical assessment of an antibody-PBD conjugate that targets BCMA on multiple myeloma and myeloma progenitor cells. *Leukemia* **33**, 766–771 (2019).

for Cohort A, the key secondary endpoint of ORR by BICR for those with EMD in Cohort A at baseline would be tested in a hierarchical fashion using the gatekeeping procedure that the ORR is ≤12% with a 1-sided significance level of 0.025. The hierarchical testing and chosen cut-offs are supported. The response criteria used to determine primary endpoint and response-defining secondary endpoints are based on the International Myeloma Working Group (IMWG) criteria, which have been used in a number or recently authorised products in the same indication.

The sample size and power considerations are acceptable. It was noted that the sample size and planned interim analysis were changed in an amendment to the study protocol. However, the applicant did not have access to the efficacy results at the timepoint where sample sizes and timepoint of interim analyses were modified which is acceptable.

The single arm design has limitations, and uncertainties remain on the potential clinical benefits of treatment due to lack of a concomitant randomised comparator and blinding. The statistical methods are in principle acceptable for a single arm trial. The definition of the analysis set may not be optimal, as it required patients to be treated. Thus, if any patient was enrolled but subsequently not treated for any reason, this could potentially have introduced selection bias. However, as all enrolled patients were treated the analysis population for efficacy is accepted.

It is noted that a one-sided significance level of α=0.025 was set independently for Cohort A and B (patients who had received prior anti-BCMA therapy) each. This is not supported, as multiplicity is not adequately addressed. However, given the positive results on ORR, this limitation does not impact the interpretation of the results.

Efficacy data and additional analyses

C1071003 Cohort A

123 subjects in Cohort A have been enrolled, all of them received treatment and all of them have been analysed for efficacy. Initial data cut-off date was 14 October 2022 (9 months after last patient was dosed) which during the procedure was updated with a new cut-off date of 16 April 2023.

The study has had 9 amendments. All modifications regarding efficacy seem contributing to more robust efficacy analysis and are accepted.

The primary endpoint was ORR by BICR which was 61.0% (95% CI: 51.8, 69.6; null rate of 30%). 35.8% (95&CI: 27.3, 44.9) achieved CR or better. That means that the treatment is efficacious but as this study is a SAT this is a limitation for granting full approval.

The key secondary endpoint of confirmed ORR by BICR baseline EMD was more favourable for patients without baseline EMD (71.4% [95% CI: 60.5, 80.8]; null rate of 38%). With baseline EMD it was 38.5% [95% CI: 23.4, 55.4]; null rate of 12%. This is welcomed and shows efficacy in EMD and non-EMD subjects. Null rates as pre-determined values have been justified by the Applicant.

Elranatamab demonstrated durable responses in participants with a confirmed objective response. The median DOR (months) by BICR was not yet reached (95% CI: NE, NE) after a median (range) follow-up from first dose of 15.21 (2.40, 16.95) months. The proportion maintaining response at 15 months or longer was 70.8% (95% CI: 58.2, 80.42).

The median PFS by BICR was not yet reached (95% CI: 9.8, NE), and the 15-month Kaplan-Meier probability of being event-free was 50.2% (95% CI: 40.2, 59.3).

Although point estimate of median for neither PFS nor OS could be estimated in Cohort A, it can be deduced that further continued follow-up would lead to median PFS point estimate of at least 15 months.

Among the 29 participants who were evaluable for MRD (those with CR/sCR and with an evaluable sample [i.e., had an identifiable index clone at screening]), MRD negativity at a sensitivity of 10^{-5} was achieved in 26 (89.7% [95% CI: 72.65, 97.81]) participants. The provided MRD data suggest that most of the CR/sCR responses are deep which is important. From the pooled MRD data from the literature, even in the last line treatment, it seems that with deeper responses at least the DOR could be improved.

Among responders by BICR who switched to Q2W dosing at least 12 weeks prior to the data cut-off (48 participants), 45 (93.8%) maintained/improved their response ≥12 weeks after the switch. Despite reducing the dosing interval, subjects were able to deepen their response even when switch was made in PR. From the convenience point of view such switch is interesting for patient well-being.

Several subgroup analyses were performed for the ORR with lower responses seen in patients with extramedullary disease and penta-refractory disease. In addition, there was a trend towards lower efficacy of patients from Europe and with renal insufficiency. The applicant clarified that multivariable logistic regression suggests that EMD and non-IgG myeloma being the only independent predictors of outcome.

C1071003 Cohort B: BCMA - pretreated

Elranatamab demonstrated in BCMA-pretreated subject a clinically meaningful ORR and durable responses by BICR per IMWG criteria after a median (range) follow-up from first dose of 9.22 (0.33, 12.32) months in a heavily pretreated population (a median of 7.5 prior anticancer therapy lines). The confirmed ORR by BICR was 34.4% (95% CI: 22.9, 47.3; null rate of 15%).

In Cohort B, the study tested the null hypothesis that the ORR by BICR as defined by IMWG is ≤15% versus the alternative hypothesis that the ORR by BICR as defined by IMWG is >15%. The justification of 15% was very weak and based on the fact that there are currently limited data available on the response rate after retreatment with a BCMA antibody drug conjugate or CAR-T therapy, but it was expected that the ORR would likely be notably lower than the BCMA naïve population.

Elranatamab demonstrated durable responses in participants with a confirmed objective response. The median DOR (months) by BICR was not yet reached (95% CI: NE, NE), after a median (range) follow-up from initial dose of 10.18 (6.41, 12.32) months and from initial response of 13.42 (2.43, 16.95) months for responders. Among responders, the Kaplan-Meier probability of maintaining response at 9 months was 85.1% (95% CI: 60.5, 95.0).

Anti-BCMA pre-treated subjects were able to achieve MRD negative status (N=2).

Among participants with prior CAR-T and prior ADC, the ORR by BICR was 42.9% (95% CI: 21.8, 66.0) and 28.3% (95% CI: 16.0, 43.5), respectively. Although the C1071003 study was not designed for direct comparison, the lower ORR by BICR observed for participants who had received prior BCMA-directed ADC (N=46, ORR 28.3% 95% CI: 16.0, 43.5), compared to those who had received prior BCMA-directed CAR-T therapy (N=21, ORR 42.9% 95% CI: 21.8, 66.0) is likely due to the less favourable baseline characteristics in the ADC group compared to the CAR-T group. Most notably, the ADC group had more baseline EMD: 60.9% vs 52.4% of participants had baseline EMD by BICR in the ADC and CAR-T groups, respectively. Additionally, other less favourable baseline characteristics in the ADC group compared to the CAR-T group included: more advanced age (23.9% vs 4.8% age ≥75 years), more prior lines of therapy (median of 8 vs 6, respectively), a higher percentage of participants with disease refractory to their prior BCMA-directed therapy (78.3% vs 19%), as well as higher

proportions of participants with ECOG performance status 2 (8.7% vs 0%) and R-ISS disease stage III (26.1% vs 14.3%).

Supportive studies

Considering lower numbers of treated subjects in supportive studies, slight differences in definition of pretreatment, definitions of relapsed/refractory or definitions of EMD, results in BCMA naïve participants from supporting Studies 1001 Part 2A and 1009 Part 1 were overall consistent with results from pivotal Cohort A in Study 1003. In Study 1001 Part 2A confirmed ORR by Investigator was 75.0% (95% CI: 46.8, 91.1). In Study 1009 Part 1, confirmed ORR by Investigator was 54.2% (95% CI: 32.8, 74.4). Due to the different populations included in these studies and/or a very short FU, no additional information relevant for elranatamab approval can be derived from them.

An additional study to compare the objective response rate (ORR) among TCR MM patients treated with elranatamab in Study C1071003 with a comparable cohort of Triple class refractory (TCR) MM patients receiving SOC therapy within external comparator arms has been provided (study C10712024). Patients were matched by Inverse Probability of Treatment Weights (IPTW). Only patients with an index date occurring between 16 November 2015 and 31 March 2022 were selected and therefore anti-BCMA therapy will not be reflected adequately in this comparison. C1071024 thus might not really reflect the state-of-the-art therapy which is an important limitation of the study. Additional limitations in RW studies performed retrospectively, is the inability to implement consistent monitoring and application of homogenous evaluation criteria (e.g., IMWG) and unmeasured confounding.

Despite these limitations elranatamab seems to perform better in these indirect comparisons. Even though this cannot be confirmed the reported results offer some context in the BCMA targeted therapy and are considered supportive for the use of elranatamab in the claimed indication.

A Matching-adjusted indirect treatment comparison (MAIC) was also provided as supportive documentation for this MAA, where elranatamab was compared to belantamab mafodotin, selinexor, teclistamab and physician´s choice of treatment. The MAIC report provides some contextualisation of ORR but does not replace proof of efficacy through a randomised comparison.

CHMP has received the patient survey performed by the patient organisation. It is neither clear whether questions have been suggestive, nor how patients have been selected for the survey. Nevertheless, CHMP took the patient consultation in consideration and especially the observation that subcutaneous administration is seen as a possible advantage.

Additional efficacy data needed in the context of a conditional MA

To confirm the positive benefit-risk profile, the applicant has initiated a confirmatory phase 3 study.

Study C1071005 is an open-label, 3-arm, multi-centre, Phase 3 randomised study of elranatamab monotherapy and elranatamab + daratumumab versus daratumumab + pomalidomide + dexamethasone in participants with relapsed/refractory multiple myeloma who have received at least one prior line of therapy including lenalidomide and a PI.

Feasibility of this confirmatory study is likely, given the different patient population and full enrolment was expected in August 2023 and the final report from this study is planned for Q2 2027.

The pivotal study C1071003 is currently on-going. Although additional follow-up data as requested by the CHMP (most recent data cut-off 16 April 2023) have been provided during the procedure, the final CSR of C1071003 will be provided in Q1 2025.

2.6.6. Conclusions on the clinical efficacy

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

• The final study report of the pivotal study C1071003 (MagnetisMM-3) should be provided.

• The final study report from study C1071005 investigating the efficacy and safety of elranatamab monotherapy or its combination with daratumumab vs. daratumumab + pomalidomide + dexamethasone in adults with relapsed/refractory multiple myeloma should be provided.

2.6.7. Clinical safety

2.6.7.1. Patient exposure

The pivotal pooled safety population for elranatamab (Pool 3) is based on 4 studies (1003, 1001, 1002 and 1009) including all participants that received at least one dose of elranatamab and that were assigned to a dose of 1000 µg/kg or fixed doe equivalent of 76 mg. Of these, 183 participants (Pool 1, which includes only patients from study 1003) have been exposed to the proposed registrational dosage (76 mg SC QW, with a 2 step-up priming dose regimen [12 mg on Day 1 and 32 mg on Day 4], reduced to 76 mg SC Q2W after at least 24 weeks for patients who have achieved a response). All other participants assigned to receive a 76 mg full dose or equivalent dose calculated on a body weight basis (1000 µg/kg) regardless of priming dose(s) were summarised in Pool 2 (N=82).

Notably, studies 1003, 1001, 1002 and 1009 are single-arm trials, and there is thus no concurrent control group against which the safety profile could be compared, which limits a comprehensive assessment.

Study 1001 was graded according to NCI CTCAE version 4.03 and all other studies were graded according to NCI CTCAE version 5.0.

Data cut-offs differ between the studies; C1071001: 22 June 2022, C1071002: 27 May 2022, C1071003: 14 October 2022, and C1071009: 29 Ju 2022. Data presented in this section use the above cut-off dates unless otherwise specified. Safety data from for study 1003 (Pool 1) are also from an updated clinical cut-off date of 16 April 2023, which corresponds to ~15 months after the last participant first dose in study 1003. Wherever relevant, the updated safety data from study 1003 will be discussed separately at the end of the respective sections.

Of the 265 participants included in the overall safety population (pool 3), 165 participants (62.3%) had discontinued treatment (62.8% in Pool 1 and 61.0% of participants in Pool 2) as of the clinical cut-off dates. The reasons for discontinuation were similar across pools and are summarised in Table 26.

Table 26. Disposition events summary – treatment (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) n (%)	Pool 2 (N=82) n (%)	Pool 3 (N=265) n (%)
Disposition phase: treatment			
Participants Entered:	183 (100.0)	82 (100.0)	265 (100.0)
Discontinued	115 (62.8)	50 (61.0)	165 (62.3)
Adverse event	17 (9.3)	7 (8.5)	24 (9.1)
Death	16 (8.7)	4 (4.9)	20 (7.5)
Lack of efficacy	4 (2.2)	1 (1.2)	5 (1.9)
Physician's decision	0	2 (2.4)	2 (0.8)
Progressive disease	70 (38.3)	28 (34.1)	98 (37.0)
Withdrawal by subject	7 (3.8)	6 (7.3)	13 (4.9)
Refused further treatment	0	2 (2.4)	2 (0.8)
Refused further study procedures	1 (0.5)	0	1 (0.4)
Ongoing	68 (37.2)	32 (39.0)	100 (37.7)

Data cut-off date: C1071001 - 22JUN2022, C1071002 - 27MAY2022, C1071003 - 14OCT2022, C1071009 - 29JUL2022

The median (range) duration of treatment was 4.67 months (0.03 to 24.41) with 112/265 (42.3%) participants treated for ≥6 months and 34/265 (12.8%) treated for ≥12 months. Overall, 77.4% of participants had at least one temporary or permanent dose reduction or interruption. Dose interruptions occurred in 76.2% of participants, with a similar proportion in Pool 1 and Pool 2. Temporary or permanent dose reductions occurred in 29.4% of participants, with a higher proportion in Pool 2 (36.6%) than in Pool 1 (26.2%). The majority of AEs was managed by dose interruption (73.2%) rather than by dose modifications. Safety data from for study 1003 are available from an updated clinical cut-off date of 16 April 2023, which corresponds to ~15 months after the last participant first dose in study 1003. The median duration of treatment was 4.11 months (0.03 to 20.27) with 55/183 (30%) treated for ≥12 months and 11/183 (6%) participants treated for more than 18 months.

2.6.7.2. Adverse events

As depicted in Table 27, all participants experienced at least one TEAE, and the majority of participants (92.8) had at least 1 treatment-related AE. Grade 3/4 AEs were reported in 72.1% of participants (and Grade 5 in 18.9%).

Table 27. Overview of treatment-emergent adverse events (All Causalities) (All the Participants as Treated)

Number (%) of Participants	Pool 1 n (%)	Pool 2 n (%)	Pool 3 n (%)
Participants Evaluable for Adverse Events	183	82	265
Number of Adverse Events	2710	1439	4149
Participants with Adverse Events	183 (100.0)	82 (100.0)	265 (100.0)
Participants with Serious Adverse Events	125 (68.3)	58 (70.7)	183 (69.1)
Participants with Maximum Grade 3 or 4 Adverse Events	130 (71.0)	61 (74.4)	191 (72.1)
Participants with Maximum Grade 5 Adverse Events	37 (20.2)	13 (15.9)	50 (18.9)
Participants with Permanent Discontinuation of Study Drug due to Adverse Events	31 (16.9)	10 (12.2)	41 (15.5)
Participants with Dose Reduction or Interruption due to Adverse Events	136 (74.3)	61 (74.4)	197 (74.3)
Participants with Dose Reduction due to Adverse Events	39 (21.3)	28 (34.1)	67 (25.3)
Participants with Dose Interruption due to Adverse Events	134 (73.2)	60 (73.2)	194 (73.2)
Participants with Adverse Events of Special Interest CRS	106 (57.9)	64 (78.0)	170 (64.2)
Participants with Adverse Events of Special Interest ICANS	6 (3.3)	10 (12.2)	16 (6.0)
Participants with Adverse Events of Special Interest Peripheral Neuropathy	35 (19.1)	18 (22.0)	53 (20.0)

Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)].
Except for the Number of Adverse Events Participants are counted only once in each row. Serious Adverse Events - according to the investigator's assessment.
In Studies C1071001 and C1071002, TEAEs leading to reductions/interruptions are derived from the AE CRF and only the latest action taken (reduction/interruption/discontinuation) in response to an AE is reported; in studies C1071003 and C1071009 TEAEs leading to reductions/interruptions are derived from the exposure CRF and linked programmatically to the adverse event CRF by the AE Identifier and all actions in response to an AE are reported.
MedDRA v25.0 coding dictionary applied. CTCAE v5 applied.
Severity of CRS and ICANS is assessed according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria (2019).
Peripheral Neuropathy includes MedDRA SMQ Peripheral neuropathy narrow and broad and SMQ Guillain-Barre syndrome narrow.
CRS includes PT "Cytokine release syndrome" collected on the AE CRF page.
ICANS includes PT "Immune effector cell-associated neurotoxicity syndrome" collected on the AE CRF page.
Data cut-off date: C1071001 - 22JUN2022, C1071002 - 27MAY2022, C1071003 - 14OCT2022, C1071009 - 29JUL2022

The AE profile of elranatamab in Pool 1 and Pool 2 showed a generally consistent pattern. Therefore, the results and findings, unless otherwise noted, are described for the pooled data (Pool 3: N=265).

Overview of Treatment-Emergent Adverse Events of study 1003 with the cut-off date of 16 April 2023 is summarised in Table 28**..**

Table 28. Overview of treatment-emergent adverse events (All Causalities) (Safety Analysis Set, cut-off date 16 April 2023)

	Pool 1
Number (%) of Participants	**n (%)**
Participants Evaluable for Adverse Events	183
Number of Adverse Events	2979
Participants with Adverse Events	183 (100.0)
Participants with Serious Adverse Events	137 (74.9)
Participants with Maximum Grade 3 or 4 Adverse Events	125 (68.3)
Participants with Maximum Grade 5 Adverse Events	42 (23.0)
Participants with Permanent Discontinuation of Study Drug due to Adverse Events	41 (22.4)
Participants with Dose Reduction or Interruption due to Adverse Events	137 (74.9)
Participants with Dose Reduction due to Adverse Events	42 (23.0)
Participants with Dose Interruption due to Adverse Events	135 (73.8)
Participants with Adverse Events of Special Interest CRS	106 (57.9)
Participants with Adverse Events of Special Interest ICANS	6 (3.3)
Participants with Adverse Events of Special Interest Peripheral Neuropathy	39 (21.3)

- **Common adverse events**

The most common TEAEs occurred primarily in the following System Organ Classes (SOCs) Blood and lymphatic system disorders, General disorders and Administration site conditions, Immune system disorders and Gastrointestinal disorders. CRS was the most commonly observed TEAE and was reported in 64.2% of the participants. Haematological TEAEs, including anaemia (52.8%), neutropenia (51.3%), thrombocytopenia (33.6%) and lymphopenia (28.-3%) were also commonly reported. Cytopenias, including Neutropenia (49.4%), Anaemia (41.1%), Lymphopenia (26.8%), Thrombocytopenia (24.5%), and Leukopenia (12.8%) were the most frequently (≥10%) reported Grade 3/4 all-causality AEs. Overall, the most frequently reported treatment-related Grade 3/4 AEs (≥10%) were Neutropenia (41.1%), Lymphopenia (21.1%), Anaemia (18.5%), and Thrombocytopenia (12.1%).

In study 1003 (cut-off date 16 April 2023), the most common TEAEs appear to be consistent with the pooled data. The most frequent adverse reactions are CRS (57.9%), anaemia (54.1%), neutropenia (44.8%), fatigue (44.3%), upper respiratory tract infection (38.8%), injection site reaction (38.3%), diarrhoea (37.7%), pneumonia (37.2%), thrombocytopenia (36.1%), lymphopenia (30.1%), decreased appetite (26.8%), rash (26.2%), arthralgia (25.1%), pyrexia (27.3%), hypokalaemia (23.0%), nausea (21.3%), and dry skin (21.3%). Of note, no changes were observed for CRS and ICANS compared what had been observed at the initial data cut-off date.

2.6.7.3. Serious adverse events/deaths/other significant events

- ***Serious adverse events***

SAEs were reported in 69.1% of participants (Table 29)

Table 29. Summary of most common treatment-emergent serious adverse events by MedDRA preferred term (All Causalities) (All Participants as Treated)

Number of Participants Evaluable for AEs Number (%) of Participants: by Preferred Term	Pool 1 (N=183) n (%)	Pool 2 (N=82) n (%)	Pool 3 (N=265) n (%)
With Any Serious Adverse Event	125 (68.3)	58 (70.7)	183 (69.1)
Cytokine release syndrome	23 (12.6)	19 (23.2)	42 (15.8)
COVID-19 pneumonia	22 (12.0)	0	22 (8.3)
Pneumonia	12 (6.6)	8 (9.8)	20 (7.5)
Disease progression	10 (5.5)	6 (7.3)	16 (6.0)
Pyrexia	4 (2.2)	5 (6.1)	9 (3.4)
Sepsis	7 (3.8)	2 (2.4)	9 (3.4)
Anaemia	8 (4.4)	0	8 (3.0)
Febrile neutropenia	4 (2.2)	4 (4.9)	8 (3.0)
Pneumocystis jirovecii pneumonia	7 (3.8)	1 (1.2)	8 (3.0)
Acute kidney injury	6 (3.3)	1 (1.2)	7 (2.6)
Plasma cell myeloma	6 (3.3)	1 (1.2)	7 (2.6)
COVID-19	5 (2.7)	1 (1.2)	6 (2.3)
Diarrhoea	3 (1.6)	3 (3.7)	6 (2.3)
Hypoxia	2 (1.1)	4 (4.9)	6 (2.3)
Septic shock	6 (3.3)	0	6 (2.3)
Urinary tract infection	5 (2.7)	1 (1.2)	6 (2.3)
Bacteraemia	4 (2.2)	1 (1.2)	5 (1.9)
Malaise	0	4 (4.9)	4 (1.5)
Muscular weakness	1 (0.5)	3 (3.7)	4 (1.5)
Pneumonia bacterial	4 (2.2)	0	4 (1.5)
SARS-CoV-2 test positive	4 (2.2)	0	4 (1.5)
Herpes zoster	0	3 (3.7)	3 (1.1)
Hypercalcaemia	1 (0.5)	2 (2.4)	3 (1.1)
Cytomegalovirus viraemia	0	2 (2.4)	2 (0.8)
Mental status changes	0	2 (2.4)	2 (0.8)

Participants are only counted once per event.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
Includes data from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)].
Summaries are ordered by alphabetical order for SOC and by descending order for PT in Pool 3 column.
PT= preferred term. For this summary, the following clustered terms for cytopenias including Thrombocytopenia (PT=Thrombocytopenia; Platelet count decreased), Anaemia (PT=Anaemia; Haemoglobin decreased; Red blood cell count decreased; Haematocrit decreased; Normochromic anaemia; Normocytic anaemia; Normochromic normocytic anaemia), Neutropenia (PT=Neutropenia; Neutrophil count decreased; Neutrophil percentage decreased; Cyclic neutropenia; Agranulocytosis; Granulocytopenia; Granulocyte count decreased),
Leukopenia (PT=Leukopenia; White blood cell count decreased), Lymphopenia (PT=Lymphopenia; Lymphocyte count decreased; Lymphocyte percentage decreased; CD4 lymphocytes decreased; CD4 lymphocyte percentage decreased; CD8 lymphocytes decreased; CD8 lymphocyte percentage decreased) are used.
(@@) Denotes AE terms that were not coded by the MedDRA dictionary.
MedDRA v25.0 coding dictionary applied.
Data cut-off date: C1071001 - 22JUN2022, C1071002 - 27MAY2022, C1071003 - 14OCT2022, C1071009 - 29JUL2022

- ***Deaths***

As of 12 January 2023, a total of 112 (42.3%) deaths were reported with 73 (27.5%) occurring within 90 days of the last elranatamab dose and 10 (3.8%) occurring within the initial month after treatment start (Table 30

). The most common cause of death in study participants was the disease under study (27.5%) followed by "other" and "unknown". In Pool 1, there were 84 (45.9%) deaths (53 [29.0%] within 90 days of the last dose and 10 [5.5%] within the initial month after treatment start) and in Pool 2 there were 28 (34.1%) deaths (20 [24.2] within 90 days of the last dose and 0 within the initial month after treatment start) in Pool 2.The primary reason for a higher incidence of deaths in Pool 1, including deaths occurring within 90 days of the last dose of elranatamab and deaths occurring very early in treatment, compared to Pool 2, was a higher incidence of deaths due to disease progression (58 [31.7%] participants in Pool 1 compared to 15 [18.3%) in Pool 2. This imbalance might be explained by the more significant underlying disease in participants in in Pool 1 compared to Pool 2 as noted in the following differential demographic characteristics:

- The median age of participants in Pool 1 was 68.0 years vs 65.5 years in Pool 2 and the number of participants ≥75 years was 19.1% compared to 9.8%.
- A higher percentage of participants had non-IgG myeloma in Pool 1 (15.8%) compared to Pool 2 (1.2%).
- The median time from first diagnosis was 80.5 months in Pool 1 compared to 73.6 months in Pool 2.
- The percentage of participants with >5 prior lines of therapy was 49.7% in Pool 1 compared to 43.9% in Pool 2.
- The percentage of participants with prior BCMA-targeted therapy was 35.0% in Pool 1 compared to 24.4% in Pool 2.
- The percentage of participants refractory to their last line of treatment was 92.9% in Pool 1 compared to 82.9% in Pool 2.

Other causes of death were reported in a similar percentage of participants in Pool 1 and Pool 2.

Table 30. Summary of deaths (All Participants as Treated)

Number (%) of Participants	Pool 1 (N=183) n (%)	Pool 2 (N=82) n (%)	Pool 3 (N=265) n (%)
Death	84 (45.9)	28 (34.1)	112 (42.3)
Cause of Death			
Disease Under Study	58 (31.7)	15 (18.3)	73 (27.5)
Study Treatment Toxicity	6 (3.3)	1 (1.2)	7 (2.6)
Other	12 (6.6)	8 (9.8)	20 (7.5)
Unknown	8 (4.4)	4 (4.9)	12 (4.5)
Death Within 90 Days After Last Dose of Study Drug	53 (29.0)	20 (24.4)	73 (27.5)
Cause of Death			
Disease Under Study	32 (17.5)	12 (14.6)	44 (16.6)
Study Treatment Toxicity	6 (3.3)	1 (1.2)	7 (2.6)
Other	11 (6.0)	5 (6.1)	16 (6.0)
Unknown	4 (2.2)	2 (2.4)	6 (2.3)
Death Within XX Days After First Dose of Study Drug	10 (5.5)	0	10 (3.8)
Cause of Death			
Disease Under Study	9 (4.9)	0	9 (3.4)
Other	1 (0.5)	0	1 (0.4)

XX=28 days for C1071002, C1071003, C1071009 and 30 days for C1071001
Data cut-off date: C1071001 - 12JAN2023, C1071002 - 12JAN2023, C1071003 - 12JAN2023, C1071009 - 12JAN2023

Grade 5 Adverse Events

The most frequently reported Grade 5 AEs (26 participants [9.8%]; 10.4% in Pool 1 and 8.5% in Pool 2) were related to disease progression. Treatment-related Grade 5 AEs were reported in 5 (1.9%) participants (Adenovirus infection, Death, Failure to thrive, Pneumonia pseudomonal, and Septic shock).

Treatment-related Grade 5 AEs were reported in 5 (1.9%) participants (3 [1.6%] in Pool 1 and 2 [2.4%] in Pool 2). The AEs leading to death were reported as Adenovirus infection, Death, Failure to thrive, Pneumonia pseudomonal, and Septic shock.

In Study 1003 (Pool 1) with a cut-off date of 16 April 2023, treatment-related Grade 5 AEs were reported in 6 (3.3%) participants. The AEs leading to death were reported as Cardiac arrest, Adenovirus hepatitis, Adenovirus infection, Pneumonia adenoviral, Pneumonia pseudomonal, Failure to thrive and Septic shock.

Adverse events of special interest

- ***Cytokine Release Syndrome***

As expected, based on the mechanism of action, CRS was observed in a high proportion of participants receiving elranatamab despite pre-medication. The overall incidence of CRS was 57.9% in Pool 1 Table 31).

Table 31. Overview of treatment emergent adverse events of special interest - CRS (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 n (%)	Pool 2 n (%)	Pool 3 n (%)
Participants Evaluable for Adverse Event CRS	183	82	265
Participants with Adverse Event CRS	106 (57.9)	64 (78.0)	170 (64.2)
Participants with Serious Adverse Event CRS	23 (12.6)	19 (23.2)	42 (15.8)
Participants with Maximum Grade 1 Adverse Event CRS	80 (43.7)	36 (43.9)	116 (43.8)
Participants with Maximum Grade 2 Adverse Event CRS	25 (13.7)	27 (32.9)	52 (19.6)
Participants with Maximum Grade 3 Adverse Event CRS	1 (0.5)	1 (1.2)	2 (0.8)
Participants with Maximum Grade 4 Adverse Event CRS	0	0	0
Participants with Maximum Grade 5 Adverse Event CRS	0	0	0
Participants with > 1 Adverse Event CRS	24 (13.1)	10 (12.2)	34 (12.8)
Participants with Adverse Events Outcome as Resolved	106 (57.9)	64 (78.0)	170 (64.2)
Participants with Permanent Discontinuation of Study Drug due to Adverse Event CRS	1 (0.5)	0	1 (0.4)
Participants with Dose Reduction or Interruption due to Adverse Events CRS	9 (4.9)	6 (7.3)	15 (5.7)
Participants with Dose Reduction due to Adverse Event CRS	4 (2.2)	1 (1.2)	5 (1.9)
Participants with Dose Interruption due to Adverse Event CRS	6 (3.3)	5 (6.1)	11 (4.2)
Participants with Adverse Event CRS Who Received Tocilizumab* and/or Steroids	41 (38.7)	44 (68.8)	85 (50.0)
Participants with Adverse Event CRS Who Received Tocilizumab*	35 (33.0)	42 (65.6)	77 (45.3)
Number of CRS Events Treated with Tocilizumab	37	44	81
Number of Grade 1 CRS treated with Tocilizumab	20 (54.1)	22 (50.0)	42 (51.9)
Number of Grade 2 CRS treated with Tocilizumab	16 (43.2)	21 (47.7)	37 (45.7)
Number of Grade 3 CRS treated with Tocilizumab	1 (2.7)	1 (2.3)	2 (2.5)
Number of Grade 4 CRS treated with Tocilizumab	0	0	0
Number of Grade 5 CRS treated with Tocilizumab	0	0	0
Participants with Adverse Event CRS Who Received Steroids	16 (15.1)	14 (21.9)	30 (17.6)
Participants with CRS after 1st Dose	79 (43.2)	54 (65.9)	133 (50.2)
Participants with Maximum Grade 1 Adverse Event CRS	60 (32.8)	29 (35.4)	89 (33.6)
Participants with Maximum Grade 2 Adverse Event CRS	18 (9.8)	24 (29.3)	42 (15.8)
Participants with Maximum Grade 3 Adverse Event CRS	1 (0.5)	1 (1.2)	2 (0.8)
Participants with Adverse Event CRS Who Received Tocilizumab* and/or Steroids	30 (38.0)	38 (70.4)	68 (51.1)
Participants with Adverse Event CRS Who Received Tocilizumab*	25 (31.6)	37 (68.5)	62 (46.6)
Number of CRS Events Treated with Tocilizumab	25	37	62
Number of Grade 1 CRS treated with Tocilizumab	12 (48.0)	17 (45.9)	29 (46.8)
Number of Grade 2 CRS treated with Tocilizumab	12 (48.0)	19 (51.4)	31 (50.0)
Number of Grade 3 CRS treated with Tocilizumab	1 (4.0)	1 (2.7)	2 (3.2)
Participants with Adverse Event CRS Who Received Steroids	13 (16.5)	11 (20.4)	24 (18.0)
Participants with CRS after 2nd Dose	35 (19.1)	11 (13.4)	46 (17.4)
Participants with Maximum Grade 1 Adverse Event CRS	30 (16.4)	10 (12.2)	40 (15.1)
Participants with Maximum Grade 2 Adverse Event CRS	5 (2.7)	1 (1.2)	6 (2.3)
Participants with Maximum Grade 3 Adverse Event CRS	0	0	0
Participants with Adverse Event CRS Who Received Tocilizumab* and/or Steroids	7 (20.0)	7 (63.6)	14 (30.4)
Participants with Adverse Event CRS Who Received Tocilizumab*	6 (17.1)	5 (45.5)	11 (23.9)
Number of CRS Events Treated with Tocilizumab	6	5	11
Number of Grade 1 CRS treated with Tocilizumab	4 (66.7)	4 (80.0)	8 (72.7)
Number of Grade 2 CRS treated with Tocilizumab	2 (33.3)	1 (20.0)	3 (27.3)
Number of Grade 3 CRS treated with Tocilizumab	0	0	0
Participants with Adverse Event CRS Who Received Steroids	2 (5.7)	4 (36.4)	6 (13.0)
Participants with CRS after 3rd Dose	13 (7.1)	5 (6.1)	18 (6.8)
Participants with Maximum Grade 1 Adverse Event CRS	9 (4.9)	4 (4.9)	13 (4.9)
Participants with Maximum Grade 2 Adverse Event CRS	4 (2.2)	1 (1.2)	5 (1.9)
Participants with Maximum Grade 3 Adverse Event CRS	0	0	0

These events were mostly Grade 1 or 2, mostly occurred during first or second step-up dose, were generally of a transient nature (median duration was 2 days), and there were very few cases with first

occurrence beyond third Treatment Dose. Overall, the observed characteristics support a view that CRS occurring in the context of elranatamab use is manageable with diligent care.

In study 1003, the use of premedication was mandated according to a specific scheme provided in the protocol, which includes step-up dose 1, step-up dose 2 and the first full treatment dose. The same scheme has been brought forward into the SmPC, and in light of the high frequency of CRS, the routine use of premedication is endorsed.

Supportive measures, including the use of tocilizumab, were used for management of CRS in a substantial proportion of participants. While the guidelines provided in the 1003 study protocol for management of CRS were not prescriptive, is noted that among patients who developed CRS 33% received tocilizumab (or siltuximab) and 15.1% received corticosteroids for treatment of CRS.

The median time to onset of CRS was 2 days. Based on the time to onset calculation for CRS ([first AE start date in the period - last non-zero dosing date on or prior to the AE] +1), the median time to CRS onset of 2.0 days represents an onset ~24 hours after elranatamab dosing (e.g., Day 2 after dose) and the 3rd quartile of time to onset was 3 days (~48 hours after the dose).

- ***Immune effector cell- associated neurotoxicity syndrome (ICANS)***

ICANS were reported in 6.0% of participants, with a lower proportion observed in participants in Pool 1 (3.3%) who received the recommended priming regimen compared with participants in Pool 2 (12.2%) who received alternative priming regimens (Table 32

). Of the 6 participants (Pool 1) with ICANS, 2 (1.1%) had GRADE 3 events and both participants had prior BCMA-directed therapy and permanently discontinued treatment due to ICANS. No ICANS were Grade 4 or 5. 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).

Table 32. Overview of treatment-emergent adverse events of special interest - ICANS (All Causalities) (All Participants as Treated)

Number (%) of Participants	Pool 1 n (%)	Pool 2 n (%)	Pool 3 n (%)
Participants Evaluable for Adverse Event ICANS	183	82	265
Participants with Adverse Event ICANS	6 (3.3)	10 (12.2)	16 (6.0)
Participants with Serious Adverse Event ICANS	2 (1.1)	1 (1.2)	3 (1.1)
Participants with Maximum Grade 1 Adverse Event ICANS	1 (0.5)	6 (7.3)	7 (2.6)
Participants with Maximum Grade 2 Adverse Event ICANS	3 (1.6)	4 (4.9)	7 (2.6)
Participants with Maximum Grade 3 Adverse Event ICANS	2 (1.1)	0	2 (0.8)
Participants with Maximum Grade 4 Adverse Event ICANS	0	0	0
Participants with Maximum Grade 5 Adverse Event ICANS	0	0	0
Participants with > 1 Adverse Event ICANS	2 (1.1)	0	2 (0.8)
Participants with Adverse Events Outcome as Resolved	6 (3.3)	10 (12.2)	16 (6.0)
Participants with ICANS concurrent with CRS	6 (3.3)	10 (12.2)	16 (6.0)
Participants with Permanent Discontinuation of Study Drug due to Adverse Event ICANS	2 (1.1)	0	2 (0.8)
Participants with Dose Reduction or Interruption due to Adverse Events ICANS	1 (0.5)	0	1 (0.4)
Participants with Dose Reduction due to Adverse Event ICANS	0	0	0
Participants with Dose Interruption due to Adverse Event ICANS	1 (0.5)	0	1 (0.4)
Participants with Adverse Event ICANS Who Received Tocilizumab* and/or Steroids	4 (66.7)	9 (90.0)	13 (81.3)
Participants with Adverse Event ICANS Who Received Tocilizumab*	2 (33.3)	8 (80.0)	10 (62.5)
Participants with Adverse Event ICANS Who Received Steroids	4 (66.7)	6 (60.0)	10 (62.5)
Participants with ICANS after 1st Dose	5 (2.7)	10 (12.2)	15 (5.7)
Participants with Maximum Grade 1 Adverse Event ICANS	1 (0.5)	6 (7.3)	7 (2.6)
Participants with Maximum Grade 2 Adverse Event ICANS	3 (1.6)	4 (4.9)	7 (2.6)
Participants with Maximum Grade 3 Adverse Event ICANS	1 (0.5)	0	1 (0.4)
Participants with ICANS concurrent with CRS	5 (2.7)	10 (12.2)	15 (5.7)
Participants with Adverse Event ICANS Who Received Tocilizumab* and/or Steroids	3 (60.0)	9 (90.0)	12 (80.0)
Participants with Adverse Event ICANS Who Received Tocilizumab*	1 (20.0)	8 (80.0)	9 (60.0)
Participants with Adverse Event ICANS Who Received Steroids	3 (60.0)	6 (60.0)	9 (60.0)
Participants with ICANS after 2nd Dose	1 (0.5)	0	1 (0.4)
Participants with Maximum Grade 1 Adverse Event ICANS	0	0	0
Participants with Maximum Grade 2 Adverse Event ICANS	0	0	0
Participants with Maximum Grade 3 Adverse Event ICANS	1 (0.5)	0	1 (0.4)
Participants with ICANS concurrent with CRS	0	0	0
Participants with Adverse Event ICANS Who Received Tocilizumab* and/or Steroids	1 (100.0)	0	1 (100.0)

Among patients who developed ICANS, 66.7% received corticosteroids, 33.3% received tocilizumab (or siltuximab), 33.3% received levetiracetam and 16.7% received anakinra for treatment of ICANS, which is adequately displayed in the SmPC.

Similar to CRS, the majority of participants had ICANS after the first step-up, the events were mostly of limited duration, but supportive treatment including tocilizumab was used in most participants developing ICANS; this should be noted in the context of most of the ICANS events occurring concurrently with CRS.

- ***Other neurologic AEs***

The incidence of all-causality neurologic AEs other than ICANS was assessed using PT pooling in the 3 categories of Encephalopathy, Motor dysfunction, and Sensory neuropathy. Overall, 29.1% of

participants had a neurologic AE in one of the 3 categories, with similar incidence in Pool 1 and Pool 3. The majority of participants had Grade 1 (15.5%) or Grade 2 (9.8%) events; 3.8% had Grade 3 events and no participant had a Grade 4 or 5 event. Treatment-related neurologic AEs were reported in 7.2% of participants, with 3.0% in the Encephalopathy category (1.5% Grade 1 and 1.5% Grade 2), 1.9% in Motor dysfunction (1.5% Grade 1 and 0.4% Grade 3) and 2.6% in Sensory Neuropathy (1.1% Grade 1, 1.1% Grade 2 and 0.4% Grade 3). At the time of the data cut-off, 45/77 (58.4%) participants had neurologic AEs that had resolved. The frequencies of permanent discontinuations (1.1%), dose reductions (1.1%), and dose interruptions (5.7%) of elranatamab treatment due to a neurologic AE were low.

Within the nervous system disorders SOC, any Grade peripheral neuropathies were reported with very common frequency, including 19.1% in Pool 1 (21.3 % in Pool 1, cut-off date 16 April 2023) and 22.0% in Pool 2. 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 Paraesthesia (4.9%), Muscular weakness (4.5%), and Peripheral sensory neuropathy (4.2%). It is stated that at the time of data cutoff, 27/53 (50.9%) participants had resolved events. Serious events of PN were reported in 6 (2.3%) participants and included Muscular weakness (4 participants [1.5%]), Guillain-Barré syndrome (1 participant [0.4%]), Neuralgia (1 participant [0.4%]), and Sensory disturbance (1 participant [0.4%]). The frequencies of permanent discontinuations (1.9%), dose reductions (1.1%), and dose interruptions (4.5%) of elranatamab treatment due to a potential PN event were low.

Of the participants who had potential PN events, 51.8% had a medical history of PN; similarly, of participants who did not have PN events, 47.4% had a medical history of PN. These findings suggest that participants with a history of PN are not at increased risk for PN when receiving elranatamab.

- ***Infections***

Patients with MM have increased infectious liability due to their underlying condition, and a high rate of infectious complications is therefore expected. Overall, 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 and 5.7% had Grade 5 events. Grade 5 events 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%). Of these events, 1 participant had both Adenovirus infection and Pneumonia adenoviral.

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%).

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.

To further characterise the pattern of infections an analysis were performed on AEs and SAEs in the SOC of Infections and infestations that occurred in the first 3 months, from 3 to 6 months, from 6 to 12 months and greater than 12 months after elranatamab initiation in participants (assessing only those still in the treatment period) in SCS Pool 1 using the 16 Apr 2023 data cut off data:

- First 3 months: 50.3 % of participants had an infection AE (20.2% a SAE of infection)
- ≥3 months up to 6 months: 44.4% of participants had an infection AE (23.9% had a SAE)

- 6 to 12 months: 59.6% of participants had an infection AE (31.5% had a SAE)
- greater than 12 months: 63.9% of participants had an infection AE (31.1% had a SAE)

In all three time periods, the types of infections that occurred commonly were generally similar.

The incidence of AEs of infection that occurred within 14 days of a participant having Grade 4 neutropenia was 4.2% compared with 95.8% of events that occurred without prior Grade 4 neutropenia. The incidence of AEs of infection that occurred within 14 days of a participant having Grade 4 lymphopenia was 12.6% compared with 87.4% of events that occurred without prior Grade 4 lymphopenia.

The monthly exposure adjusted incidence rate was 0.52 (95% CI: 0.29, 0.85) with Grade 4 neutropenia vs 0.32 (95% CI; 0.29, 0.35) without Grade 4 neutropenia and 0.46 (95% CI: 0.35, 0.60) with Grade 4 lymphopenia vs 0.31 (95% CI: 0.28, 0.34) without Grade 4 lymphopenia Table 33

and Table 34.

Among all participants, the median time with Grade 4 neutropenia/lymphopenia was much shorter than the time without Grade 4 neutropenia/lymphopenia.

Table 33. Summary of infections in participants with/without neutropenia

	Number of Infections With Neutropenia	Number of Infections Without Neutropenia	Exposure Adjusted Rate (95% CI) With Neutropenia in Months	Exposure Adjusted Rate (95% CI) Without Neutropenia in Months
Time in Months				
n			46	183
Mean (STD)			0.63 (0.687)	7.93 (6.564)
Median (Range)			0.36 (0.03, 3.32)	5.19 (0.23, 21.16)
All Infections	15	460	0.51531 (0.28841, 0.84992)	0.31684 (0.28855, 0.34716)
Bacterial	3	144	0.10306 (0.02125, 0.30119)	0.09919 (0.08365, 0.11677)
Fungal	1	34	0.03435 (0.00087, 0.19141)	0.02342 (0.01622, 0.03273)
Viral	6	189	0.20612 (0.07564, 0.44864)	0.13018 (0.11228, 0.15012)
Pathogen unspecified	5	93	0.17177 (0.05577, 0.40085)	0.06406 (0.05170, 0.07847)

Table 34. Summary of infections in participants with/without lymphopenia

	Number of Infections With Lymphopenia	Number of Infections Without Lymphopenia	Exposure Adjusted Rate (95% CI) With Lymphopenia in Months	Exposure Adjusted Rate (95% CI) Without Lymphopenia in Months
Time in Months				
n			103	181
Mean (STD)			1.14 (1.927)	7.53 (6.499)
Median (Range)			0.36 (0.03, 11.60)	5.09 (0.10, 21.16)
All Infections	54	421	0.46092 (0.34625, 0.60139)	0.30870 (0.27991, 0.33965)
Bacterial	20	127	0.17071 (0.10427, 0.26365)	0.09312 (0.07763, 0.11080)
Fungal	3	32	0.02561 (0.00528, 0.07483)	0.02346 (0.01605, 0.03312)
Viral	20	175	0.17071 (0.10427, 0.26365)	0.12832 (0.11001, 0.14880)
Pathogen unspecified	11	87	0.09389 (0.04687, 0.16800)	0.06379 (0.05110, 0.07869)

Two cases of progressive multifocal leukoencephalopathy (PML) have been reported. One occurred while on Elrexfio therapy but outside the pivotal trial and another occurred 4 months after Elrexfio discontinuation in the pivotal trial.

- ***Cytopenias***

Cytopenias, including Grade 3 and 4 events, were frequently reported across all classes of blood cells. Although cytopenia can be considered as expected due to the underlying clinical condition, the absence of a control group complicates the assessment as regards any contributory role of elranatamab on the risk of cytopenias. The most frequently reported all Grade and Grade 3/4 individual cytopenia AEs (≥20% all Grade) were Anaemia (52.8% [41.1%]), Neutropenia (34.0% [33.2%]), and thrombocytopenia (22.3% [17.7%]). Dose interruptions were the primary method for management of cytopenias. In study 1003, 74/187 (39.6%) participants received immunostimulants (e.g., G-CSF) for neutropenia/improved neutrophil production, and 77/187 (41.2%) participants received transfusion support for anaemia or thrombocytopenia.

One of the main risks associated to thrombocytopenia is an increased risk of bleeding. The applicant provided an analysis for ISS/SCS Pool 3 participants in order to identify TEAEs considered bleeding events (excluding the non-haemorrhagic PT Immune thrombocytopenia, with data as of the 12 January 2023). The majority of participants had Grade 1 (11.7%; n=31/46) AEs, with 3.0% Grade 2 events, 2.3% Grade 3 events and 0.4% (1 participant) Grade 4 events; there were no Grade 5 events. Epistaxis was the most common bleeding event (3.8%), followed by contusion (1.9%), haematoma (1.5%), and haematuria, ecchymosis and petechiae (each at 1.1%). The Grade 4 event of subdural haematoma occurred in a 56 year-old male participant on study day 18 in the context of fatal disease progression, which included Grade 4 thrombocytopenia and G2 renal failure and was considered unrelated to elranatamab by the Investigator.

Bleeding events following a thrombocytopenic event were observed in 31 participants (11.7%) compared to 15 participants (5.7%) that had an AE of haemorrhage that had a normal platelet count (Grade 0) prior to the AE. Grade of platelet count decrease did not impact the incidence of haemorrhage AEs and did not appear to impact the Grade of haemorrhage AE.

- ***Hypogammaglobulinemia***

All causality hypogammaglobulinemia AEs were reported in 14.3% of participants.

- ***Hypersensitivity***

All causality hypersensitivity AEs, excluding injection site reactions, were reported in 28.7% of participants and were primarily Grade 1 or Grade 2 skin rashes and no participant had a serious event.

The most frequently reported all-causality hypersensitivity AEs (≥2%) included Rash and Rash maculo-papular (7.5% each), and infusion related reaction (2.6%). None of the Infusion related reactions were treatment related. No participant permanently discontinued elranatamab due to a hypersensitivity reaction.

- ***Injection Site Reactions***

All causality injection site reaction AEs were reported in 42.3% of participants. Local injection site reactions mostly comprised injection site reactions and erythema. One participant had a serious injection site reaction (injection site reaction). Injection site reactions had resolved in the majority of participants (103/112 [91.7%]) using resolution data as of 12 January 2023. Among the 9 participants who still had unresolved injection site reactions, none had received any treatment. The Investigators confirmed that 4 participants had resolved ISR that were not updated in the database at the cut-off date and that 4 participants died prior to ISR resolution. One participant had intermittent ISR thus the status was reported as unresolved.

- ***Secondary Primary Malignancies***

Secondary primary malignancies were reported in 2.3% of participants including skin malignancies in 5 participants (3 with squamous cell carcinoma of the skin [1.1%], 1 with squamous cell carcinoma and 1 with basal cell carcinoma [0.4% each]) and myelodysplastic syndrome in 1 participant (0.4%). All of the participants had underlying risk factors including prior therapy with lenalidomide.

The applicant therefore evaluated if there were any laboratory features indicative of TLS. An analysis was conducted to determine if there were participants in study 1003 with ≥25% increases from baseline in uric acid or potassium, or ≥25% decreases in calcium, during the first 14 days after the start of elranatamab treatment. Of the 179 participants evaluable for laboratory features of TLS, 21 (11.7%) met at least one of the TLS criteria, with the majority (19/21) of participants having only a single electrolyte/metabolite change. Two (1.1%) participants met 2 of the TLS criteria and no participant met all 3 of the criteria. One participant with a ≥25% increase in uric acid also had an AE of hyperuricaemia on Day 28 and died on Day 52 due to disease progression. Another participant, with an ≥25% increase in uric acid and potassium was diagnosed with myeloma cast nephropathy on Day 8 and discontinued elranatamab due to disease progression on the same day.

2.6.7.4. Laboratory findings

- **Haematology**

Worsening postbaseline shifts from Grade ≤2 at baseline to Grade 3/4 post-baseline were commonly observed. Changes in haematological parameters are commonly observed in MM patients, and in the absence of a control group, the effect of elranatamab vs. disease-associated changes cannot be assessed. There was no notable change in median neutrophil counts over time. There appeared to be a decrease in the median platelet count within the first cycle, followed by recovery. Consistent with the mechanism of action of elranatamab, a decrease in lymphocyte counts was observable early with some recovery at later time points. Median haemoglobin was unchanged through the first 2 cycles and then appeared to gradually increase over time.

- **Chemistry Laboratory Evaluations**

The majority of chemistry parameters had low proportions of participants that shifted from Grade ≤2 at baseline to Grade 3/4 post-baseline as detailed below. Chemistry parameters with ≥10% of participants with shifts from Grade ≤2 at baseline to Grade 3 or 4 post-baseline were limited to Hyponatremia (11.0%).

Of the liver function test categories, the most frequent abnormalities (≥10%) included ALT ≥3x ULN (11.3%), AST ≥3x ULN (10.3%) and ALT or AST ≥3x ULN (13.6%). ALT ≥5x ULN, AST ≥5x ULN and ALT or AST ≥5x ULN occurred in 5.3%, 6.1% and 7.9% of participants, respectively; greater elevations occurred in ≤3.4% of participants. Total bilirubin ≥2x ULN occurred in 3.4% of participants. Transaminase elevations associated with other laboratory values that met the biochemical definition of Hy's Law (ALT or AST ≥ 3x ULN and total bilirubin ≥2x ULN and ALP ≥ 2x ULN or missing) occurred in 7 (2.7%) participants. Median ALT, AST and bilirubin were unchanged over time. There were no clinically relevant differences in median ALT or median change from baseline in participants with CRS compared to those without CRS.

A total of 7 cases of potential Hy's law were reported, however, 6 had alternative aetiologies for the abnormal laboratory values and 1 participant had increases due to an unknown aetiology but continued treatment without reoccurrence.

2.6.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.7.6. Safety in special populations

There were no clinically relevant differences in the safety of elranatamab with respect to age, sex, race, renal function at baseline, hepatic function at baseline, geographic region, and formulation strength.

TEAEs during the treatment period by age category are summarised in Table 35.

Table 35. Treatment-emergent adverse events summary during the treatment period by age category (All Causalities)

	Pool 3 (N=265)			
	Age < 65 (N=110)	Age 65-74 (N=112)	Age 75-84 (N=40)	Age 85+ (N=3)
Number (%) of Subjects with:	n (%)	n (%)	n (%)	n (%)
Any AEs	110 (100.0)	112 (100.0)	40 (100.0)	3 (100.0)
Serious AE - Total	73 (66.3)	79 (70.5)	28 (70.0)	3 (100.0)
-Fatal	18 (16.3)	21 (18.7)	9 (22.5)	1 (33.3)
-Hospitalization/prolong existing hospitalization	68 (61.8)	73 (65.1)	26 (65.0)	3 (100.0)
-Life-threatening	11 (10.0)	12 (10.7)	6 (15.0)	0
-Disability/incapacity	3 (2.7)	5 (4.4)	2 (5.0)	0
-Other (medically significant)	16 (14.5)	14 (12.5)	7 (17.5)	1 (33.3)
-N/A	0	0	0	0
AE leading to drop-out	17 (15.4)	14 (12.5)	9 (22.5)	1 (33.3)
Psychiatric disorders	23 (20.9)	35 (31.2)	10 (25.0)	2 (66.6)
Nervous system disorders	61 (55.4)	54 (48.2)	21 (52.5)	2 (66.6)
Accidents and injuries	14 (12.7)	27 (24.1)	8 (20.0)	2 (66.6)
Cardiac disorders	18 (16.3)	22 (19.6)	8 (20.0)	0
Vascular disorders	19 (17.2)	22 (19.6)	11 (27.5)	1 (33.3)
Cerebrovascular disorders	2 (1.8)	2 (1.7)	1 (2.5)	0
Infections and infestations	80 (72.7)	78 (69.6)	22 (55.0)	3 (100.0)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	18 (16.3)	27 (24.1)	9 (22.5)	2 (66.6)

- **Pregnancy and lactation**

Pregnant and breastfeeding women were excluded from participation in clinical studies. According to the applicant, there were no reports of pregnancy or breastfeeding during the clinical development programme.

2.6.7.7. Immunological events

ADA detection

Pooling for the immunogenicity analyses used three different pools:

- IG Pool 1: all participants in the IV cohorts from study 1001 [N=23]

- IG Pool 2: all participants in the SC cohorts from 1001, 1002, 1003, and 1009 at all dose levels up to SC 1000 µg/kg or its fixed dose equivalent 76 mg monotherapy full dose [N=288]

- IG Pool 3: all participants randomised to receive either SC 1000 µg/kg monotherapy (from studies 1001, 1002) or its fixed dose equivalent 76 mg monotherapy full dose (from studies 1001, 1003, and 1009) [N=264]. This is the same pool as safety Pool 3.

As dose and route of administration may affect immunogenicity, the IG Pool 3, with patients treated at the proposed full dose level for elranatamab, is the most relevant pool to capture and present data on immunogenicity.

The sampling schedules allowed detection of early development of ADA, assessment of persistence of any ADA response, and the assessment of the potential impact, if any, of ADA and/or NAb on PK, efficacy, and safety.

The same ADA and NAb assays were used for all four clinical studies. The drug tolerance of the ADA assay allowed detection of clinically relevant ADA presence (>100 ng/mL) at drug concentrations <100 µg/mL. With one exception, all ADA samples for all 4 clinical studies were within the drug tolerance limit of 100 µg/mL elranatamab. Hence, the drug tolerance is considered sufficient.

ADA incidence

In IG Pool 3 there were 34 participants that were positive for ADA at baseline (14.2%, 34/240), which is considered to be a high baseline prevalence. However, baseline ADA was not associated with loss of efficacy or with any safety risk. Only four of the baseline positive subjects developed treatment-boosted ADA.

The incidence of treatment-induced ADA was 16/240 (6.7%). The total incidence of treatment-induced and treatment-boosted ADA was 8.3% (20/240) in IG Pool 3. Ten of the treatment-induced ADA positive patients were also positive for NAb (10/239, 4.2%).

The applicant provided an analysis of ADA and Nab incidence stratified by prior BCMA therapy for IG Pool 3. The incidence of baseline positive ADA study participants was higher 20.8% (15/72) for participants with prior compared to participants no prior BCMA therapy 11.3% (19/168). Incidence of NAb at baseline was comparable (1.4% (1/72) and 4.2% (7/167) for participants with or without prior BCMA-directed therapy, respectively. However, as stated by the applicant, these incidences did not appear to impact the risk for developing a treatment-boosted ADA response which was low for both groups (incidence 0.0% (0/72) and 2.4% (4/168) in participants with or without prior BCMA-directed therapy, respectively. The incidence of treatment-induced ADA was similar for participants with or without prior BCMA-directed therapy, respectively. The incidence of treatment-induced NAb also followed similar trends (2.8% (2/72) and 4.8% (8/168) with or without prior BCMA-directed therapy, respectively.

Both baseline ADA and treatment-induced ADA were generally of low titre (≤ 300, except for 4 of the ADA-positive participants where the titre was > 2000 during or at end of treatment).

The Applicant states that the duration of ADA response appeared to be transient. However, there were only three patients who were reported to have become ADA negative after having been ADA positive at some point. 14 patients in IG Pool 3 were ADA positive at the End of treatment visit.

Impact of ADA on PK efficacy and safety

The comparison of elranatamab C_{trough} concentrations by ADA status in study 1003 indicated clinically non-significant differences between ADA-negative and ADA-positive patients. Based on this comparison and the results from a modelling exercise, the applicant concluded that immunogenicity had no significant effects on elranatamab pharmacokinetics.

The impact of immunogenicity on efficacy and safety was evaluated via a multi-variable logistic regression modelling approach in which baseline ADA status and treatment-induced/boosted ADA status were tested as covariates for the exposure-response relationship. None of the ADA-related covariates were identified to be statistically significant in the exposure-response analysis for efficacy or safety parameters (infections, neutropenia and QT-interval).

COVID-19 Summary of Impact on Safety

COVID-19 had an impact on the safety findings of Study 1003 and therefore Pool 1. Overall, 18.5% of participants had a COVID-19 related AE, including 24.6% in Pool 1 and 4.9% in Pool 2. Six participants (2.3%) died due to a COVID-19 AE, including 4 (1.5%) participants with COVID-19 pneumonia and 2 (0.8%) participants with COVID-19 (0.8%).

2.6.7.8. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with elranatamab.

2.6.7.9. Discontinuation due to adverse events

Permanent discontinuation of elranatamab treatment due to all-causality AEs occurred in 15.5% of participants and the frequency of discontinuations was similar in Pool 1 (16.9%) and Pool 2 (12.2%).

The overall frequency of discontinuations due to treatment-related AEs was 7.5% and similar in Pool 1 (8.2%) and Pool 2 (6.1%). The treatment-related AEs leading to discontinuation of elranatamab in more than 1 (≥0.5%) participant were Neutropenia, Thrombocytopenia, and ICANS, which all occurred in 2 participants (0.8%).

AEs leading to a dose interruption and/or dose reduction occurred in 74.3% of participants, with a similar frequency in Pool 1 (74.3%) and Pool 2 (74.4%). The SOCs with the highest incidence of AEs leading to a dose interruption (≥20%) were Infections and infestations (44.9%) and Blood and lymphatic system disorders (37.4%). The most frequently reported AEs (≥5%) leading to dose interruption were Neutropenia (32.5%), COVID-19 (15.1%) Pneumonia (7.2%), Anaemia (7.2%), Thrombocytopenia (6.8%), and Upper respiratory tract infection (6.0%). The SOC with the highest incidence of AEs leading to dose reduction (≥10%) was Blood and lymphatic system disorders (16.2%). The most frequently reported AE (≥2%) leading to dose reduction was Neutropenia (14.0%).

The nature of AE's leading to treatment discontinuation or requiring treatment modifications is consistent with the general safety profile of elranatamab, the common reasons being neutropenia, and thrombocytopenia.

2.6.7.10. Post marketing experience

Not applicable.

2.6.8. Discussion on clinical safety

The analysis of clinical safety is based on three different patient pools from monotherapy studies with elranatamab: Pool 1 (N=183) includes patients on the proposed registrational dose (including proposed step-up), Pool 2 (N=82) includes patients on other dosing regimens, and Pool 3 (N=265) includes all treated patients. The pooling strategy is considered appropriate and enables a reasonable characterisation of the safety profile, although the comprehensiveness is limited by the lack of a concurrent control group in all the studies. Notably, all safety endpoints were assessed in the on-treatment period, defined as the time from the first dose of study intervention through the minimum of [90 days after last dose, or (start day of new anticancer therapy – 1 day)].

An update of the safety tables for the 183 participants that received the recommended dosing regimen (study 1003, Pool 1) using a data cut-off date of 16 April 2023, was provided during the evaluation of this application which corresponds to ~15 months after the last participant first dose in study 1003.

Patient exposure

At data cut-off, median follow-up since initial dose was 10.38 (0.23, 20.14) months for Cohort A of Pool 1 (patients naïve to BCMA-directed therapies) and 9.22 (0.33, 12.32) months for Cohort B of Pool 1 (patients with previous exposure to BCMA-directed therapies). Median duration of treatment was 4.1 (range 0.03 to 14.8) months in Pool 1 and 4.7 (range 0.03 to 24.4) months in Pool 3. At the time of data cut-off, of the 265 participants, 62.3% had discontinued treatment with similar frequency between Pool 1 and Pool 2. The reasons for discontinuation were also similar across pools. The most frequent reason for discontinuation of treatment was progressive disease (37.0%). The other reasons for discontinuation of treatment reported in ≥5% of participants included AEs (9.1%) and death (7.5%). Overall, 74.9% of participants had at least one temporary or permanent dose reduction or

interruption, with a similar proportion in Pool 1 and Pool 2. The majority of AEs was managed by dose interruption rather than by dose modifications. As treatment discontinuation due to an AE only occurred in 9% of the participants, dose interruption seems to be an efficient means to manage emerging tolerability issues. The dose interruption guidelines from study 1003 have been brought forward to the SmPC which is considered acceptable.

With the updated safety data from for study 1003 with clinical cut-off date of 16 April 2023, the median duration of treatment was 4.11 months (0.03 to 20.27) with 55/183 (30%) treated for ≥12 months and 11/183 (6%) participants treated for more than 18 months.

The duration of exposure to treatment, even though adequate for a conditional marketing authorisation, remain limited and the potential adverse effect of longer exposure to elranatamab is expected to be further characterised through data collected in the ongoing study 1003.

The safety profile of elranatamab across studies and pools showed a generally consistent pattern that was anticipated based on the mechanism of action and disease under study. Most patients developed at least one treatment-emergent adverse event (TEAE) during the study. The most commonly affected system organ classes (SOCs) for both any grade TEAEs and Grade 3/4 TEAEs were Blood and lymphatic system disorders, Immune system disorders and Infections and infestations.

In general, safety findings were similar in participants naïve to BCMA directed therapies and those who had prior exposure to BCMA-directed ADCs or CAR-T cell therapy, and therefore risks and mitigations are applicable to all participants.

Adverse events of special interest

As expected, based on the mechanism of action, cytokine release syndrome (CRS) was observed in a high proportion of participants receiving elranatamab despite pre-medication. In Pool 1, the vast majority of CRS was Grade 1 (43.7%) or Grade 2 (13.7%), with only one case of Grade 3 CRS and no cases of Grade 4 or 5 CRS being reported. Among patients who developed CRS, associated symptoms included fever (99.0%), hypoxia (11.4%), and hypotension (21.0%) and 33% received tocilizumab (or siltuximab) and 15.1% received corticosteroids for treatment of CRS. As the occurrence of CRS events occurred mostly after the first and second step-up dosing, the precautions regarding intensified monitoring, as currently proposed in the SmPC, are endorsed. The applicant's efforts to define, within the studies, an appropriate premedication regimen and step-up dosing scheme to minimise occurrence of severe CRS are acknowledged; these measures have been adequately adopted into the SmPC. Supportive measures, including the use of tocilizumab, were used for management of CRS in a substantial proportion of participants. The CRS management guidelines proposed by the applicant in the SmPC are consistent with those provided in the 1003 protocol. To further minimise this risk, the applicant will ensure that all patients treated with elranatamab will receive a Patient Card in order to inform them about the risks of CRS and when to seek urgent attention from the healthcare provider or seek emergency help.

Neurological TEAEs, including CNS manifestations such as encephalopathy, were frequently reported; the majority of these events were Grade 1 or 2. Neurological TEAEs also included peripheral neuropathy, reported in 19.1% of Pool 1 participants. The frequency of ICANS was lower in Pool 1 with the proposed registrational step-up scheme compared to Pool 2 with alternative step-up schemes (3.3% vs. 12.2%), supporting a favourable profile with the registrational scheme. Among patients who developed ICANS, 66.7% received corticosteroids, 33.3% received tocilizumab (or siltuximab), 33.3% received levetiracetam and 16.7% received anakinra for treatment of ICANS, which is adequately reflected in the SmPC. As it is important for patients to understand the signs and symptoms of ICANS and how and when they should seek additional attention from the healthcare provider, such information will be included in the patient card that will be given to all patients that will be treated with

elranatamab. Additional information to further characterise the incidence and nature or this type of adverse reactions will be provided by the final study report of study 1003.

Important neurologic ADRs other than ICANS included peripheral neuropathy (PN). Any grade PN were reported with very common frequency, including 19.1% in Pool 1 and 22.0% in Pool 2. The majority of participants had Grade 1/2 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 Paraesthesia, Muscular weakness, and Peripheral sensory neuropathy. At the time of data cutoff, 27/53 (50.9%) participants had resolved events. Serious events of PN were reported in 6 (2.3%) participants and included Muscular weakness (4 participants), Guillain-Barré syndrome (1 participant), Neuralgia (1 participant), and Sensory disturbance (1 participant [0.4%]). Of the participants who had potential PN events, 51.8% had a medical history of PN; similarly, of participants who did not have PN events, 47.4% had a medical history of PN. These findings suggest that participants with a history of PN are not at increased risk for PN when receiving elranatamab.

Infections were reported in a high proportion of patients. Infections were frequently Grade 3 to 4 / serious TEAEs, and (apart from disease progression) were also the most common class of Grade 5 TEAEs. 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, and a high rate of infectious complications is therefore expected. Grade 5 events 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%). Of these events, 1 participant had both Adenovirus infection and Pneumonia adenoviral. Opportunistic infections were reported in 9.4% of participants. 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. To further characterise the pattern and severity of late-onset AEs in the SOC of Infections and infestations that occurred in the first 3 months, from 3 to 6 months, from 6 to 12 months and greater than 12 months after elranatamab initiation in participants were analysed. In all three time periods, the types of infections that occurred commonly were generally similar. Additional information on this risk is expected to be collected through the ongoing pivotal study which is expected to be completed in 2025.

The impact of elranatamab-induced cytopenias on the development of infections was assessed, however, the dataset was too limited to exclude that neutropenia and lymphopenia may contribute to an increased risk for infections. The SmPC includes a recommendation to consider antiviral and antimicrobial prophylaxis prior to starting elranatamab.

Two cases of progressive multifocal leukoencephalopathy (PML) have been reported. One occurred while on elranatamab therapy but outside the pivotal trial and another occurred 4 months after elranatamab discontinuation in the pivotal trial. Considering the severe nature of PML, treating physicians should be vigilant in monitoring for early signs of potential PML, and therefore a specific mention of PML in the Infections subsection of SmPC Section 4.4.has been included.

Cytopenias, were frequently reported across all cell classes; cytopenias also were the most frequently reported Grade 3/4 TEAEs. Although cytopenia can be considered as expected due to the underlying clinical condition, the absence of a control group complicates the assessment as regards any contributory role of elranatamab on the risk of cytopenias. In study 1003, 74/187 (39.6%) participants received immunostimulants (e.g., G-CSF) for neutropenia/improved neutrophil production, and 77/187 (41.2%) participants received transfusion support for anaemia or thrombocytopenia. Complete blood cell counts should be monitored at baseline and periodically during treatment. Treatment with elranatamab should be withheld as indicated in the SmPC. Patients with neutropenia should be

monitored for signs of infection. Supportive therapy should be provided according to local institutional guidelines.

Bleeding events following a thrombocytopenic event were observed in 31 participants (11.7%) compared to 15 participants (5.7%) that had an AE of haemorrhage that had a normal platelet count (Grade 0) prior to the AE. Grade of platelet count decrease did not impact the incidence of haemorrhage AEs and did not appear to impact the Grade of haemorrhage AE. All causality hypogammaglobulinemia AEs were reported in 14.3% of participants. Hypogammaglobulinemia is a common observation in MM patients a. Thus, assessment of a potential contributory role of elranatamab is complicated by the absence of a concurrent control group, and no robust conclusions can currently be made. However, as elranatamab is expected to reduce B cells which may lead to newly onset or worsening hypogammaglobulinemia, eventually resulting in an increased risk of serious infections. Hypogammaglobulinemia is included in the Warning and Precaution Section of the SmPC, which is endorsed.

All causality injection site reaction AEs were reported in 42.3% of participants. Local injection site reactions mostly comprised injection site reactions and erythema. One participant had a serious injection site reaction (injection site reaction). Injection site reactions had resolved in the majority of participants (103/112 [91.7%], cut-off date 12 Jan 2023). No treatments were reported for any of the unresolved reactions. The SmPC includes a warning that elranatamab should not be injected into areas where the skin is red, bruised, tender, hard, or areas where there are scars.

Secondary primary malignancies were reported in 2.3% of participants. All of the participants had underlying risk factors including prior therapy with lenalidomide and thus no warning in the product information is currently warranted.

An analysis of laboratory features indicative of TLS was provided by the Applicant. Of the 179 participants evaluable for laboratory features of TLS, 21 (11.7%) met at least one of the TLS criteria, with the majority (19/21) of participants having only a single electrolyte/metabolite change. Two (1.1%) participants met 2 of the TLS criteria and no participant met all 3 of the criteria. The applicant has committed to closely monitor cases of tumour lysis syndrome in the upcoming PSURs.

Deaths and serious adverse events

As of 12 January 2023, a total of 112 (42.3%) deaths were reported with 73 (27.5%) occurring within 90 days of the last elranatamab dose and 10 (3.8%) occurring within the initial month after treatment start. The most common cause of death in study participants was the disease under study (27.5%) followed by "other" and "unknown". In Pool 1, there were 84 (45.9%) deaths (53 [29.0%] within 90 days of the last dose and 10 [5.5%] within the initial month after treatment start) and in Pool 2 there were 28 (34.1%) deaths (20 [24.2] within 90 days of the last dose and 0 within the initial month after treatment start) in Pool 2.

The primary reason for the higher incidence of deaths in Pool 1, including deaths within 90 days of the last dose of elranatamab and deaths occurring very early in treatment, compared to Pool 2 was a higher incidence of deaths due to disease progression (58 [31.7%] participants in Pool 1 compared to 15 [18.3%] participants in Pool 2). This imbalance may be explained by the more severe underlying disease in participants in Pool 1 compared to Pool 2, as indicated by differences in demographic characteristics.

Grade 5 AEs were reported in 50 (18.9%) participants; 9.8% had events related to disease progression. The majority of deaths not related to disease progression were due to AEs of infection (5.7%).

Treatment-related Grade 5 AEs were reported in 5 (1.9%) participants (3 [1.6%] in Pool 1 and 2 [2.4%] in Pool 2). With the updated cut-off date of 16 April 2023 in Pool 1, treatment-related Grade 5 AEs were reported in 6 (3.3%).

SAEs were reported in 69.1% of participants. The most common individual event was CRS, reported in 15.8% of participants and all of them were treatment related. Overall, no unexpected characteristics or clustering of events are seen among the reported deaths or non-fatal serious TEAEs.

Interaction with other medicinal products

No interaction studies have been performed with elranatamab which is acceptable due to its nature.

The initial release of cytokines associated with the start of elranatamab may suppress cytochrome P450 (CYP) enzymes. The highest risk of interaction is expected to occur during and up to 14 days after the step-up dosing as well as during and up to 14 days after CRS. During this time period, toxicity or medicinal product concentrations (e.g., cyclosporine) should be monitored in patients who are receiving concomitant sensitive CYP substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

The safety of immunisation with live viral vaccines during or following treatment with elranatamab has not been studied. Vaccination with live virus vaccines is not recommended within the 4 weeks prior to the first dose, during treatment, and at least 4 weeks after treatment.

Safety in special populations

There were no clinically relevant differences in the safety of elranatamab with respect to age, sex, race, renal function at baseline, hepatic function at baseline, geographic region, and formulation strength. This is line with the PK analysis indicating that there was no clinically relevant effect of age, sex and body weight on the PK of elranatamab. As anticipated, the incidence of fatal SAEs and vascular disorders was higher in participants 75 to 84 years of age compared to younger participants. Participants 75 to 84 years of age also had a higher incidence of AEs leading to treatment discontinuation. The incidence of events in SOCs that represent identified risks for elranatamab, such as Nervous system disorders and Infections and infestation were not increased in older compared to younger participants.

Immunogenicity

The methods to detect ADA and NAb formation were adequate. The incidence of ADA and NAb was moderate and the titres were generally low. Neither baseline ADA nor treatment induced ADA seemed to have any impact on PK, efficacy or safety. The information on immunogenicity in the product information is sufficient and in line with the findings.

Additional safety data needed in the context of a conditional MA

As duration of exposure to elranatamab and corresponding follow-up of patients in MAGNETISMM-3 (C1071003) is relatively short, further data from subsequent data lock-points are needed in order to further characterise the long-term safety of elranatamab and the important identified risks associated with its use. This includes the final CSR for MAGNETISMM-3 which is expected to be available by Q2 2025.

Additional safety data for the known important identified risks with elranatamab, will be required from the ongoing comparative MAGNETISMM-5 (C1071005) study.

2.6.9. Conclusions on the clinical safety

The safety profile of elranatamab monotherapy, when used in the management of MM patients, has been studied in 4 studies including all participants that were assigned to a fixed dose equivalent to 76 mg. Of those, 183 participants have been exposed to the proposed registrational dosage including a 2 step-up priming dose. The lack of a control group and limited availability of long-term data, limits a comprehensive assessment.

Consistent with the mechanism of action of elranatamab, the key risk with elranatamab is CRS, although the step-up scheme and recommended pre-medications seem to effectively mitigate the occurrence of severe CRS. It is however recommended to fully implement the CRS and ICANS management schemes of Study C1071003 in the SmPC. These risks are expected to be further minimised with the provision of a patient card to help early identification of symptoms and help patients seek prompt medical advice. For other relevant risks (such as cytopenias and infections), it is considered that treatment interruption guidelines for elranatamab are sufficient, and no additional guidance for management of such complications is needed in the Product Information.

CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

• The final study report of the pivotal study C1071003 (MagnetisMM-3) should be provided.

• The final study report from study C1071005 investigating the efficacy and safety of elranatamab monotherapy or its combination with daratumumab vs. daratumumab + pomalidomide + dexamethasone in adults with relapsed/refractory multiple myeloma should be provided.

2.7. Risk Management Plan

2.7.1. 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	• Long term safety

2.7.2. Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
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				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
C1071003 On-going	**Primary** To determine the efficacy of elranatamab in Cohort A and Cohort B **Secondary Safety** To determine the safety and tolerability of elranatamab	CRS, Neurologic toxicities including ICANS, Serious infections, Long-term use	Final report:	Mar 2025

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures
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
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
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.
Long-term safety	Routine risk minimisation measures: None. Additional risk minimisation measures: None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable. The applicant took the opportunity to up-version the RMP to version 1.0 before the CHMP Opinion.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14.08.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Elrexfio (elranatamab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is submitting a Marketing Authorisation Application for consideration of conditional approval of elranatamab as monotherapy for patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior therapies including a proteasome inhibitor, an immunomodulatory agent and a monoclonal anti-CD38 antibody and have demonstrated disease progression on the last therapy.

According to the International Myeloma Working Group (IMWG) criteria (Rajkumar et al. 2011), RRMM is defined as disease that is nonresponsive while on salvage therapy or progresses within 60 days of last therapy. Relapsed and refractory subjects must have had achieved minimal response (MR) or better at some point previously, before then progressing in their disease course.

The course of MM is characterised by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapeutic line. Drug resistance to prior regimens in patients with RRMM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008).

3.1.2. Available therapies and unmet medical need

To date, 7 drugs 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. 4 of those 7 drugs share a mechanism of action (MoA) directed to BCMA corresponding to 3 different BCMA modalities and include belantamab mafodotin (an ADC), idecabtagene vicleucel and ciltacabtagene autoleucel (CAR-Ts), and teclistamab (BsAb). The remaining 3 therapies, talquetamab, melphalan flufenamide and selinexor have a MoA different to targeting BCMA.

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities and organ reserve, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e., clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed). Some clinicians switch however treatment even in PR if they expect higher response with alternative treatment. This is to protect organs, especially kidneys.

Although advances in the clinical management of MM, including diagnostic methods and treatment options, have extended life expectancy of patients with MM, the disease prognosis remains poor. Median OS in patients who have received at least three prior multiple myeloma lines of therapy and are refractory to both an IMiD and a PI is only 13 months (Kumar 2017). The reported ORR for fully approved therapies for the population of heavily pre-treated and refractory patients with multiple myeloma, is approximately 30%. The lack of effective and durable therapeutic options or their toxicity and/or immediate availability issues (CAR-Ts) highlights the unmet medical need in the RRMM patient population. Furthermore, each subsequent line of therapy renders the patient more refractory to treatment, demonstrating that additional treatment approaches are required for RRMM.

Overall, there is still an unmet medical need for more treatment options capable of achieving deep and durable responses, possibly also such that afford the opportunity for treatment-free intervals and improved quality of life (QoL) for patients with RR MM who have received ≥ 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 mAb.

3.1.3. Main clinical studies

The main evidence in support of this application comes from the MAGNETISMM-3 study (C1071003), an open-label, multicentre, non-randomised phase 2 study of elranatamab monotherapy in participants with multiple myeloma who are refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody. Cohort A in this study recruited subjects that have not received prior BCMA-directed therapy. Cohort B has recruited subjects that have received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy, either approved or investigational. Enrolled participants received SC elranatamab with a 2 step-up priming regimen of 12 mg on C1D1 and 32 mg on C1D4 followed by the first full dose (76 mg) of elranatamab on C1D8 and QW thereafter, except for the first 4 participants that received 1 step-up priming dose of 44 mg on C1D1 followed by the first full dose (76 mg) on C1D8. Each participant received study intervention until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

3.2. Favourable effects

Primary efficacy data considered pivotal in Study C1071003 are available for 123 participants in Cohort A. Results presented here are based on updated data cut-off date: 16 Apr2023.

The ORR as confirmed by BICR was 61.0% (95% CI: 51.8, 69.6); 56.1% of patients achieved VGPR or better and 35.8% achieved CR or better. Responses deepened over time with 10 (8.1%) new patients achieving a best overall response of CR or sCR in this updated analysis. Eight (6.5%) responders are still on-treatment and have not achieved CR.

Among responders, after a median (range) follow-up from initial response of 15.21 (2.40, 24.21) months, the median DOR (months) was not yet reached (95% CI: NE, NE), and the Kaplan-Meier probability of maintaining response at 15 months was 70.8% (95% CI: 58.2, 80.2).

The median PFS by BICR in months was not yet reached (95% CI: 9.8, NE), and the Kaplan-Meier probability of being event-free at 15 months was 50.2% (95% CI: 40.2, 59.3). OS data were immature as of the data cut-off date, 56 (45.5%) participants had died. The median OS (months) was not yet reached (95% CI: 13.4, NE), and the Kaplan-Meier probability of being alive at 15 months was 56.3% (95% CI: 47.0, 64.6).

In the overall population, there were 26 (21.1% [95% CI: 14.30, 29.42]) participants who were MRD-negative at a sensitivity of 10^{-5}. Among participants with sCR/CR (n=44), 59.1% (95% CI: 43.25, 73.66) were MRD negative and among evaluable participants (those with sCR/CR and with an evaluable sample, n=29), 89.7% (95% CI: 72.65, 97.81) were MRD negative.

3.3. Uncertainties and limitations about favourable effects

One limitation of the study is the single-arm design, since the phase 2 study was conducted without an active control arm. Single arm study setting always brings uncertainties to efficacy assessment, especially for time to event endpoints, like PFS and OS which have the highest clinical relevance in this indication. In the context of a CMA, this uncertainty is acceptable, and confirmation of the efficacy of

the product is expected to be provided through the ongoing confirmatory Phase 3 study MAGNETISMM-5 (C1071005).

The median overall duration of response cannot be estimated at this point due to the limited overall follow-up time of the participants in the trial. Current data however suggest a durable and clinically meaningful response.

3.4. Unfavourable effects

The overall safety profile of elranatamab pooled safety data from 265 participants that were assigned to a dose of 1000 µg/kg or fixed dose equivalent of 76 mg (pooled safety population [Pool 3]). Based on the totality of the safety data, the key risks for elranatamab are CRS, neurologic toxicity including ICANS, infections and cytopenias, as these events have the potential to be life-threatening or fatal if not properly managed.

CRS was observed in a high proportion of participants (64.2%) receiving elranatamab despite administration of pre-medications to minimise the incidence of such events. In the pivotal study (Safety Pool 1) the majority of participants (43.2%) of participants had Grade 1 events and 13.7% had Grade 2 events; one participant had a Grade 3 event. Recurrent CRS occurred in 13.1% of participants. Median time to onset was 2 days, and median event duration was 2 days. Events of CRS was fully reversible and was managed with standard supportive care and in some cases with tocilizumab (or siltuximab) and/or corticosteroids.

Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 3.3% of participants who received the proposed registrational dosage. Events were Grade 1 or Grade 2 and most of the participants recovered. While 2 (1.1%) participants had serious events, symptoms were limited to changes in the level of consciousness and ICE score. All ICANS events resolved and were managed with standard supportive care and in some cases with the use of corticosteroids, tocilizumab (or siltuximab) and anakinra. All initial ICANS events occurred concurrently with CRS.

Cytopenic events were reported in the majority of subjects. The most frequently reported all Grade and Grade 3/4 individual cytopenia AEs (≥20% all grade) were Anaemia (52.8% [41.1%]), Neutropenia (34.0% [33.2%]), and Thrombocytopenia (22.3% [17.7%]). Cytopenia AEs led to permanent discontinuation of elranatamab in 2.3% of participants.

In general, safety findings were similar in participants naïve to BCMA directed therapies and those who had prior exposure to BCMA-directed ADCs or CAR-T cell therapy.

3.5. Uncertainties and limitations about unfavourable effects

The key uncertainty is related to the nature of the C1071003 study design; it is a single-arm study, and the absence of a concurrent control group in a heavily pre-treated patient population with multiple disease-associated complications severely limits the ability to robustly assess the safety profile of elranatamab.

The limited duration follow-up complicates assessment of any longer-term effects for a treatment that is foreseen to continue until disease progression. The uncertainty is particularly pertinent related to effects that have a high underlying prevalence in the relevant patient population, i.e. cytopenias and infections.

Also, some important adverse event categories (e.g., cytopenias and infections) cannot be comprehensively assessed. Moreover, the limited duration of follow-up also limits the ability to characterise longer-term effects.

The long-term safety profile of elranatamab will be further characterised through the ongoing MAGNETISMM-3 study and additional information will be collected through the randomised phase 3 study MAGNETISMM-5

3.6. Effects Table

Table 36. Effects table for elranatamab as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent (data cut-of: 16 April 2023).

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	Percentage of participants with a confirmed PR or better according to the 2016 IMWG Response Criteria by BIRC	%	76 mg SC QW elranatamab	61% (51.8, 69.6)	No control arm, interpretation of ORR is difficult (with median DOR not reached).	MAGNETISMM-3 (C1071003), Cohort A (N=123)
DOR	Time from first documented evidence of PR or better until the earliest date of documented PD per IMWG, or death due to PD	months		NE (NE, NE)	Median DOR not reached with median FU since initial response 15.21 (2.40, 24.21) months for Cohort A	
Unfavourable Effects						
CRS	Any grade	%	76 mg SC QW elranatamab	58%	No control arm Grade 3 or 4: 0.5%	MAGNETISMM-3 (C1071003), Cohort A+ Cohort B (N=183)
ICANs				3.3%	No control arm Grade 3 or 4: 1.1%	

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Cytopenias				81%	No control, possible confounding by disease progression and/or previous treatments Grade 3 or 4: 77%	
Infections				67%	As above Grade 3 or 4: 31%	

Abbreviations: ORR: objective response rate; DOR: duration of response; IMWG: International Myeloma Working Group; PD: progressive disease; SC QW: subcutaneous once a week; NE: not estimable; CRS: cytokine release syndrome; ICANS: Immune effector cell-associated neurotoxicity syndrome

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The use of elranatamab as a single-agent therapy demonstrated a clinically meaningful antitumour activity. With the limits of naïve indirect comparisons in a heterogeneous condition such as MM, the observed ORR with elranatamab is

- higher than that observed with some other agents in similar patient populations: 32% (95%CI: 22, 44) ORR with belantamab mafodotin, 25.3% (95%CI: 16.4, 36) with selinexor in combination with dexamethasone, or with melphalan flufenamide ORR 28.8% (95%CI: 17.1, 43.1)
- comparable to teclistamab – ORR 63% (95%CI: 55.2, 70.4), talquetamab – ORR 74.1 (95% CI: 66.1, 81.1) and 71.7 (95% CI: 63.7, 78.9) in 0.4 mg/kg QW, or 0.8 mg/kg Q2W, respectively and the CAR T product idecabtagene vicleucel (Abecma) – ORR 67.1% (95%CI: 59.4, 74.9) in the ITT population.
- Possibly inferior to CAR-T product ciltacaptagene autoleucel (Carvykti) – ORR 84.1% (95%CI: 76, 90.3)

Despite recent approvals of these products, these heavily pre-treated RRMM patients will eventually relapse and require alternative treatment options.

Based on the totality of the safety data, the key risks for elranatamab are CRS, neurological toxicity including ICANS, and infections as these events have the potential to be life-threatening or fatal if not properly managed. CRS and ICANS were reversible and manageable with appropriate premedication and standard therapies. The SmPC includes management guidelines for CRS and ICANs that are largely consistent with those used in Study 1003, and this approach is endorsed.

3.7.2. Balance of benefits and risks

The observed BOR (defined as PR and higher) and DOR, reported with elranatamab, are considered clinically relevant for the RRMM patient population, especially in the late line setting claimed with this application. Furthermore, efficacy has been seen in all relevant subgroups.

The CHMP requested that the indication for elranatamab is revised to 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 to better reflect the patient population of the pivotal study.

The main risks associated with elranatamab use, such as CRS, ICANS, infections and cytopenias were largely reversible and manageable with appropriate premedication and standard therapies.

The key uncertainty is related to the short follow-up at this stage of the clinical development; in this respect, the safety profile and certainty about DOR are still evolving. All uncertainties are expected to be addressed by submitting longer FU data with the final CSR of the registrational study and the final results from the confirmatory Phase 3 study.

In the context of a CMA, the B/R balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

It is acknowledged that conducting an RCT is challenging in a late line RRMM setting.

This application is based on a single arm trial which has been accepted for the purpose of MAA in scientific advice, and similar evidence base has supported several recent conditional marketing authorisations. Nevertheless, the evidence for efficacy generated in a single arm trial is less robust and subject to different types of bias, most notably selection bias. Time-to-event endpoints are considered important for demonstration of clinical benefit, but cannot be reliably assessed in a SAT setting. Thus, the pivotal SAT can be considered adequate to demonstrate clinical benefit in this patient population within the context of a CMA, but not to provide comprehensive data.

External comparisons (MAIC report as well as comparison with RWD) have been provided to contextualise the data. The pharmacological rationale is strong and there are no doubts on causality of effects.

Even though ORR is accepted as an endpoint for regulatory purposes if SAT is used, the ultimate patient benefit as reflected in OS cannot be reliably determined in a single arm trial. The observed ORR is likely an over-estimation due to a selected patient population, but the magnitude is sufficient to assume clinically relevant efficacy also in a broader patient population. Although the median duration of response has not been reached, the rate at 15 months is highly suggestive of a clinically relevant duration of response in a heavily pre-treated patient population. Ultimately, however RCT data are needed to determine the true treatment effect of the product.

In terms of safety, the number of patients exposed to elranatamab and duration of follow-up is currently limited. Findings to date are in line with what is expected based on the mechanism of action of the product but need to be confirmed in a randomised setting and over a longer period of time.

In summary the data provided for MA are regarded as sufficient for CMA but not comprehensive due to lack of interpretable time-to-event endpoints to determine treatment benefit and the duration of follow-up.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

  To confirm results obtained from the pivotal single-arm study (C1071003), the Applicant is conducting an open-label, 3-arm, multicentre, randomised Phase 3 study to evaluate the efficacy and safety of elranatamab monotherapy and elranatamab + daratumumab versus daratumumab + pomalidomide + dexamethasone in participants with RRMM who have received at least 1 prior line of therapy, but not more than 3, including lenalidomide and a PI. (MagnetisMM-5 also referred as Study C1071005). Additional information will be obtained through the provision of the final CSR from study C1071003.

  The patient population enrolled in the proposed confirmatory study is different from the more heavily pre-treated patient population defined by the proposed indication. However, the study is acceptable as a confirmatory study as a randomised trial in the approved indication is not feasible due to clinical equipoise. The study will provide comparative data on efficacy and safety of elranatamab monotherapy as compared to an adequate active comparator. Importantly, the study will address one of the main uncertainties by providing time-to-event data on PFS and OS.
- Unmet medical needs will be addressed.

  To date, 7 drugs are for the treatment of patients with relapsed and refractory multiple myeloma who have received at least a PI, an IMiD, and an anti-CD38 mAb. Elranatamab efficacy results from C1071003 showed a confirmed ORR by BICR of 61.0% in cohort A patients notably exceeding the ORR of Blenrep, Nexpovio and Pepaxti and similar to the ORR reported for teclistamab, talquetamab and idecabtagene vicleucel and slightly inferior to ciltacaptagene autoleucel. Elranatamab and teclistamab (also approved under conditional marketing authorisation) share the same mechanism of action and thus can be expected to address the unmet medical need in the target population to the same extent. Elranatamab may offer an important alternative treatment to ciltacaptagene autoleucel considering that the immediate availability and the convenience of SC administration.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required, as an additional therapy option for RRMM patients with three or more previous systemic therapies is considered beneficial.

3.8. Conclusions

The overall benefit/risk balance of Elrexfio is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Elrexfio is not similar to Darzalex, Imnovid, Farydak, Kyprolis, Ninlaro, Blenrep, Abecma, Carvykti and Talvey within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Elrexfio is favourable in the following indication:

Elrexfio is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2)

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

Alert Card also includes a warning message for healthcare provider treating the patient that the patient is receiving elranatamab.

The Patient Alert Card will contain the following key messages:

- A description of the key signs and symptoms of CRS and ICANS
- Reminder that 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
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or ICANS present themselves
- The prescribing physician's contact details

Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:>

Description	**Due date**
In order to confirm the efficacy and safety of elranatamab 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, the MAH shall submit the results of study C1071005 a Phase 3 Randomised Study of Elranatamab Monotherapy and Elranatamab + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma who have received at least one prior line of therapy including lenalidomide and a PI.	June 2027
In order to further characterise the duration of response and long-term safety in subjects with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, the MAH shall submit the final study report of C1071003, a Phase 2, open-label, multicentre, non-randomised study of elranatamab monotherapy in participants with MM who are refractory to at least one PI, one IMiD, and one anti-CD38 Ab.	March 2025

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that elranatamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.