Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Elrexfio

Active ingredient: Elranatamab

Sponsor: Pfizer Australia Pty Ltd

October 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The TGA assesses applications to enter therapeutic goods in the Australian Register of Therapeutic Goods (ARTG).
- Australian Public Assessment Reports (AusPARs) provide information on the evaluation of prescription medicines and the considerations that led the TGA to approve or not approve their entry in the ARTG. AusPARs are an important part of the transparency of the TGA's decision-making process.
- AusPARs are compiled and published by the TGA using extracts from scientific evaluations and risk-benefit assessments.
- Each AusPAR relates to a prescription medicine application at a particular point in time. A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine.
- More information can be found in Australian Public Assessment Report (AusPAR) guidance.

Contents

List of abbreviations

Abbreviation	Meaning
ΔOFV	Change in the objective function value
χ^2	Chi-square distribution
ABC	Advanced breast cancer
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event(s) of special interest
AI	Aromatase inhibitor
AIC	Akaike information
AJCC	American Joint Committee on Cancer
AKT	AKT serine/threonine kinase (protein)
AKT1	AKT serine/threonine kinase 1 (gene)
A_{lag}	Absorption time lag
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}12}$	Area under the plasma concentration-time curve from zero to 12 hours
$AUC_{0\text{-}th}$	Area under the plasma concentration-time curve from zero to x hours
$AUC_{12h,ss}$	Area under the plasma concentration-time curve from zero to 12 hours
B-	Blood
BD	Twice daily
BIC	Bayesian information criterion
BICR	Blinded independent central review
BLQ	Below the limit of quantification
BMI	Body mass index
BoR	Best objective response
BRCA1/2	Breast cancer gene 1/2
C	Cycle

Abbreviation	Meaning
C_{xh}	Plasma concentration at x hours
CBR	Clinical benefit rate
CDK4/6	Cyclin-dependent kinase 4/6
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
C_{max}	Maximum observed plasma (peak) concentration
$C_{max,ss}$	Maximum observed plasma (peak) concentration at steady state
CMH	Cochran-Mantel Haenszel
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CR	Complete response
CRCL	Creatinine clearance
CT	Computerised tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour DNA
Ctrough	Observed capivasertib plasma concentration in samples collected pre-dose
CV	Coefficient of variation
CWRES	Conditional weighted residuals
CxWyDz	Cycle X, Week Y Day Z
CYP	Cytochrome P450
DBL	Database lock
DCO	Data cut-off
DCO1	Data cut-off 1, 15th August 2022
DCO2	Data cut-off 2
DCO3	Data cut-off 3
dECG	Digital electrocardiogram
DF	Degrees of freedom
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid

Abbreviation	Meaning
DoR	Duration of response
DRR	Durable response rate
EBE	Empirical Bayes estimate
EC	Exclusion criteria
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EBE	Empirical Bayes estimate
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-BR23	EORTC Quality of Life questionnaire breast cancer specific module
EORTC QLQ-C30	EORTC Quality of Life questionnaire core 30 items
EQ-5D	European Quality of Life 5-Domain
EQ-5D-5L	European Quality of Life 5-Domain 5-level scale
EQ-VAS	European Quality of Life visual analogue scale
ER	Oestrogen receptor
ER+	Oestrogen receptor-positive
ER-	Oestrogen receptor-negative
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FSK	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	γ glutamyl transferase
GMR	Geometric mean ratio
GOF	Goodness of fit
HbA1c	Glycosylated haemoglobin
HBV	Hepatitis B virus
HDL	High-density lipoprotein
HER2	Human epidermal growth factor 2
HER2-	Human epidermal growth factor 2-negative
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A

Abbreviation	Meaning
HR	Hazard ratio
HR	Hormone receptor
HR+	Hormone receptor-positive
HR+/HER2-	Hormone receptor-positive, human epidermal growth factor receptor 2 negative
HRQoL	Health-related quality of life
IB	Investigator's brochure
IC	Inclusion criteria
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IIV	Inter-individual variability
IMP	Investigational medicinal product
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIR	Important identified risk
IPD	Important protocol deviation
IPR	Important potential risk
IPRED	Individual predictions
IQR	Interquartile range
ISH	In situ hybridisation
ITT	Intention to treat
IV	Intravenous
IVD	In vitro diagnostic
IVRS	Interactive voice response system
IWRS	Interactive web response system
IXRS	Interactive web/voice response system
k_a	First order absorption rate constant
KM	Kaplan Meier
LDL	Low-density lipoprotein
LFT	Liver function test
LHRH	Luteinising-hormone releasing hormone
LLOQ	Lower limit of quantification
LoD	Limit of detection

Abbreviation	Meaning
LPFV	Last patient first visit
LMWH	Low molecular weight heparin
LS	Least square
LVEF	Left ventricular ejection fraction
MATE1	Multidrug and toxin extrusion protein 1
MATE2K	Multidrug and toxin extrusion protein 2K
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed model repeat measures
MRI	Magnetic resonance imaging
MS	Modelling and simulation
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MTP	Multiple testing procedure
MUGA	Multiple gated acquisition (scan)
NA	Not applicable
NC	Not calculable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NGS	Next-generation sequencing
NTD	Non-tolerated dose
NR	Not reported
NTL	Non target lesion
NMPA	National Medical Product Administration
NONMEM	Nonlinear mixed effects modelling
NPDE	Normalised prediction distribution error
NYHA	New York Heart Association
OCT2	Organic cation transporter 2
OFV	Objective function value
ORR	Objective response rate
OS	Overall survival
pAKT	Phosphorylated AKT

Abbreviation	Meaning
PARP	Poly (ADP-ribose) polymerase
pcVPC	Prediction corrected visual predictive check
PD	Progressive disease
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PFS	Progression free survival
PFS2	Time from randomisation to second progression or death
PGI-TT	Patient Global Impression-Treatment Tolerability
PGIC	Patient Global Impression-Change
PGIS	Patient Global Impression-Severity
PI	Principal Investigator
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Phosphatidylinositol-4.5-biphosphate 3-kinase catalytic subunit alpha (gene)
PK	Pharmacokinetic
PKB	Protein kinase B
PKPD	Pharmacokinetic-pharmacodynamic
popPK	Population pharmacokinetic
PR	Partial response
PR, PR+, PR-	Progesterone receptor, PR-positive, PR-negative
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PS	Performance status
PsN	Perl-speaks-NONMEM
PT	Preferred term
PTEN	Phosphatase and tensin homolog (protein)
PTEN	Phosphatase and tensin homolog (gene)
PS	Performance status
Q	Intercompartmental clearance
Q1	First quartile
Q3	Third quartile
QC	Quality control
QoL	Quality of life

Abbreviation	Meaning
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fridericia's formula
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumours
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
RNA	Ribonucleic acid
RSE	Relative standard error
RUV	Residual unexplained variability
SAE	Serious adverse event
SAEM	Stochastic approximation expectation-maximisation
SAS	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SERDs	Selective oestrogen receptor degrader
SGLT2	Sodium-glucose cotransporter-2
SMQ	Standardised MedDRA query
SoA	Schedule of activities
SOC	System organ class
S/P-	Serum/plasma-
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half-life
T4	Thyroxine
TEAE	Treatment emergent adverse event
TFSC	Time to first subsequent chemotherapy or death
TL	Target lesion
t_{max}	Time to reach peak or maximum observed concentration following drug administration
TNBC	Triple-negative breast cancer
UK	United Kingdom
ULN	Upper limit of normal

Abbreviation	Meaning
US	United states
UTI	Urinary tract infection
V	Volume of distribution
VAS	Visual analogue scale
V/F	Apparent volume of distribution
VPC	Visual predictive check.
Vs	Versus
WHO	World Health Organisation

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Elrexfio, elranatamab 44 mg/1.1 mL solution for injection vial Elrexfio, elranatamab 76 mg/1.9 mL solution for injection vial
Active ingredient:	elranatamab
Decision:	Provisional approval
Date of decision:	26 June 2024
Date of entry onto ARTG:	28 June 2024
ARTG numbers:	408212 (44 mg/1.1 mL solution for injection vial) 408213 (76 mg/1.9 mL solution for injection vial)
, *Black Triangle Scheme for the current submission:*	Yes
Sponsor's name:	Pfizer Australia Pty Ltd
Dose form:	Injection, solution
Strength:	44 mg/1.1 mL solution for injection vial
Container:	Vial – Glass Type I Clear
Pack size:	1 vial
Approved therapeutic use for the current submission:	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody and have demonstrated disease progression on the last therapy.
Route of administration:	Subcutaneous
Information on use:	For information on the use of Elrexfio (such as dosage, pregnancy category, contraindications, and precautions etc.) refer to the Product Information (PI) document or contact a doctor or pharmacist. Use the TGA PI/CMI search facility to view the current Product Information (PI) and Consumer Medicines Information (CMI).

Product background

This AusPAR provides information on the assessment of Elrexfio (elranatamab) 44 mg/1.1 mL solution for injection and 76 mg/1.9 mL solution for injection for the following proposed indication.

> *Elrexfio has provisional approval in Australia and is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD-38 monoclonal antibody.*

Multiple myeloma (MM)

Multiple myeloma (MM) is a malignant plasma cell (B-cell) disorder in which there is clonal proliferation of terminally differentiated plasma cells in the bone marrow.[1] Multiple myeloma is the second most common haematological malignancy, and the thirteenth most common cancer in Australia.[2] Australia has one of the highest age-standardised incidence rates internationally,[3] with the 2023 estimated incidence of 10.1 per 100,000 population. It most commonly affects patients aged > 60 years and affects more men than women.[4]

Disease is produced by the proliferation of plasma cells and their production of paraprotein (M protein), abnormal immunoglobulin in serum and/or urine, or free immunoglobulin light chain.

There are two phases that precede MM – a premalignant phase termed monoclonal gammopathy of uncertain significance (MGUS) and smouldering (or asymptomatic myeloma). [5]

MM is defined by the evidence of end-organ harm; the CRAB features (hypercalcaemia, renal impairment, anaemia, and bone lesions). The International Myeloma Working Group (IMWG) has set out criteria for the diagnosis of MM: 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 (FLC) ratio > 100 provided the FLC is ≥100 mg/L or >1 focal lesion on MRI).[6]

Bone lesions, either lytic lesions or diffuse osteopenia, are a hallmark of MM. Myeloma cells promote osteoclast differentiation and activation and there is a decrease in osteoblast activity. Hypercalcaemia can result from the increased osteoclast activity and can contribute to renal disease. Renal involvement is common and can include immunoglobulin related and immunoglobin unrelated mechanisms. A complex interplay between myeloma cells, bone marrow cells and cytokine regulation contribute to immune dysfunction, and crowding of marrow with myeloma cells can result in cytopenias.

MM is a heterogenous disease with multiple clones or subclones, that can emerge with dominance or develop drug-resistance throughout its course. The disease typically has a period of control after the first therapy then relapse. With each subsequent therapy the duration of response (time to relapse) decreases, and with disease progression there is a greater likelihood

[1] Palumbo A Anderson K *Multiple Myeloma* N Engl J Med 2011;264(11):1046-1060
[2] Overview of Cancer in Australia 2023 Australian Institute of Health and Welfare (Cancer data in Australia, Overview of cancer in Australia, 2023 - Australian Institute of Health and Welfare (aihw.gov.au)) accessed 28 January 2024
[3] MSAG Myeloma Clinical Practice Guideline 2022myeloma_clinical_practice_guideline_oct19.pdf
[4] Cancer Data in Australia; AIHW-can-122-CDiA Book 1a – cancer incidence (age standardised rates and 5-year age groups) downloaded from Cancer data in Australia, Data - Australian Institute of Health and Welfare (aihw.gov.au)
[5] Rajumkumar SV, Merlini G, San Miguel JF *Haematological cancer :Redefining Myeloma* Nat Rev Clin Oncol 2012;9:494-496
[6] Landgren O, Kyle RA, Pfeiffer RM et al *monoclonal Gammopathy of Undetermined Significance (MGUS) consistently precedes multiple myeloma: a prospective study* Blood 2009;113:5412-5417

of end-organ damage (renal, bone marrow, etc). Newer treatments such as ASCT have improved life expectancy, but multiple myeloma is incurable. The Cancer.org 2023 relative survival estimates (using data from the Surveillance, Epidemiology, and End Results [SEER] database) patients with localised disease (solitary plasmacytoma) have a 5-year relative survival of 79%, but if there is distant spread the 5-year survival for multiple myeloma is 57%. [7]

Current treatment options

The general principles of myeloma treatment are that the best treatment option should be used early in the disease and not saved for subsequent treatments.

There is no standard sequence or algorithm of treatment for patients with relapsed MM. The choice of regimen is influenced by patient age and frailty, the rate of relapse and disease risk factors, and the response to prior treatments. The Medical Scientific Advisory Group (MSAG) guidelines note 'the first 3 lines of treatment are perhaps the most important in dictating a person's overall survival, as less than 40% of people with MM reach 4th line therapy'. [8]

The main treatment options include an immunomodulator (IMiD) (e.g. thalidomide, lenalidomide or pomalidomide) and proteasome inhibitor (PI) (e.g. bortezomib or carfilzomib), anti-CD38 monoclonal antibody (e.g. daratumumab), usually given in combination doublet or triplet regimens, or alkylating agents, anthracyclines, corticosteroids, and in some patients, high dose therapy followed by autologous stem cell transplant (ASCT). Elotuzumab (a signalling lymphocytic activation molecule, family member 7, SLAMF7) in combination with lenalidomide and dexamethasone is a second line option. Selinexor is registered for use after 4 prior therapies.

In relapsed MM the Australian MSAG guidelines[8] recommend the following.

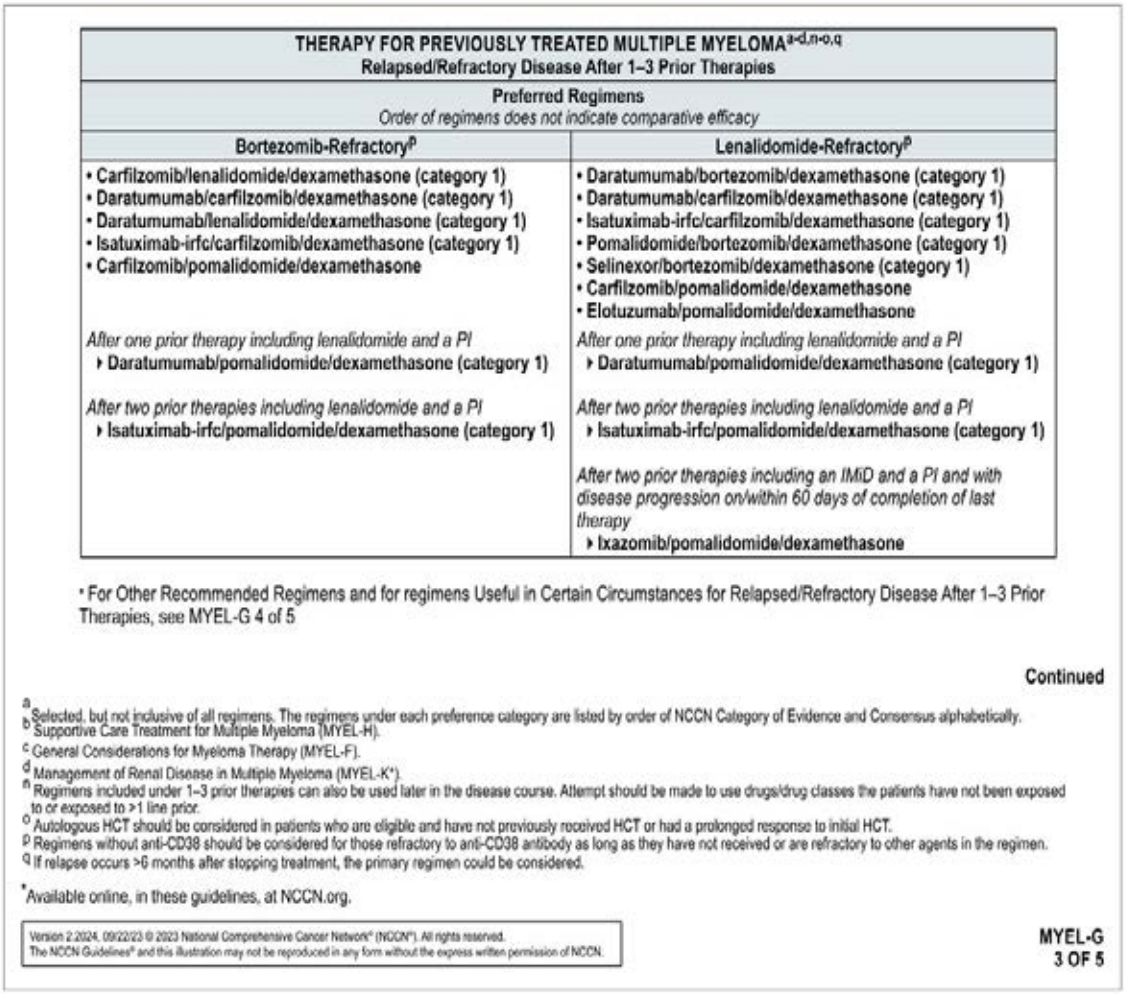
- Enrolment in a clinical trial (if available) as a first option.
- Switching drug class, especially if remission to prior drug was short or the patient has concerning toxicity.
- If relapse occurs > 12 months following cessation of the last treatment regimen, the same regimen can be considered although there is likely to be an inferior duration and quality of response.
- A second ASCT can be considered for patient who achieved at least a partial response and durable remission (e.g. >9 months) to the first ASCT.
- When all novel agents and different treatment combinations have been exhausted, conventional moderate doses of cyclophosphamide, non-myeloablative doses of melphalan, or low-modest doses of corticosteroids remain viable options as is palliation in patients who cannot tolerate any further therapy.

The proposed treatment is in patients with RR MM who have had three prior treatments. The MSAG guidelines note the options for these patients are limited. Carfilzomib + dexamethasone or pomalidomide + bortezomib + dexamethasone are suggested if the regimens have not been used in earlier treatment lines. The response rate and PFS gains are modest with these regimens in later lines of treatment.

[7] American Cancer Society: Survival Rates for Multiple Myeloma Survival Rates for Multiple Myeloma | American Cancer Society, accessed 28 January 2024.
[8] MSAG Myeloma Clinical Practice Guideline 2022 Myeloma_clinical_practice_guideline_oct19.pdf

The 2024 National Comprehensive Cancer Network (NCCN) guidelines list similar preferred regimens for early relapsed multiple myeloma (after 1 – 3 prior therapies). These list triplet therapy options for patients who are bortezomib refractory and those that are lenalidomide refractory.[9]

Table 1: NCCN 2024 Guidelines - Previously treated Multiple Myeloma preferred regimens for early treatment



THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o,q]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Preferred Regimens
Order of regimens does not indicate comparative efficacy

Bortezomib-Refractory[p]	Lenalidomide-Refractory[p]
• Carfilzomib/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone *After one prior therapy including lenalidomide and a PI* ‣ Daratumumab/pomalidomide/dexamethasone (category 1) *After two prior therapies including lenalidomide and a PI* ‣ Isatuximab-irfc/pomalidomide/dexamethasone (category 1)	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Selinexor/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Elotuzumab/pomalidomide/dexamethasone *After one prior therapy including lenalidomide and a PI* ‣ Daratumumab/pomalidomide/dexamethasone (category 1) *After two prior therapies including lenalidomide and a PI* ‣ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) *After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ‣ Ixazomib/pomalidomide/dexamethasone

• For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Relapsed/Refractory Disease After 1–3 Prior Therapies, see MYEL-G 4 of 5

Continued

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K*).
[n] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[p] Regimens without anti-CD38 should be considered for those refractory to anti-CD38 antibody as long as they have not received or are refractory to other agents in the regimen.
[q] If relapse occurs >6 months after stopping treatment, the primary regimen could be considered.

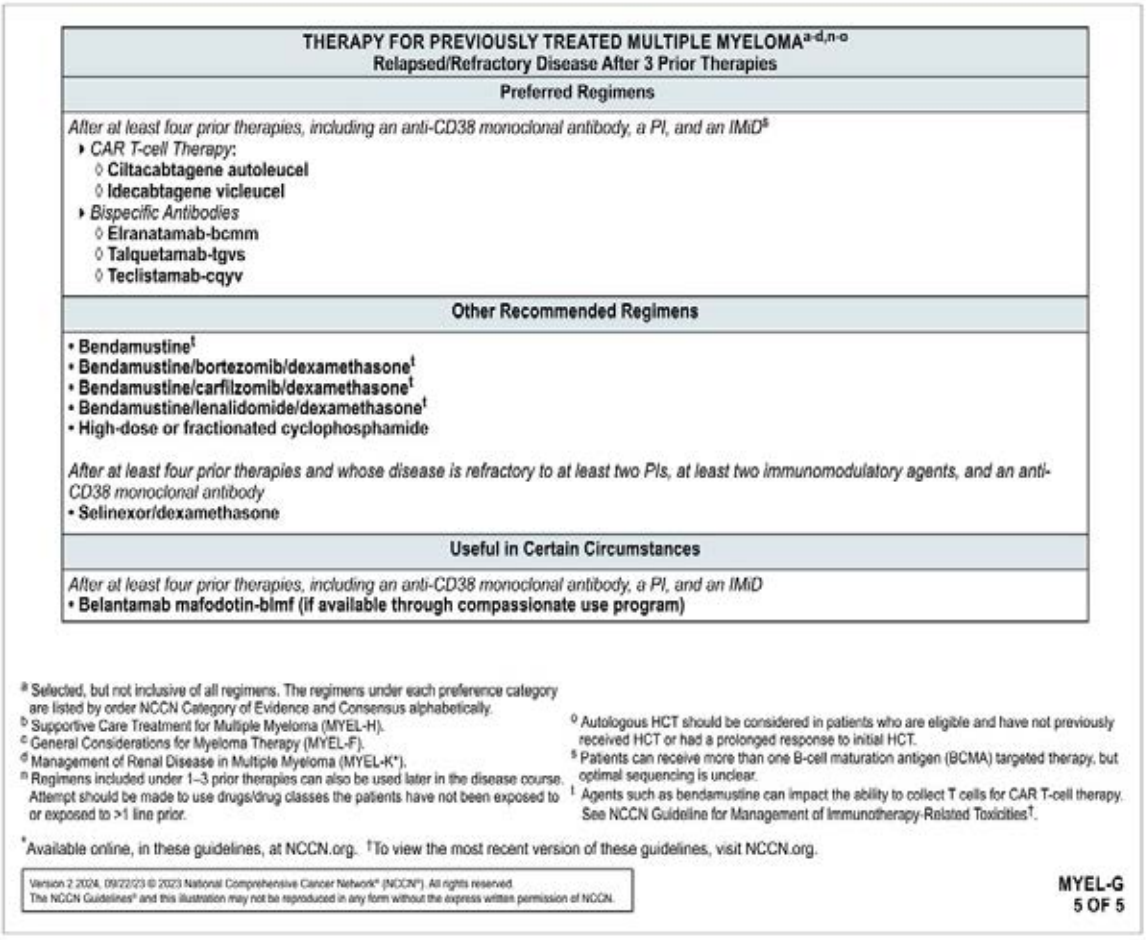
*Available online, in these guidelines, at NCCN.org.

MYEL-G
3 OF 5

For patients who have received more than 3 therapies, the NCCN guidelines recommend the following (Table 2).

[9] Kumar SK, Callander NS, Adekola K et al *Multiple Myeloma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology* Journal of the National Comprehensive Cancer Network: JNCCN 2023;21(12):1281-1301

Table 2: NCCN Guidelines recommendations for previously treated Multiple Myeloma relapsed/refractory after 3 prior therapies



THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o]
Relapsed/Refractory Disease After 3 Prior Therapies

Preferred Regimens

After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD[g]
- *CAR T-cell Therapy*:
  - Ciltacabtagene autoleucel
  - Idecabtagene vicleucel
- *Bispecific Antibodies*
  - Elranatamab-bcmm
  - Talquetamab-tgvs
  - Teclistamab-cqyv

Other Recommended Regimens

- Bendamustine[t]
- Bendamustine/bortezomib/dexamethasone[t]
- Bendamustine/carfilzomib/dexamethasone[t]
- Bendamustine/lenalidomide/dexamethasone[t]
- High-dose or fractionated cyclophosphamide

After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody
- Selinexor/dexamethasone

Useful in Certain Circumstances

After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD
- Belantamab mafodotin-blmf (if available through compassionate use program)

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K*).
[n] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[s] Patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy, but optimal sequencing is unclear.
[t] Agents such as bendamustine can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities[†].

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

MYEL-G
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Of the late line options for triple class refractory patients in the above list only ciltacabtagene autoleucel has full registration in Australia.

Carvytki (ciltacabtagene autoleucel) was registered in June 2023 for adult patients with relapsed or refractory multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.[10]

Idecabtagene is not registered in Australia. Teclistamab has provisional registration in Australia[11] and talquetamab, currently under evaluation, was granted provisional determination. Xpovio, in the other recommended regimens of Table 2, is registered in combination with other medicines in earlier and late line multiple myeloma.[12]

Clinical rationale

Elranatamab is a bispecific antibody, which has been engineered to bind to two targets: the B cell maturation antigen (BCMA) on the surface of bone marrow cancer cells and CD3 on the surface of T cells (cells of the immune system that are capable of killing cancer cells). Elranatamab brings these two cell types together. This activates the T cells, which then kill the cancer cells.

[10] Carvykti (ciltacabtagene autoleucel) Product Information pdf (tga.gov.au)
[11] Tecvayli (teclistamab) Product Information pdf (tga.gov.au)
[12] Xpovio (selinexor) Product Information Product Information (tga.gov.au)

Regulatory status

Australian regulatory status

Elranatamab has not previously been approved for entry in the ARTG.

International regulatory status

Elranatamab is approved internationally as follows.

USA

FDA - accelerated approval

> *ELREXFIO is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.*
>
> *This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).*

Elrexfio carries a boxed warning for Cytokine Release Syndrome and neurological toxicity including Immune Effect Cell-Associated Neurotoxicity Syndrome (ICANS) consistent with the US labelling for teclistamab.

The US Food and Drug Administration required a Risk Evaluation and Management Strategy (REMS) for Elrexfio. The aim is to mitigate the risk of CRS and neurological toxicity including ICANS by educating prescribers on the importance of monitoring patients for signs and symptoms of these conditions. The REMS requires prescribers to be certified through review of a prescriber training program and adverse reaction management guide with knowledge assessment and completion of a prescriber enrolment form. The REMS also includes a patient wallet card. There is a pharmacy and healthcare setting training program and enrolment with reporting requirements if elranatamab is dispensed, and wholesalers are required to limit distribution to certified pharmacies and healthcare settings.

European Union

EMA - conditional authorisation

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

Canada

Health Canada - conditional approval

> *ELREXFIO is indicated as monotherapy for the treatment of adult patients with relapsed or 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.*

Switzerland

Swissmedic - temporary authorisation

> *Elrexfio is indicated as monotherapy for the treatment of relapsed or refractory multiple myeloma in adult patients whose multiple myeloma is refractory to at least one immunomodulatory agent, one proteasome inhibitor, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy (see << Clinical efficacy>>).*
>
> *This medicinal product Elrexfio has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After these have been met, the temporary authorisation can be transformed into an ordinary authorisation.*

Registration timeline

The following table captures the key steps and dates for this submission.

Table 3: Timeline for submission PM-2023-01920-1-6

Description	Date
Provisional Determination granted	3 April 2023
Submission dossier accepted and first round evaluation commenced	31 May 2023
First round evaluation completed	31 October 2023
Second round evaluation completed	4 January 2024
Delegate's[13] Overall benefit-risk assessment and request for Advisory Committee on Medicines (ACM) advice	4 March 2024
Advisory Committee meeting	April 2024
Registration decision (Outcome)	26 June 2024
Administrative activities and registration in the ARTG	28 June 2024
Number of working days from submission dossier acceptance to registration decision*	246 days

*Statutory timeframe for standard submissions is 255 working days

*The COR-A process has a 120 working day evaluation and decision timeframe.

*The COR-B process has a 175 working day evaluation and decision timeframe.

[13] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Submission overview and risk-benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Manufacturing and quality evaluation summary

There are objections on quality grounds to the approval of Elrexfio because Good Manufacturing Practice (GMP) clearance for all manufacturing sites has not been obtained by the sponsor.

Elranatamab is produced using cell culture techniques and recombinant DNA technology in Chinese Hamster Ovary cells.

The following are key findings from the quality evaluation.

Drug substance

- The anti-BCMA antibody and the anti-CD3 antibodies are manufactured separately. The bispecific antibody is formed by a redox reaction of the two component monoclonal antibodies. Details of the drug substance manufacturing steps have been provided.
- Excipients in the drug substance and in the final product include L-histidine, L-histidine hydrochloride monohydrate, edetate disodium dihydrate, polysorbate 80, sucrose and water for injection.
- Based on submitted data the drug substance has a recommended shelf-life of 24 months when stored at -20±5°C.

Drug product

- Details of the drug product manufacturing have been provided. The evaluator concluded that all manufacturing steps and analytical procedures are validated.
- The drug product contains no preservative and is for single use only.
- The drug product is photostable.
- The drug product is supplied in a 5 mL glass vial. It has a stopper made of chlorobutyl rubber with a fluoropolymer film, and an aluminium seal with flip-off plastic cap.
- There are two strengths: 44 mg in 1.1 mL and 76 mg/1.9 mL. The vials of each strength have an approximate overfill of 0.3 mL to allow the nominal volume to be withdrawn.
- Based on submitted data the drug product has a recommended shelf-life of 24 months when stored at 5±3°C.
- In-use stability data for batches placed for 4 and 24 hours at 30°C under ambient light conditions prior to simulated dose preparation and administration supported an in-use shelf life of 24 hours when stored at 2°C to 8°C, or 6 hours when stored at below 30°C for the product prepared and ready for use.
- Stability data indicate that there were no significant changes in terms of quality, purity, or potency for the drug product when exposed to cyclical conditions with a cumulative exposure of up to 30 ± 2 °C/ 65 ± 5% relative humidity for 12 days and -20 ± 5 °C for 9 days.

Good manufacturing practice certification

- The quality evaluator noted outstanding GMP certification for the site identified as PPD Development Client ID 40863, 8551 Research Way Suite 90 Middleton WI 53562 USA.
- The Delegate notes an application for certification of that site was received on 23 February 2024.
- The Delegate also notes the certification for another site, 19118 – BioReliance Corporation, at which the manufacture and/or maintenance of master cell bank and/or working cell bank and testing biological are listed as manufacturing steps is due to expire on 31 May 2024.

Conditions of registration

The quality evaluator recommended conditions of registration, which were adopted by the Delegate and included in Specific conditions of registration applying to these goods.

Nonclinical evaluation summary

The nonclinical evaluator had no objections to the provisional registration of Elrexfio for the proposed indication from a nonclinical perspective.

The evaluator found this was a high-quality nonclinical dossier, and that all pivotal studies were GLP-compliant.

The key findings included the following.

- Elranatamab is a recombinant bi-specific IgG2 monoclonal antibody directed against BCMA and CD3 that is intended to simultaneously bind the BCMA target on myeloma cells and effector T cells to cause T cell activation and target cell lysis. The evaluator noted the BCMA component also binds to plasma cells, plasmablasts and subsets of mature B cells.
- In vitro, the binding to BCMA was with picomolar affinity and to CD3 with nanomolar affinity. It displayed sub-nanomolar cytotoxic potency against the human myeloma cell lines, including primary tumours cells from patients with relapsed/refractory/progressive multiple myeloma. It showed concentration-dependent induction of T-cell cytotoxicity towards BCMA-expressing cells and T-cell activation.
- The Fc effector function of the Fc region of elranatamab is diminished through introduced mutations compared with wildtype IgG2.
- Off-target binding to various epithelia of human or monkey origin were thought unlikely to be of toxicological significance. Due to its size elranatamab is generally unlikely to reach the cytoplasmic component of cells.
- Elranatamab was dosed subcutaneously in cynomolgus monkeys and showed slow subcutaneous (SC) absorption, moderately high bioavailability, a long serum half-life and a limited volume of distribution. The evaluator found this was similar to humans and typical of a monoclonal antibody.
- Cynomolgus monkeys were selected as the pharmacologically relevant species for single-and repeat-dose toxicity studies. The primary toxicity findings were cytokine release and depletion of BCMA-expressing antibody secreting cells and B cells, resulting in immunosuppression and secondary infection. Although minimal to moderate inflammation was the main injection site finding from the repeat dose studies the evaluator noted the highest tested strength of solution tested was 10 mg/mL whereas the proposed strength for the registration formulation is 40 mg/mL.

- Consistent with relevant ICH guidelines, no genotoxicity or carcinogenicity studies were conducted.
- The evaluator assigned Pregnancy Category C to elranatamab. The repeat dose toxicity studies in monkeys did not suggest organ effects in males or females that would suggest a potential impairment of fertility. The role of BCMA does not pre-dispose it to a potential role in teratogenicity however there may be a risk of fetal or neonatal B-cell depletion and cytokine release syndrome (CRS) poses a risk for embryofetal loss.
- Currently, elranatamab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.
- The evaluator had specific comments regarding the nonclinical sections of the draft Elrexfio Product Information. The draft Elrexfio Product Information in sequence 0005 has included the recommended changes.

Clinical evaluation summary

Pharmacology

The pharmacology data were derived from the dose escalation study C1071001, dose findings studies C1071002 and C1071009, and from the main study C1071003.

Pharmacokinetics (PK)

The popPK modelling included data from 321 patients from Studies 1001, 1002, 1003, and 1004. The final model was a semi-mechanistic target-mediated drug disposition (TMDD) model that parameterised free elranatamab, free serum BCMA (sBCMA) and the elranatamab-sBCMA complex. The model assumes these parameters are in equilibrium.

Key findings from the PK assessment included the following.

- The model-predicted mean bioavailability after SC administration was 56.2%. Abdominal injections sites were preferred per protocol for study C1071003.
- The median Tmax after SC administration was 7 days (range 3, 7 days).
- The estimated central and peripheral Vd were 4.78 L (CV 69%) and 2.83 L, respectively, and overall 7.76 L at steady state.
- Specific studies investigating elranatamab metabolism were not conducted. Elranatamab is expected by undergo metabolism by catabolic degradation after endocytosis by mononuclear phagocytosis.
- The estimated clearance of unbound elranatamab was 0.324L/day.
- The median accumulation ratio for AUC after 24 weeks of 76 mg dosing was 11.2 for free and 8.0 for total elranatamab.
- Half-life was 22 days after a 76 mg dose.
- Elranatamab showed dose proportionality over the dosing range 6 mg to 76 mg SC.
- Lower free elranatamab concentrations were found in patients with higher sBCMA at baseline.
- Extramedullary disease did not have a statistically significant effect on elranatamab exposure.

- Elranatamab PK did not appear to be affected by race, age, sex, or the presence of anti-elranatamab anti-drug antibodies (ADA).
- Renal function (eGFR ≥30 mL/min) did not appear to impact PK, but the impact of more severe renal disease is unknown. The sponsor does not propose dose adjustment based on renal function.
- Mild hepatic Impairment (total BR 1 to ≥1.5 x ULN or any AST > ULN) did not impact elranatamab PK, but the impact of more severe hepatic impairment is unknown. The sponsor does not propose dose adjustment based on hepatic function.
- Body weight was identified as a statistically significant covariate for central Vd but simulated exposures were similar across a range of body weights (10^{th} – 90^{th} percentile), supporting flat dosing for elranatamab.

Exposure response analyses showed:

- a trend between free elranatamab (C ave, Day 28) and ORR. Objective response rate (ORR) and complete response rate (CRR) generally increased with increasing dose, with a plateau at 76 mg
- fewer prior lines of therapy and the absence of extrameduallary disease may correlate with a higher proportion of responders
- exposure safety analyses at the proposed dose did not demonstrate clear relationships for Grade ≥2 Adverse events (AEs) AEs, Grade ≥3 AEs, Grade ≥3 neutropenia, any grade cytokine release syndrome (CRS) and Grade ≥2 CRS
- no relationship between QTc and total and free elranatamab concentration.

No *in vitro* interactions studies were conducted. Elranatamab transiently increases cytokine levels, which may result in inhibition of CYP enzymes during the period of elevation (see Pharmacodynamics comments, below). The risk of elevation of reduces after the first cycle of treatment.

Quantitative systems pharmacology (QSP).

- Virtual patient simulations of switching from QW to Q2W dosing after 24 weeks for responders predicted maintenance of response, supporting direct patient observation from cohort A of Study C1071003.

Pharmacodynamics (PD)

The primary pharmacology data are derived from the nonclinical studies.

Cytokines were most elevated 72 hours after the first step up dose, and mostly returned to baseline before the first full 76 mg dose.

Immunogenicity

ADAs were developed by 15 patients from study C1071003. Patient had low median titers (≤ 300). Nine patients developed neutralising antibodies. Because of small patients numbers the impact of neutralising antibodies on PK, PD, safety, or efficacy could not be established.

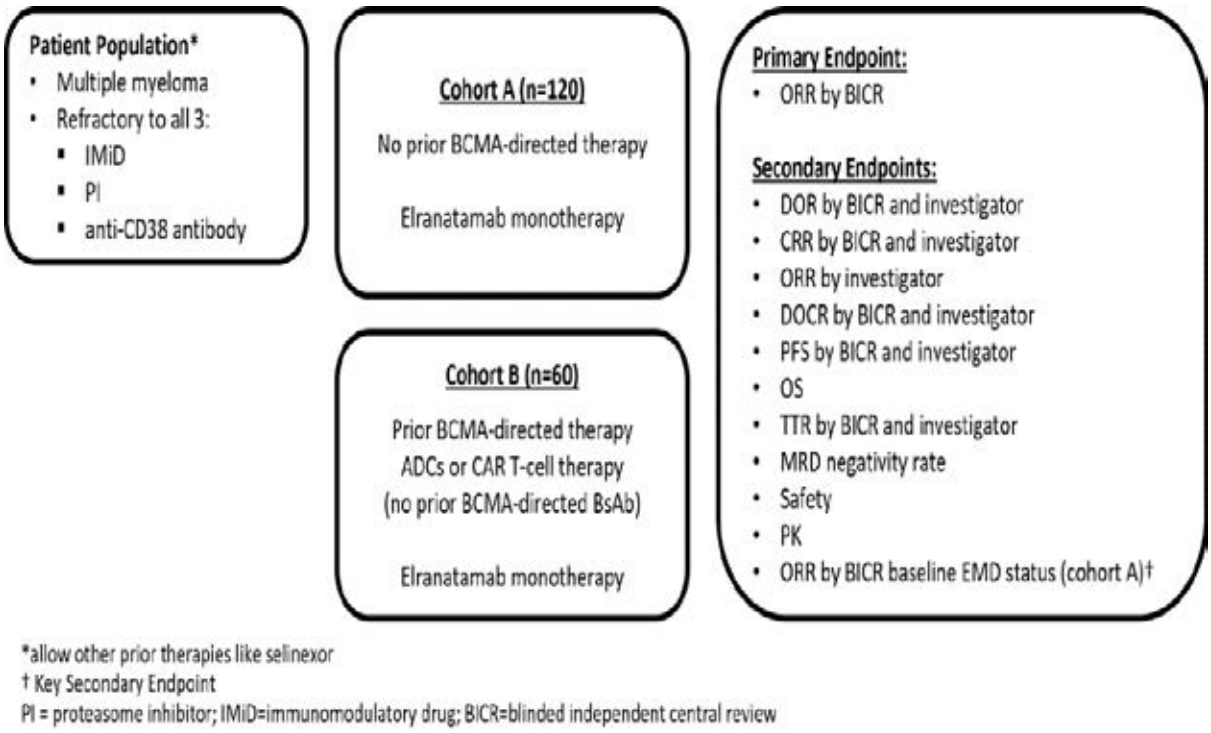
Efficacy

The main efficacy study is Study C1071003.

Study C1071003

Study 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.

Figure 1: Study C1071003 Study Schematic



*allow other prior therapies like selinexor
† Key Secondary Endpoint
PI = proteasome inhibitor; IMiD=immunomodulatory drug; BICR=blinded independent central review

The main inclusion and exclusion criteria are shown in Table 4.

Table 4: Study C1071003 - main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Aged ≥18 years Prior diagnosis of MM as defined according to IMWG criteria Measurable disease based on IMWG criteria as defined by at least 1 of the following: Serum M-protein ≥0.5 g/dL by serum protein electrophoresis (SPEP) Urinary M-protein excretion ≥200 mg/24 hours by urine protein electrophoresis (UPEP) Serum immunoglobulin free light chain (FLC) ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda FLC ratio (<0.26 or >1.65) Refractory to at least one IMiD Refractory to at least one PI Refractory to at least one anti-CD38 antibody *Note:* refractory is defined as having disease progression while on therapy or within 60 days of the last dose in any line, regardless of response Cohort A: has not received prior BCMA-directed therapy Cohort B: has received prior BCMA-directed antibody drug conjugate ADC or BCMA-directed chimeric antigen receptor T-cell (CAR-T) therapy, either approved or investigational ECOG performance status ≤2 LVEF ≥40% by multigated acquisition (MUGA) scan or echocardiogram Adequate hepatic, renal and bone marrow function	Smouldering MM Active plasma cell leukemia Amyloidosis Polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes (POEMS) syndrome Stem cell transplant within 12 weeks prior to enrolment or active GvHD Ongoing Grade ≥2 peripheral sensory or motor neuropathy History of any grade peripheral sensory or motor neuropathy with prior BCMA-directed therapy (Cohort B) History of Guillain-Barre syndrome (GBS) or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy Active HBV, HCV, SARS-CoV2, HIV or active, uncontrolled bacterial, fungal or viral infection.Active infections must be resolved ≥14 days prior to treatment Prior anti- BCMA treatment

The participant disposition at the 16 April 2023 data cut is shown in Table 5.

Table 5: Disposition events (Safety Analysis Set)

	Cohort A (N=123)	Cohort B (N=64)	Total (N=187)
Number (%) of Participants	**n (%)**	**n (%)**	**n (%)**
Disposition Phase: Treatment			
Participants Entered:	123 (100.0)	64 (100.0)	187 (100.0)
Discontinued	83 (67.5)	53 (82.8)	136 (72.7)
Adverse Event	18 (14.6)	7 (10.9)	25 (13.4)
Death	9 (7.3)	9 (14.1)	18 (9.6)
Lack of Efficacy	3 (2.4)	1 (1.6)	4 (2.1)
Progressive Disease	48 (39.0)	31 (48.4)	79 (42.2)
Withdrawal by Subject	4 (3.3)	4 (6.3)	8 (4.3)
Global Deterioration of Health Status	1 (0.8)	0	1 (0.5)
Refused Further Study Procedures	0	1 (1.6)	1 (0.5)
Ongoing	40 (32.5)	11 (17.2)	51 (27.3)

Treatment

Treatment commenced with a step-up regimen of 12 mg SC on cycle 1 day 1, and 32 mg SC on cycle 1 day 4 during the first week of treatment.

Thereafter, elranatamab was dosed weekly (QW) by SC injection on Days 1, 8, 15 and 22 of a 28-day cycle.

Patients who received QW dosing for at least 6 cycles and who achieved a partial response or better (per IMWG criteria) that persisted for at least 2 months could move to second weekly (Q2W) dosing.

Dosing was to continue until one of disease progression, unacceptable toxicity, withdrawal of consent or study termination. Patients whose treatment discontinued remained in the study for safety, disease, and survival assessments.

Premedication with paracetamol, diphenhydramine, and dexamethasone was required for the two step-up doses and the first full 76 mg dose. Thereafter, pre-treatment prior to elranatamab dosing was discretionary.

Hospitalisation was required for at least 2 days with the first dose, and for at least 1 day for the second dose with the option of hospitalisation for subsequent dosing. During hospitalisation patients were monitored for cytokine release syndrome (CRS) and immune-effector cell-associated neurotoxicity (ICANS).

Endpoints

Local evaluation of disease response per the IMWG criteria was to be performed at 28-day intervals. Imaging was to be performed at screening, at suspected (stringent) complete response (CR/sCR), at suspected progressive disease from extramedullary disease (EMD), and annually if not done within the previous 12 months. Bone marrow assessments were to be conducted at screening, suspected CR and then after 6 months, 12 months, and yearly after achieving CR (if CR was maintained clinically).

Efficacy data underwent blinded independent central review (BICR) using IMWG response criteria. ORR by BICR was the primary endpoint and included confirmed sCR, CR, very good partial response (VGPR), and PR. Except for stable disease, all response categories required confirmation by 2 consecutive assessments.

Secondary endpoints included ORR by BICR baseline EMD status in Cohort A, ORR by investigator, duration of response (DOR), progression-free-survival (PFS), overall survival (OS), and minimal residual disease (MRD) negativity rate.

The time to event endpoints of progression free survival and overall survival are difficult to interpret in the context of a single arm trial. The outcomes are therefore considered exploratory.

Protocol amendments and violations

There were 9 protocol amendments.

A high number of protocol violations (around 79.1%) were reported. The majority were related to procedures and reporting of events. The evaluation found these were unlikely to impact the conclusions of the analysis.

Sample size and statistics

For Cohort A the null hypothesis tested was that is ORR per IMWG per BICR is ≤30%, and for Cohort B the ORR per IMWG per BICR is ≤15%.

A sample size of 120 enrolled participants in Cohort A provides 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 of 0.025.

A sample size of 60 enrolled participants in Cohort B provides approximately 91% 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 of 0.025.

Baseline patient demographics and disease characteristics

Table 6: Study C1071003 Patient baseline demographics and disease characteristics

Participants n (%)	**Naïve to BCMA-directed therapy (Cohort A) (N=123)**	**Received prior BCMA- directed therapy (Cohort B) (n=64)**	**Total (N=187)**
Age (Years)			
Median (range) years	68.0 (36, 89)	67.0 (41, 84)	68.0 (36, 89)
18 - <65 (n (%))	43 (35.0)	28 (43.8)	71 (38.0)
≥65 - <75 (n (%))	56 (45.5)	24 (37.5)	80 (42.8)
≥75 (n (%))	24 (19.5)	12 (18.8)	36 (19.3)
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)
Unknown	2 (1.6)	1 (1.6)	3 (1.6)
Not reported	24 (19.5)	16 (25.0)	40 (21.4)
Disease Stage (R-ISS)			
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)
ECOG Performance Status			

Participants n (%)	Naïve to BCMA-directed therapy (Cohort A) (N=123)	Received prior BCMA- directed therapy (Cohort B) (n=64)	Total (N=187)
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
Baseline bone marrow plasma cells			
< 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)
Cytogenetic Risk			
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 BICR			
Yes	39 (31.7)	37 (57.8)	76 (40.6)
No	84 (68.3)	27 (42.2)	111 (59.4)
Number Prior Lines of			
Median (range) prior lines	5.0 (2, 22)	7.5 (3, 19)	5.0 (2, 22)
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 Bispecific	0	1 (1.6)	1 (0.5)
Triple-class exposed	123 (100.00)	64 (100.0)	187 (100.0)
Penta-class exposed	87 (70.7)	54 (84.4)	141 (75.4)
Triple-class refractory	119 (96.7)	62 (96.9)	181 (96.8)
Penta-drug Refractory (refractory to at least 2 PIs, 2 IMiDs and 1 anti-CD38)	52 (42.3)	33 (51.6)	85 (45.5)
Refractory to last line of therapy	118 (95.9)	56 (87.5)	174 (93.0)

In Cohort A, 17.1% had received 3 prior lines of anticancer therapy, 26.8% 4 lines, 17.9% 5 lines, 13.0% 6 lines, 8.1% 7 lines, 3.3% 8 lines, 3.3% 9 lines, 4.1% received 10 lines and 2.4% received >10 prior lines of anticancer therapy. In Cohort B patients were more heavily pre-treated, with 76.6% having received more than 5 prior lines of therapy and 15.6% have received more than 10 prior lines of therapy.

Across the study, the most commonly used:

- IMiDs were lenalidomide (97.9%) and pomalidomide (89.1%)
- proteasome inhibitors were bortezomib (96.8%) and carfilzomib (79.7%)
- anti-CD38 was daratumumab (92.5%).

Approximately 73.3% had received an autologous stem cell transplant.

Results

Results from 16 April 2023 Data Cut Off

On 31 July 2023, the sponsor provided an efficacy data update from the 16 April 2023 data cut. The median follow-up was 15.9 (range: 0.23, 26.18) months for Cohort A and 9.89 months (0.3, 18.4) for Cohort B. The Cohort A results are pivotal to the indication and are shown in Table 7.

Table 7: Study C1071003 Main efficacy outcomes – 16 April 2023 data cut-off

Parameter	Cohort A (n=123)
Best Overall response, n%	
Stringent Complete Response (sCR)	15.4%
Complete Response (CR)	20.3%
Very Good Partial Response (VGPR)	20.3%
Partial Response (PR)	4.9%
Minimal Response (MR)	0
Stable Disease (SD)	17.1%
Progressive Disease (PD)	17.9%
Not evaluable (NE)	4.1%
Objective Response Rate (sCR+CR+VGPR+ PR)	**61.0% (95% CI: 51.8%, 69.6%)**
Complete Response Rate (sCR+CR)	**35.8% (95% CI: 27.3%, 44.9%)**

In Cohort A, among responders, the median (range) follow-up from time of initial response was 15.21 (2.4, 24.21) months. Among the 75 responders, the median time to first response was 1.22 months (range 0.9, 7.4 months), and the median duration of response had not yet been reached (95% CI: NE, NE).

Minimal residual disease (sensitivity 10^{-5}) was reported as follows.

- Overall population: 21.1% (95% CI: 14.3, 29.42)
- Patients with sCR or CR and evaluable sample (n=29): 89.7% (95% CI: 72.65, 97.81)

In Cohort B, among responders, the median (range) follow up was 13.42 months (2.43, 16.95). The ORR was 34.4% (95% CI: 22.9, 47.3), with 10.9% achieving CR or sCR, and 32.8% achieving VGPR or better. Only two patients had samples evaluable for MRD negativity limiting conclusions that can be drawn.

The median (range) follow-up from time of initial response was 13.42 (2.43, 16.95) months. Among the responders, the median time to first response was 1.92 months (range 0.92, 6.74) and the median duration of response had not yet been reached (95% CI: 11.8, NE).

Results from 14 October 2022 data cut-off

Table 8: Study C1071003 Efficacy findings 14 October 2022 data cut-off

Parameter	Cohort A (n=123)	Cohort B (n=64)
Best Overall response, n%		
Stringent Complete Response (sCR)	13.0%	0
Complete Response (CR)	14.6%	7.8%
Very Good Partial Response (VGPR)	27.6%	25.0%
Partial Response (PR)	5.7%	1.6%
Minimal Response (MR)	0	0
Stable Disease (SD)	17.1%	26.6%
Progressive Disease (PD)	17.9%	28.1%

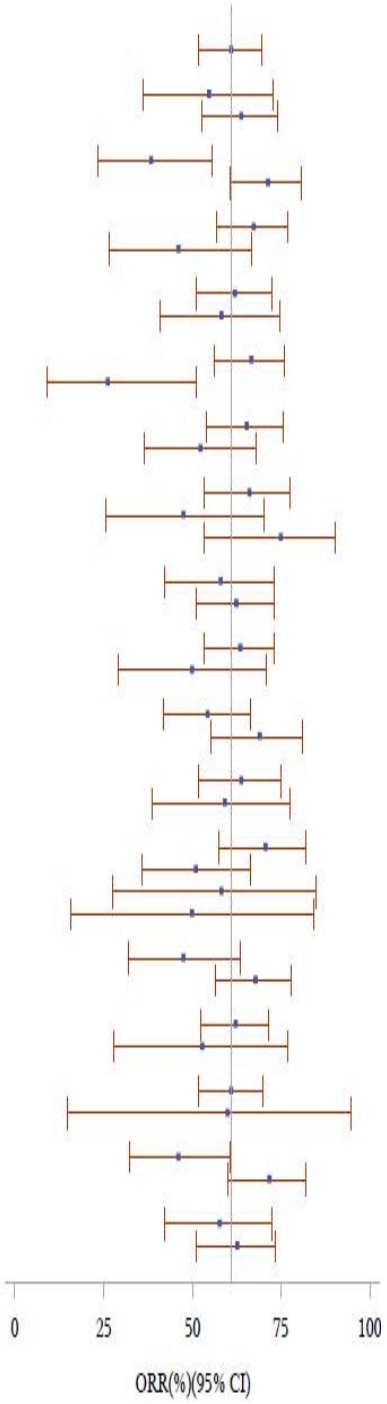
Not evaluable (NE)	4.1%	10.9%
Objective Response Rate (sCR+CR+VGPR+ PR)	**61.0% (95% CI:51.8%, 69.9%)**	**34.4% (95% CI:22.9%, 47.3%)**
Complete Response Rate (sCR+CR)	**27.6% (95% CI: 20.0%, 36.4%)**	**7.8% (95% CI:2.6%, 17.3%)**

At the time of the analysis, 17.9% of responders in Cohort A and 18.8% of responders in Cohort B were still on-treatment without progression and a confirmed complete response, and 2.4% of responders in Cohort A were still on-treatment without progression and a confirmed VGPR.

The study was not designed for comparison of subgroups, so the analysis conducted using data from the 14 October 2022 data cut off, presented in Table 9, is considered exploratory.

Table 9: Study C1071003 Cohort A forest plot – subgroup analysis by selected baseline characteristic – 14 October 2022 data cut-off

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)



While the findings for patients with extramedullary disease were appear less favourable than those without, the null for ORR with EMD was set at ≤12%.

In Cohort B, for patients who had received prior CAR-T or prior ADC ORR was 42.9% (95% CI: 21.8, 66.0) and 28.3% (95% CI: 16.0, 43.5), respectively. Differences in prognostic baseline characteristics between the 2 groups were noted, limiting conclusions that could be drawn.

Evidence to support reduced frequency dosing for responders after 24 weeks of treatment.

The most robust evidence to support this dosing instruction is derived from Cohort A patients. This was assessed using the October 2022 data cut.

QSP virtual patient simulation supported the transition from QW to Q2W dosing for responders.

Supportive studies

Supportive studies were included in the submission. Pharmacology data from the PK studies were incorporated into the main clinical pharmacology analyses.

Study C1071001

This was a phase 1 open-label, multidose, multicentre, dose escalation, safety PK and PD study of elranatamab as a single agent and in combination with lenalidomide, pomalidomide or dexamethasone in 101 adult patients with advanced RRMM. The single dose components included exploration of elranatamab IV doses 0.1 to 50 µg/kg, SC doses of 80 to 1000 µg/kg, the introduction of priming doses, including a 44 mg SC priming dose before a 76 mg SC QW full dose regimen.

Study C1071002

This was a phase 1, open-label study conducted in Japanese patients with advanced RRMM that enrolled 4 patients.

Study C1071009

This was phase 1/2, open-label, multicentre study to evaluate a dosing regimen with 2 step-up priming doses and longer dosing intervals of elranatamab monotherapy in 76 patients with RRMM. The primary objective of the study was to assess the rate of Grade ≥2 CRS with the studied regimens.

Safety

Safety data was collected from 265 patients who had received at least one subcutaneous 1mg/kg dose or 76 mg SC. The sponsor presented the safety information using 3 safety pools. Pool 1 included safety data from 183 patients from study C1071003 (phase 2 MagnetisMM-3 study) who received the recommended priming regimen of step-up dosing 12mg and 32mg. Pool 2 included other patients who received 1 mg/kg or 76 mg SC regardless of the priming dose regimen, and Pool 3 included all patients who received at least one dose of elranatamab (Pool 1 + Pool 2). Results for patients who received the recommended step-up dosing regimen (Pool 1), are considered the most relevant for establishing the safety of elranatamab for the proposed use.

On 31 July 2023, the sponsor provided a top-line safety data update from the 16 April 2023 data cut from study C1071003.

The median duration of exposure was 4.1 months, (range 0.03, 20.27) months, and of those 42% had received treatment for 6 months or more.

All patients reported a treatment emergent adverse event (TEAE). Permanent discontinuation of the study drug due to adverse events was reported for 22.4% of patients, while 73.8% had a dose interruption and 23.0% had a dose reduction due to adverse event.

Of the TEAEs, the most commonly reported (≥15%) were cytokine release syndrome (57.9%), neutropenia (36.1%), anaemia (26.8%), lymphopenia (24.0%), injection site reaction (21.9%), thrombocytopenia (19.7%), headache (19.1%) fatigue (16.4%), and decreased appetite (15.4%).

Grade 3 or 4 AEs were reported in 68.3%. The common events occurring in ≥10% of patients were neutropenia (43.2%), anaemia (42.6%), lymphopenia (27.9%), thrombocytopenia (26.2%), and leukopenia (12.6%).

AEs with a fatal outcome were reported in 23.0%. Events reported for more than one patient were disease progression (5.5%), septic shock (2.7%), COVID-19 pneumonia (2.2%), plasma cell myeloma (3.3%), acute respiratory distress syndrome (1.1%). Of these events in 6 (3.3%) patients were considered treatment related, and included one event each of cardiac arrest, failure to thrive, septic shock, pseudomonal pneumonia, adenoviral pneumonia, adenoviral infection, adenoviral hepatitis.

Serious adverse events (SAEs) were reported in 74.9%. Aside from disease progression, those occurring in ≥3% were COVID-19 pneumonia (13.1%), cytokine release syndrome (12.6%), pneumonia (9.8%), sepsis (4.9%), COVID-19 (4.4%), anaemia (4.4%), septic shock (3.8%), pneumocystis jiroveci (3.8%), acute kidney injury (3.8%).

Cytokine Release Syndrome (CRS)

CRS was reported as an AE for 57.9% of patients in study C1071003. Among those patients, 130 events were reported.

Grade 1 events were reported for 43.7%, 13.7% had a Grade 2 event and 0.5% had a Grade 3 event. More than one CRS event was experienced by 24 patients (13.1%). CRS was reported as a SAE in 12.6%. Only one patient permanently discontinued due to CRS.

Around 43% reported CRS events with the first dose, 19.1% with the second dose, 7.1% with the third dose, and 3 patients (1.6%) with subsequent doses. The Grade 3 event occurred with the first dose.

An IL-6 inhibitor and/or steroid use was at the discretion of the investigator. Systemic treatment with either corticosteroids or tocilizumab was received by 38.7% of patients with events; IL-6 inhibitor in 33.3% and corticosteroids in 15.1%.

ICANS

ICANS was reported as an adverse events for 3.3% (6 patients. Of those 6 patients, 1 (0.5%) had a Grade 1 event, three had a Grade 2 event (1.6%) and two (1.1%) had a grade 3 events. There were no Grade 4 or 5 events. Most patients had a single event, but 2 patients had recurrent events. For the 4 patients with single events all occurred concurrently with a CRS event. For patients with recurrent events, CRS occurred with the first ICANS event. Five patients had an event with the first step up dose, and one of those, had a further event with the subsequent dose. One patient had their first event with the first 76 mg dose and had recurrent events after the 4th and 6th doses. The patients with the Grade 3 events permanently discontinued elranatamab, and another patient had a dose interruption.

The median time to onset after the previous dose was 3 days and all events had resolved within 18 days (median of 2 days).

Four patients received corticosteroids, two patients received an IL-6 inhibitor, 2 patients received leviteracetam, and one patient received anakinra.

Neurological toxicity

Headache (19.1%), encephalopathy (13.1%), peripheral neuropathy (21.3%) and Guillain Barre Syndrome (0.5%) were reported neurological adverse events.

Opportunistic infections

Opportunistic infections occurred in 12.0% of patients. CMV reactivation, pneumocystis jiroveci and bronchopulmonary aspergillosis all occurred in more than one patient.

Injection site reactions

Injection site reactions were reported in 42.3% of patients overall and 37.2% of Pool 1. These were mostly local and had resolved.

Other (e.g. companion diagnostic considerations, drug delivery device)

The submission did not rely on real world data. There are no specific companion diagnostic or drug delivery system considerations of relevance for this submission.

Risk Management Plan (RMP) evaluation

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 10.

Table 10: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Cytokine Release Syndrome (CRS)
	Neurologic toxicity including Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)
	Serious infections
Important potential risks	None
Missing information	Long term safety

The evaluator recommended a Patient Alert Card.

Matters referred to the Delegate for resolution raised in the RMP evaluation report have been incorporated into the considerations of this Delegate's Overview, so are not discussed separately in this section.

The RMP evaluator has made recommendations regarding the conditions of registration. The recommendations have been taken into account, and the proposed conditions of registration are included in Specific conditions of registration applying to these goods.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. More information on the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Delegate's considerations

The Sponsor is seeking provisional registration for elranatamab as monotherapy in the fourth line setting for relapsed or refractory MM.

The clinical evidence is of a type consistent with preliminary clinical evidence seen with provisional registration submissions. In MM, ORR has previously been accepted in the provisional registration setting as an endpoint that demonstrates activity of a medicine and that might reasonably predict clinical benefit.

The main clinical study provides data to support use in a specific subset of MM patients: those with relapse or refractory disease whose disease had been refractory to each of an IMiD, a PI and an anti-CD-38 antibody.

The main patient cohort (Cohort A) included 123 participants who had not previously received anti-BCMA therapy. At the 16 April 2023 data cut the ORR was 61% (95% CI: 51.8%, 69.6%), with stringent Complete Response (sCR) and Complete Response (CR) achieved by 15.4% and 20.3% of participants, respectively. The median duration of response (DOR) was not estimable. The additional follow up from the October 2022 data cut of the same study shows for some participants responses deepen with time. Although of lesser magnitude, there was evidence of benefit in patients with extramedullary disease. A diminished response is not unexpected in this subgroup, based on historical data. MRD negativity was not evaluable for all participants, but the outcomes were encouraging and supportive of the clinical benefit of elranatamab in this highly refractory cohort of MM patients.

An important clinical question is whether there is activity in patients who have already received a BCMA-directed therapy. Cohort B addresses this question. Data from the 64 enrolled participants showed an ORR of 34.4% (95% CI: 22.9, 47.3), with 10.9% achieving CR or sCR, and 32.8% achieving VGPR or better after a median (range) follow up of 13.42 months (2.43, 16.95). The ORR in this cohort is greater than the prespecified threshold of ORR of 15%. The proposed indication is silent on prior anti-BCMA treatment, and this is appropriate given the response rate in this cohort.

The impact of dose interruption can be an uncertainty with early clinical data. Dose interruptions occurred for over 70% of participants, and dose interruptions are likely during treatment in the clinical setting. The estimate of clinical benefit (ORR) shows a sufficient effect size even with those dose interruptions to provide preliminary evidence of efficacy.

Uncertainties with the efficacy include, but are not limited to, uncertain durability of effect. Study C1071003 is ongoing, and more data will become available with time. It is uncertain where elranatamab should be optimally placed in the clinical algorithm for multiple myeloma, and whether its use places limitations on next subsequent therapy is yet to be fully characterised. These are limitations to the efficacy conclusions that can be drawn but this level of uncertainty is acceptable in the setting of provisional registration.

The safety assessment of the proposed dosing regimen and proposed population was derived from the 187 participants in Study C1071003, of whom 42% had received at least 6 months treatment. All patients experienced at least one adverse event, Grade 3 or 4 events were reported in 68.4%, and there were fatal events unrelated to disease progression.

Based on the mechanism of action and evidence of clinical safety from related medicines, CRS and ICANS are expected safety issues with elranatamab. Both are potentially life-threatening events. Mitigation strategies that will continue with the use of elranatamab outside the clinical trial setting include step up dosing at initiation of treatment and if there is a dose delay. Step-up dosing after a dose delay is discussed in a later part of this session. Pre-treatment prior to step-up dosing and the first full dose of elranatamab is recommended in the draft PI.

Warnings statements in the PI and CMI and a Patient Alert Card are all proposed as risk mitigation strategies. A major difference between the risk mitigation in clinical trials and the risk mitigation in clinical use is that there is no recommendation for in-patient care during the initiation of treatment. Whether risk mitigation and risk communication strategies are adequate for the more frequently encountered event of CRS is discussed further in this overview and is the subject of the Delegate's question to the ACM.

Among other events, cytopenias were common. The sponsor does not consider these to be a specific off-target effect, rather a consequence of the targeting of BCMA expressing cells in the bone marrow. Pro-inflammatory chemokine and cytokine production as part of the local immune response can result in sequestration or the lack of production of neutrophils and hence reduced circulating cells. The sponsor also notes contributions to bone marrow health in general from patient age, secondary infection, disease burden and residual bone marrow toxicities from prior multiple myeloma therapies. The Delegate notes cytopenias are also a consequence of disease infiltration from myeloma cells. Febrile neutropenia occurred in 2.7% of participants. Infections included pneumonia and urosepsis. Septic shock and infection associated with death were reported in small numbers. Cytopenias and their management are familiar to health professionals assessing patients with haematological malignancies under treatment. The proposed PI statements appear adequate to mitigate this risk.

Elranatamab does not appear to be strongly immunogenic. There are insufficient data to fully understand any impact of ADAs and neutralising antibodies on efficacy or safety currently.

Clinical development plan

Study C1071005 (MagnetisMM-5) is the main study proposed to confirm the clinical benefit of elranatamab in RRMM. It is an open-label, 3-arm, multicentre, randomised Phase 3 study to evaluate the efficacy and safety of elranatamab monotherapy vs elranatamab + daratumumab vs daratumumab + pomalidomide + dexamethasone in patients with RRMM who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor.

The study will be conducted in 2 Parts. Part 1 will examine dose limiting toxicities, safety, and tolerability of elranatamab + daratumumab to determine the recommended phase 3 doses (RP3D) for the combination in Part 2 of the study (RP3D).

The primary endpoint of Part 2 will be PFS per BICR per IMWG for elranatamab monotherapy (Arm A) vs daratumumab + pomalidomide + dexamethasone (Arm C). Elranatamab (Arm B) vs Arm C will be an exploratory analysis.

The Clinical Study Plan is dated February 2023. It has a projected primary completion date of the study of Q4 2024, and projected last patient last visit of Q4 2025. The study was underway at that time and 281 patients had been randomised.

A specific safety concern has arisen in Arm B of the study. In early cycles increased mortality in compared the comparator Arm C, mostly due to infection was noted. This arm is closed to further enrolment. Monotherapy with elranatamab was to be offered to patients who had completed fewer than three cycles of therapy, and ongoing randomised Arm B treatment would continue only if patients remained on treatment, if they had already successfully completed at least 3 months of study treatment, and re-signed consent.

The sponsor will be asked to provide an update on the enrolment of the study as a whole and status of Arm B of the study. A comparison of Arm A with Arm C could be acceptable approach to the confirmation of clinical benefit.

Key issues for the submission

Based solely on the assessments of the clinical evidence of benefit, the clinical evidence of harms, and the uncertainty associated with each in the context of the provisional registration, the Delegate finds there is sufficient clinical benefit in this highly refractory MM population to outweigh the uncertainties and harms.

However, the Delegate notes there are outstanding issues for the submission that require resolution, including the quality issue that currently precludes approval.

Unresolved quality issues precluding approval

The preliminary nature of the data for provisional registration is limited to the clinical data. The quality of the medicine must be established in the same way that it is established for a fully registered medicine. GMP certification for all manufacturing sites is a requirement to satisfactorily establish the quality of the product. GMP certification is not in place for all sites, and this is needed to establish quality and for the submission to proceed.

Boxed Warning for CRS

The US FDA has required a REMS with a restricted access program that restricts distribution of, and access to elranatamab that includes dispensing only by trained pharmacists and prescription only by trained physicians.

Elranatamab is a new, subcutaneously administered medicine with significant and potentially life-threatening toxicities that may begin with non-specific symptoms and where a high index of suspicion is needed to recognise these conditions early. The health professionals first assessing and treating patients in an out-patient and emergency setting are unlikely to be representatives of the patient's haematology team. Therefore, the Elrexfio PI needs to quickly alert treating health professionals to the urgently actionable and potentially unexpected adverse events for elranatamab.

There is a Risk Management Plan. Routine risk minimisation through the PI and CMI and additional risk minimisation through a Patient Alert Card underpin the risk mitigation for this risk. The evaluator proposed a boxed warning, but the Sponsor has expressed a view that the currently proposed strategies to are sufficient to reduce the risk without one, referencing the absence of this requirement in the EU.

The PI recommends the patient remain within proximity of a healthcare facility to allow monitoring for 48 hours. In the Australian context, that instruction is ambiguous as proximity is a relative concept. The nearest healthcare facility may not be the healthcare facility that administered the elranatamab dose, and not all healthcare facilities have staff trained in the recognition and management of CRS or are equipped to deal with it. The Patient Card and warnings in the CMI are both risk mitigation tools, but both have limitations. The ACM advised a boxed warning for CRS for teclistamab, and one is in place. Within the limitations of cross-trial comparison, the reasons for concern given the context of use appear similar to those for teclistamab, and the Delegate does not see a compelling case to manage the risk communication for these 2 medicines differently. ACM advice is sought on this matter.

Indication

The sponsor proposes the following indication:

> *ELREXFIO has provisional approval in Australia and is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD-38 monoclonal antibody.*
>
> *The decision to approve this indication has been made on the basis of the overall response rate in a single arm study. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

The proposed indication requires the patient to have received 3 prior therapies. Consistent with previous indications in this setting, this aspect of the indication statement is understood to reflect the need to have received at least 3 lines of therapy and at least 3 classes of therapy.

In Study C1071003, 95.6% of the studied population were refractory to their last treatment. This should be reflected in the indication statement.

In further support of this position, the Delegate notes the Sponsor's statement in a response to another Project ORBIS partner dated 14 August 2023, which suggests the Elrexfio indication should be:

> *Elfexfio (elranatamab solution for injection is a B-cell maturation antigen (BCMA)-directed and CD3-directed bispecific antibody for:*
>
> *The treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior therapies including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who have demonstrated disease progression on the last therapy.*

The Delegate agrees with this expressed position of the Sponsor. Taking into account the typical construction of an indication statement in Australia, the Delegate proposes the indication will be:

> *ELREXFIO is indicated as monotherapy for the treatment of adult patients with relapsed or 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 decision to approve this indication has been made on the basis of the overall response rate in a single arm study. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

Proposed action

The Delegate is of the view that it is likely all the outstanding issues for the submission are resolvable within the current submission. Once the issues are resolved, the Delegate considers the submission could be approved.

However, for reasons outlined above, the Delegate is not currently in a position to approve the medicine.

Independent expert advice

The Delegate received the following independent expert advice.

Advisory Committee on Medicines (ACM) considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

ACM advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***CRS events were reported for elranatamab more frequently during the initiation of treatment. The sponsor proposes that patients will not be hospitalised for the step-up doses as they were in the clinical trials. Warnings in Section 4.4 of the Elrexfio PI are proposed as is a patient card. Is a boxed warning also warranted as an additional risk communication measure? Should a boxed warning for CRS be imposed for the class of bispecific anti-BCMA anti-CD3 antibodies?***

The ACM noted that while CRS (and ICANS) are expected safety issues for elranatamab, they are both potentially life threatening and require early recognition, rapid treatment and appropriate risk mitigation strategies.

The ACM noted that CRS occurred in 57.9% of patients in the pivotal study. Most events occurred during one of the initial 3 doses, with the third dose being the first full treatment dose but 3 patients (1.6%) had a CRS event after a subsequent dose. Given that bispecific anti-BCMA anti-CD3 antibodies are a newer treatment option and outside of the haematology/oncology profession there may be limited knowledge of the adverse event profile of these antibodies, the ACM recommended in-patient administration of the first 3 doses.

The ACM noted there is a risk of patients presenting with the symptoms of CRS outside of the treatment centre could have the diagnosis confused with febrile neutropenia or sepsis.

The ACM advised that education and information regarding the safety profile of this class of bispecific anti-BCMA anti-CD3 antibodies is critical, and the boxed warning is an important example of this.

The ACM advised that a boxed warning for CRS should be included in the PI for elranatamab, and that the medicine should be included in the Black Triangle Scheme.

The ACM also considered the risk of ICANS with bispecific anti-BCMA anti-CD3 antibodies and was of the view that a boxed warning, in addition to the warnings and precautions included in the PI, is needed to mitigate the risk.

The ACM advised that a boxed warning for CRS and ICANS should be included in the PI for all bispecific anti-CD3 antibodies and CAR-T cells for haematological malignancies, as part of education and familiarisation with this class of medicines. While clinicians in tertiary centres will become familiar with the safety profile of these medicines, patients with CRS or ICANS may present in a variety of healthcare settings; the prominent boxed warning on page 1 of the Product Information will assist with early recognition and treatment.

The ACM also encouraged the inclusion of management protocols for CRS and ICANS in relevant guidelines (i.e., triaging sepsis guidelines).

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for provisional registration.

Regulatory decision

Based on the assessment of quality, safety, and efficacy, the TGA decided to provisionally register Elrexfio (elranatamab) 44 mg/1.1 mL solution for injection vial and Elrexfio (elranatamab) 76 mg/1.9 mL solution for injection vial.

The provisionally approved indications for the medicines are:

> *Elrexfio has provisional approval in Australia and is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 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 decision to approve this indication has been made on the basis of the overall response rate in a single arm study. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

Specific conditions of registration applying to these goods

Elrexfio (elranatamab) is to be included in the Black Triangle Scheme. The PI and CMI for Elrexfio must include the black triangle symbol and mandatory accompanying text for 5 years, or the product's entire period of provisional registration, whichever is longer. The black triangle is a visual reminder to encourage health practitioners and patients to report a problem or side effect with this medicine.
The Elrexfio RMP and routine pharmacovigilance will be implemented in Australia. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). PSURs are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Submission of a PSUR does not constitute an application to vary the product registration.

All batches of Elrexfio (elranatamab) supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

The final clinical study report (CSR) for Study C1071003 is to be submitted to the TGA for evaluation.

Study C1071005 (MagnetisMM-5) is to be conducted and the clinical data submitted to the TGA for evaluation.

Attachment - Product Information (PI)

The Product Information (PI) approved with this submission is at Attachment 1. It may have been superseded. To view the current PI and Consumer Medicines Information (CMI), use the TGA PI/CMI search facility.

Therapeutic Goods Administration

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https://www.tga.gov.au

Reference/Publication #