Single Technology Appraisal

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Pfizer**

2. **Clarification questions and company responses**
   a. Company's clarification question responses
   b. Supplementary materials, NICE real-world evidence framework, DataSAT
   c. Supplementary materials, NICE real-world evidence framework, Methods to Address Bias reporting template

3. **Patient and professional group submissions** from:
   a. Myeloma UK - endorsed by patient expert Dr Scott Purdon
   b. UK Myeloma Society / Royal College of Physicians / Royal College of Pathologists

4. **Expert personal perspectives** from Jon Missin – Patient expert, nominated by Myeloma UK

5. **External Assessment Report** prepared by Aberdeen HTA Group

6. **External Assessment Report – factual accuracy check**

7. **External Assessment Report – Addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

The company unmarked some of its confidential information prior to the committee meeting. This information may not be fully visible in the committee papers, however it is available in the committee meeting slides.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]

Document B

Company evidence submission

October 2023

File name	Version	Contains confidential information	Date
ID4026_Elranatamab_Document B_25032024_[noCIC]POSTACM1_FINAL	1.2	Yes	25/032024

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long, it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ADC	Antibody–drug conjugate
AE	Adverse event
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
BCMA	B-cell maturation antigen
BIC	Bayesian information criterion
BICR	Blinded independent central review
BoD	Burden of disease
BORT	Bortezomib
CAR	Carfilzomib
CAR-T therapy	Chimeric antigen receptor T-cell therapy
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CI	Confidence interval
COVID-19	Coronavirus disease-19
CR	Complete response
CRR	Complete response rate
CRS	Cytokine release syndrome
CYC	Cyclophosphamide
DARA	Daratumumab
DEX	Dexamethasone
DoR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
ECA	External control arm
ECOG	Eastern Cooperative Oncology Group
EMD	Extramedullary disease
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Multiple Myeloma Quality of Life Questionnaire
EQ-5D-3L	EuroQol 5 Dimensions questionnaire descriptive system 3 levels
EQ-5D-5L	EuroQol 5 Dimensions questionnaire descriptive system 5 levels
FACT-G	Functional Assessment of Cancer Therapy – General
GHS	Global health status
HR	Hazard ratio
HRQL	Health-related quality of life
ICANS	Immune-effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio

Abbreviation	Definition
IgG	Immunoglobulin G
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
ISA	Isatuximab
ISS	International Staging System
ITC	Indirect treatment comparison
IV	Intravenous
IVIG	Intravenous immunoglobulin
IXA	Ixazomib
KM	Kaplan–Meier
LEN	Lenalidomide
LoT	Lines of therapy
LSM	Least square mean
LY	Life year
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MM	Multiple myeloma
MRD	Minimal residual disease
NE	Not evaluable
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PANO	Panobinostat
PAS	Patient access scheme
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PGI-C	Patient Global Impression of Change
PH	Proportional hazard
PI	Proteasome inhibitor
POM	Pomalidomide
PPS	Post-progression survival
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PV	Prognostic variables
Q2W	Every 2 weeks
QALY	Quality-adjusted life year
QoL	Quality of life

Abbreviation	Definition
QW	Once weekly
RDI	Relative dose intensity
R-ISS	Revised International Staging System
RRMM	Relapsed/refractory multiple myeloma
RWE	Real world evidence
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
sCR	Stringent complete response
SCT	Stem cell transplant
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
TA	Technology appraisal
TCE	Triple-class exposed
TCR	Triple-class refractory
TEAE	Treatment-emergent adverse event
THAL	Thalidomide
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
VAS	Visual analogue scale
VGPR	Very good partial response
WTP	Willingness to pay

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication. A summary of how the decision problem is addressed by this submission is presented in Table 1.

Table 1: The decision problem

	Draft scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with relapsed or refractory multiple myeloma after at least 3 prior therapies	Adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy	Aligns with anticipated marketing authorisation. While the anticipated indication is broader than the MagnetisMM-3 study population which was a TCR cohort (as per its eligibility criteria, see Section B.2.3.1), the majority of UK patients will in fact be TCR, as per the anticipated label indication. This is due to the use of multi-drug combination therapies early in the pathway and fact patients are treated to progressive disease from second line of therapy onwards. In addition, UK clinicians have stated that the MagnetisMM-3 data is generalisable to the anticipated label population in the real world.[1-3]
Intervention	Elranatamab	As per draft scope	Not applicable
Comparator(s)	• Lenalidomide plus dexamethasone • Panobinostat plus bortezomib and dexamethasone • Pomalidomide plus low-dose dexamethasone • Daratumumab monotherapy • Ixazomib plus lenalidomide and dexamethasone • Belantamab mafodotin • Cyclophosphamide	• Pomalidomide plus low-dose dexamethasone	All proposed comparators have been carefully considered, with each justification for exclusion based on real world evidence studies using SACT and NHS centre data and extensive clinical guidance from practising NHS clinicians provided during: an advisory board meeting with 9 clinicians, NICE Early Scientific Advice, HTA Access Forum meeting, NICE decision problem meeting, and individual clinician interviews. In addition, previous MM technology appraisals were reviewed, and the conclusions below reflect decisions on relevant comparators: • Pomalidomide plus low-dose dexamethasone (TA427) was included in the draft scope and is a relevant comparator for elranatamab in patients who have received 3 prior therapies, including a PI, an IMiD and an anti-CD38 mAb. Furthermore, pomalidomide plus low-dose dexamethasone has been accepted as a relevant comparator in prior NICE multiple myeloma appraisals (TA783, TA658).[4, 5] The appropriateness of this comparator was reiterated by practising clinicians at a Pfizer advisory board (May 2023)[1], the HTA Access Forum meeting (July 2023)[2] and individual clinician validation

	Draft scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	plus dexamethasone		interview (August 2023).[3] It is also supported by real-world evidence generated from the national SACT database[6] • Lenalidomide plus dexamethasone (TA171) is not a relevant comparator for elranatamab in this setting, as clinical experts in TA505 stated that lenalidomide plus dexamethasone is mainly used after 2 prior therapies.[7] This is supported by the Pfizer BoD study where lenalidomide was most commonly given at second and third-line.[6] Furthermore, due to the recent approval of daratumumab in combination with lenalidomide and dexamethasone as first-line therapy in transplant ineligible patients (ID4014)[8] and lenalidomide maintenance following ASCT (TA680), nearly all patients will be lenalidomide refractory after first-line[9] • Panobinostat plus bortezomib and dexamethasone (TA380) is no longer a relevant comparator in this setting in the UK due to toxic adverse events and lack of efficacy, meaning it is typically used after 4 previous lines of treatment, as confirmed through Committee conclusions in TA658 and TA783[4, 5] • While daratumumab monotherapy (TA783)[5] is recommended in patients with relapsed or refractory multiple myeloma after 3 prior therapies, patients eligible for elranatamab will, after three therapies, be refractory to an anti-CD38, having relapsed on either daratumumab in combination with lenalidomide and dexamethasone (ID4014), or daratumumab in combination with bortezomib and dexamethasone (TA897).[8, 10] UK clinicians confirmed that re-challenging patients with this drug class would be inappropriate in patients who had become refractory to daratumumab.[1, 4] Therefore, as the majority (96.7%) of patients in the MagnetisMM-3 trial were TCR, most would have received daratumumab before or in the line they become TCR. In addition, during TA783, the CDF clinical lead stated that the use of daratumumab monotherapy in the fourth-line setting had fallen following NICE's recommendation of isatuximab

	Draft scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			with pomalidomide and dexamethasone.[4, 5] At the HTA Access Forum meeting (July 2023) the CDF clinical lead repeated that daratumumab would not be a suitable comparator for the reasons stated above.[2] This is further supported by the Pfizer BoD study where <5 patients received daratumumab monotherapy as their next treatment after becoming triple class exposed (TCE) (n = 848)[6] • Ixazomib plus lenalidomide and dexamethasone (TA870) is not a relevant comparator for elranatamab in the current context, based on expert clinical opinion and in line with the final scope for ID1635, which only lists comparators for patients who have had at least 1 (second line) or 2 (third line) therapies. This combination is predominantly used in the third line. Patients must be lenalidomide sensitive, which precludes any patients who have received lenalidomide maintenance following ASCT (TA680)[9], daratumumab in combination with lenalidomide and dexamethasone in first-line (ID4014)[8], lenalidomide in combination with dexamethasone or carfilzomib in combination with lenalidomide and dexamethasone at second-line.[11, 12] According to clinician feedback, (given prior to the approval of daratumumab in combination with lenalidomide and dexamethasone) transplant ineligible patients will typically receive ixazomib in combination with lenalidomide and dexamethasone in the line in which they become TCR[1] • Belantamab mafodotin is not a relevant comparator. It is currently being evaluated by NICE in two separate appraisals: ID5108: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 2 therapies.[13] This appraisal was suspended on 16 November 2022. Therefore, this treatment option will not be part of UK clinical practice at the time of submission

	Draft scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			ID2701: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies.[14] As per NICE final draft guidance (July 2023), belantamab mafodotin is not recommended in this indication and, therefore, should not be considered a relevant comparator for this appraisal[15] • Cyclophosphamide plus dexamethasone is not a relevant comparator for elranatamab in this setting, as confirmed by clinical experts during individual interviews.[3] When used, cyclophosphamide plus dexamethasone is given at third-line as a 'bridging therapy' to meet the unmet need (i.e. third-line gap) when lenalidomide has been given in prior lines.[3] It is, however, not considered as standard of care as part of the NICE care pathway
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse events • Health-related quality of life	As per draft scope	Not applicable.
Key: ASCT, autologous stem cell transplant; BOD, Burden of Disease; CDF, Cancer Drugs Fund; HTA, health technology assessment; IMiD, immunomodulatory drug; KOL, key opinion leader; mAb, monoclonal antibody; MM, multiple myeloma; NHS, National Health Service; NHSE, National Health Service England; PI, proteasome inhibitor; SACT, Systemic Anti-Cancer Therapy; TCR, triple class refractory.			

B.1.2. Description of the technology being evaluated

The draft summary of product characteristics (SmPC) and the draft European Public Assessment Report (EPAR) is presented in Appendix C.

Table 2 provides a summary of the technology being appraised.

Table 2: Technology being evaluated

UK approved name and brand name	Elranatamab (ELREXFIO®)
Mechanism of action	Elranatamab is a bispecific BCMA-directed T-cell engaging antibody that binds CD3-epsilon on T-cells and B-cells and BCMA on plasma cells, plasma blasts and MM cells.[16] Binding of elranatamab to BCMA on tumour cells and CD3 on T cells is independent of native T cell receptor specificity or reliance on major histocompatibility Class 1 molecules. Elranatamab activated T cells, led to proinflammatory cytokine release, and resulted in MM cell lysis.
Marketing authorisation/CE mark status	GB MAA: MHRA, EC Decision Reliance Procedure. Elranatamab obtained PRIME designation on 26 March 2021 and is designated as an orphan medicine. Positive CHMP opinion was granted on 12 October 2023, with EC Decision and EU MA granted in [redacted]. GB MA: MAA submission (following CHMP positive Opinion) to MHRA in [redacted] with GB MA granted in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication of interest within this submission is: "Elranatamab 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."
Method of administration and dosage	Treatment with elranatamab should be initiated and supervised by physicians experienced in the treatment of MM.[16] Elranatamab should be administered by a healthcare provider with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including CRS and ICANS.[16] Prior to initiating treatment, complete blood count should be performed. Any possibility of active infections and/or pregnancy in women of child-bearing potential should be ruled out.[16] The recommended doses of elranatamab subcutaneous injection are step-up doses of 12 mg on Day 1 and 32 mg on Day 4 followed by a full treatment dose of 76 mg weekly from Week 2 to Week 24.[16] For patients who have received at least 24 weeks of treatment with elranatamab and have achieved a response, the dosing interval should transition to an every 2 week schedule.[16] Elranatamab should be administered according to the step-up dosing

	schedule in the SmPC to reduce the incidence and severity of CRS and ICANS.[16] Due to the risk of CRS and ICANS, patients should be monitored for signs and symptoms for 48 hours after administration of each of the 2 step-up doses and instructed to remain within proximity of a healthcare facility.[16] Treatment with elranatamab should be continued until disease progression or unacceptable toxicity.[16]
Additional tests or investigations	No additional tests are required.
List price and average cost of a course of treatment	Please note the proposed list price has not yet been approved by the department of health and social care. [redacted]
Patient access scheme (if applicable)	A simple patient access scheme has been approved by PASLU. A PAS discount of [redacted] has been submitted to reduce the net price [redacted]
Key: BCMA, B-cell maturation antigen; CHMP, Committee for Medicinal Products for Human Use; CRS, cytokine release syndrome; EC, European Commission; EMA, European Medicines Agency; EU, European Union; GB, Great Britain; ICANS, immune effector cell-associated neurotoxicity syndrome; MA, marketing authorisation; MAA, marketing authorisation application; MHRA, Medicines and Healthcare products Regulatory Agency; MM, multiple myeloma; PAS, Patient Access Scheme; PASLU, Patient Access Scheme Liaison Unit.	

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

Multiple myeloma (MM) is a plasma cell malignancy characterised by abnormal growth of clonal plasma cells in the bone marrow which secrete a monoclonal paraprotein. Common sequelae of MM include hypercalcaemia, renal impairment, anaemia, bone fractures and susceptibility to infections.[17] The accumulation of myeloma cells in bone marrow can lead to bone destruction and marrow failure.[18, 19] Malignant plasma cells can also be extramedullary, being found in the peripheral blood, soft tissues or organs, this can result in additional features as a result of compression in other anatomic locations.[18, 19]

In the UK, MM is the nineteenth most common cancer (eighteenth most common in women and sixteenth most common in men), accounting for 2% of all new cancer cases.[20] Between 2016 and 2018, there were approximately 6,000 new cases of MM

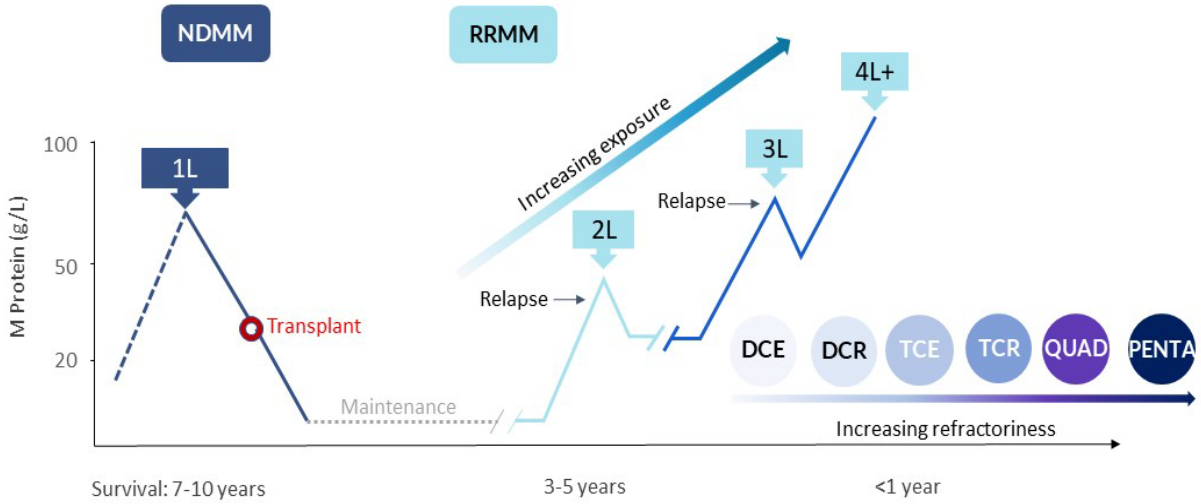
per year in the UK (~2,500 cases in women and ~3,400 cases in men), equating to an age-standardised incidence rate of 9.7 cases per 100,000 population (7.6 cases per 100,000 women and 12.4 cases per 100,000 men).[20] MM is a disease of the elderly, with a median age of diagnosis of 74.2 years in the UK.[21] Incidence rates have been shown to rise steadily from 44–54 years of age, and then steeply from 60–64 years of age.[20] The 5-year aged-standardised survival rate for newly diagnosed patients in the UK is 55.5%, reducing to 35.8% in patients aged ≥ 75 years.[22]

The treatment paradigm for MM is rapidly evolving, with combination therapies comprising multiple drug-classes approved for the treatment of early and relapsed disease. National Health Service England (NHSE) patients with newly diagnosed transplant-eligible MM can now receive triplet or quadruplet therapy, including an anti-CD38 monoclonal antibody (mAb), at first or second-line (see Section B.1.3.3).[8, 10, 23]

However, despite the addition of novel agents and highly efficacious combination therapies MM is considered incurable, as all patients treated with current therapies will ultimately experience disease progression or relapse, thus requiring further treatment with different therapies (i.e. relapsed and refractory MM [RRMM]).[6, 18, 24] The use of triplet and quadruplet combinations in front and second-line therapy has led to improved outcomes. However, consequently the pattern of drug class refractoriness is shifting, with higher levels of class refractoriness now existing earlier in the treatment pathway.[25-27]

Figure 1 presents a schematic of the progressive nature of MM along with drug class exposure. With each relapse, patients may be re-treated with different drugs from classes to which they have already become refractory. Patients therefore accumulate refractoriness within and across drug classes as they progress through the treatment pathway. Real-world evidence (RWE) has demonstrated a decreasing rate and depth of response in each successive line of therapy (LoT), leading to shorter progression-free survival (PFS) and increased resistance to available therapies.[18, 28]

Figure 1: Disease course of active MM



Key: 1L, first-line; 2L, second-line; 3L, third-line; 4L+, fourth- or later-line; ASCT, autologous stem cell transplant; DCE, double-class exposed; DCR, double-class relapsed (or refractory); IMiD, immunomodulatory drug; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PENTA, penta- refractory; PI, proteasome inhibitor; QUAD, quadruple-refractory; RRMM, relapsed or refractory multiple myeloma; TCE, triple-class exposed; TCR, triple-class refractory.
Notes: All patients are considered for ASCT prior to therapy; however, not all patients receive one. DCE, exposed to one ImiD and one PI; DCR, exposed to one ImiD and one PI and develops relapsed or refractory disease; TCE, exposed to one ImiD, one PI and one anti-CD38 mAb; TCR, exposed to one ImiD, one PI and one anti-CD38 mAb and develops relapsed or refractory disease; QUAD, progressed after exposure to two ImiDs and two Pis; PENTA, progressed after exposure to two ImiDs and two Pis and an anti-CD38 mAb. Survival estimates in the x-axis represent averages.
Source: Adapted from Costa et al. 2023[29] ; Durie et al. 2011[30]; Goel et al. 2023[31]; Rajkumar et al. 2022[32]; Varughese et al. 2023.[33]

Heavily pre-treated RRMM patients in later lines of therapy eventually become triple class refractory (TCR: refractory to at least one immunomodulatory drug (ImiD), one proteasome inhibitor (PI) and one anti-CD38 mAb), outcomes in these patients are poor.[29] The TCR cohort is the population of interest in this submission (Section B.1.1). Published RWE studies estimate a PFS of 2.8–3.9 months in the next line of therapy, and a median overall survival (OS) of 9.2–11.1 months in TCR MM patients (Table 3).[34-36] Outcomes deteriorate as refractoriness increases, with median OS of 5.6 months in penta-refractory MM patients (refractory to two ImiDs, two PIs and one anti-CD38 mAb; Table 3).[36]

The current NICE approach is structured by “lines of therapy”. Consequently, the submission will often discuss treatments in reference to prior lines based on previous reimbursement decisions. However, with the increasingly complex therapy landscape, with multiple novel therapies currently in development, this approach may no longer be appropriate. UK healthcare professionals have stated a preference for

drug reimbursement decisions in multiple myeloma that align with class sensitivity[1]. Indeed, whilst treatment outcomes deteriorate with each successive line, evidence suggests that class-refractoriness maps more closely to outcomes.[18, 28, 29, 31] This is discussed further in section B.1.3.3.

Table 3: Real-world outcomes in TCE, TCR and penta-refractory MM patients

RWE study	Outcome	Population		
		TCE[a]	TCR[b]	Penta-refractory[c]
LocoMMotion[34]	Response rates	ORR: 29.8% (95% CI: 24.2, 36.0) DoR: 7.4 months (95% CI: 4.7, 12.5)	ORR: 25.1% (95% CI: 19.0, 32.1) DoR: 4.5 months (95% CI: 3.7, NE)	N/A
	PFS	4.6 months (95% CI: 3.9, 5.6)	3.9 months (95% CI: 3.4, 4.6)	N/A
	OS	12.4 (95% CI: 12.28, NE)	11.1 months (95% CI: 8.8, 14.2)	N/A
Elsada et al. 2021[35]	OS	8.2 months (95% CI: 7.1, 9.6)	N/A	N/A
MAMMOTH[36]	Response rates	ORR: 38.0%	ORR: 29.0%	ORR: 30.0%
	PFS	3.4 months	NR	NR
	OS	11.2 months (95% CI: 5.4, 17.1)	9.2 months (95% CI: 7.1, 11.2)	5.6 months (95% CI: 3.5, 7.8)

Key: CI, confidence interval; DoR, duration of response; N/A, not applicable; NE, not evaluable NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression free survival; RRMM, relapsed or refractory multiple myeloma; TCE, triple-class exposed; TCR, triple-class refractory.
Notes: [a] Exposed to one IMiD, one PI and one anti-CD38 mAb; [b] Exposed to one IMiD, one PI and one anti-CD38 mAb and develops relapsed or refractory disease; [c] Progressed after exposure to two IMiDs and two PIs and an anti-CD38 mAb.

B.1.3.2. Burden of disease

B.1.3.2.1. Symptom burden

Regardless of disease stage, patients with MM experience a substantial symptom burden[37, 38], with fatigue (87.6%), pain (71.5%) and shortness of breath (60.8%) being the most frequently reported complaints in a UK cross-sectional survey (n = 557).[39] A substantial proportion of patients also report symptoms of depression and anxiety.[40, 41] Pain is a significant feature of MM which can be challenging to treat.[40, 41] In interviews with UK TCR MM patients, most had experienced pain[42],

noting that ineffective treatment for this restricted normality and that pain medication causes other issues, such as leaving them "muddled and confused".[42]

Patients tend to become more frail and as they progress through sequential therapies.[37, 43] Increasing frailty and susceptibility to disease-related effects, such as bone fractures and renal impairment, as well as the accumulation of treatment-related toxicities, such as myelosuppression and peripheral neuropathy, make these patients vulnerable to complications.[43, 44] These toxicities and comorbidities deteriorate with each additional treatment line[28], which can make treatment selection increasingly challenging as patients progress through the treatment pathway.[26]

B.1.3.2.2. Health-related quality of life

Health-related quality of life (HRQL) is severely diminished in patients with MM due to the substantial symptom and treatment burden.[37, 45-48]

Generic and disease-specific HRQL metrics have been shown to fall in RRMM patients with each additional LoT, with treatment toxicities being a major contributing factor.[46] Similarly, HRQL diminishes with increasing disease refractoriness, with a substantial decline in EQ-5D utility index, EQ-5D visual analogue scale (VAS) and Functional Assessment of Cancer Therapy–General (FACT-G) total score observed 1 year after becoming TCR.[49, 50]

HRQL outcome measures also correlate to treatment response, with patients achieving deeper responses scoring higher on HRQL metrics.[46, 51] UK patients with TCR MM, described remission as their best chance of some 'life', both through feeling physically better and also due to the increased independence that remission can provide.[42] These data highlight the need for efficacious novel therapies that may improve HRQL.

B.1.3.2.3. Treatment burden

The treatment for MM typically involves multidrug regimens which often require intravenous (IV) administration.[9, 23, 52-54] These therapies are associated with a number of toxicities that may negatively impact patients' HRQL.[55]

Most regimens include long-term corticosteroids, the negative impact of which has been highlighted in interviews with UK TCR MM patients.[42] Steroid side effects were the most referenced toxicities, with their use being associated with fatigue, insomnia, and dramatic mood swings that even damaged relationships.[42] Severe toxicities including thrombosis, immunosuppression with subsequent infections, gastrointestinal bleeding and psychosis can also occur.[56, 57]

Many MM treatments (particularly bortezomib [BORT] and thalidomide [THAL]) cause peripheral neuropathy, which can severely limit function and cause neuropathic pain.[58, 59] Carfilzomib (CAR) use can result in hypertension, dyspnoea and cardiac dysfunction, while the use of IMiDs significantly increases the risk of venous thromboembolism, necessitating anti-coagulant treatment.[59] As discussed in Section B.1.3.2.1, the accumulation of toxicities in RRMM patients contributes to frailty and further limits treatment options.

The modality of treatment delivery is also relevant. Interviews with UK TCR MM patients have demonstrated the preference for less time-consuming and invasive treatments[42], with patients indicating their preference for subcutaneous (SC) over IV therapies.[42, 60]

B.1.3.2.4. Caregiver burden

Caregivers of patients with MM can experience a substantial impact on their HRQL as they often neglect their own needs to provide physical and emotional support.[61, 62] Caregivers have described MM as a ‘time bomb’ because of significant fears and uncertainty about the future, whilst also reporting that they have to stay positive for patients.[63] They have also noted that sometimes a lack of communication between the patient and caregiver can lead to feelings of isolation and increased the emotional burden.

Caregivers are also affected by patients’ treatment regimens, in part due to the large time commitments they require to administer.[63] Caregivers can also suffer financial difficulties as a result of a relative being diagnosed with MM; they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds.[64, 65]

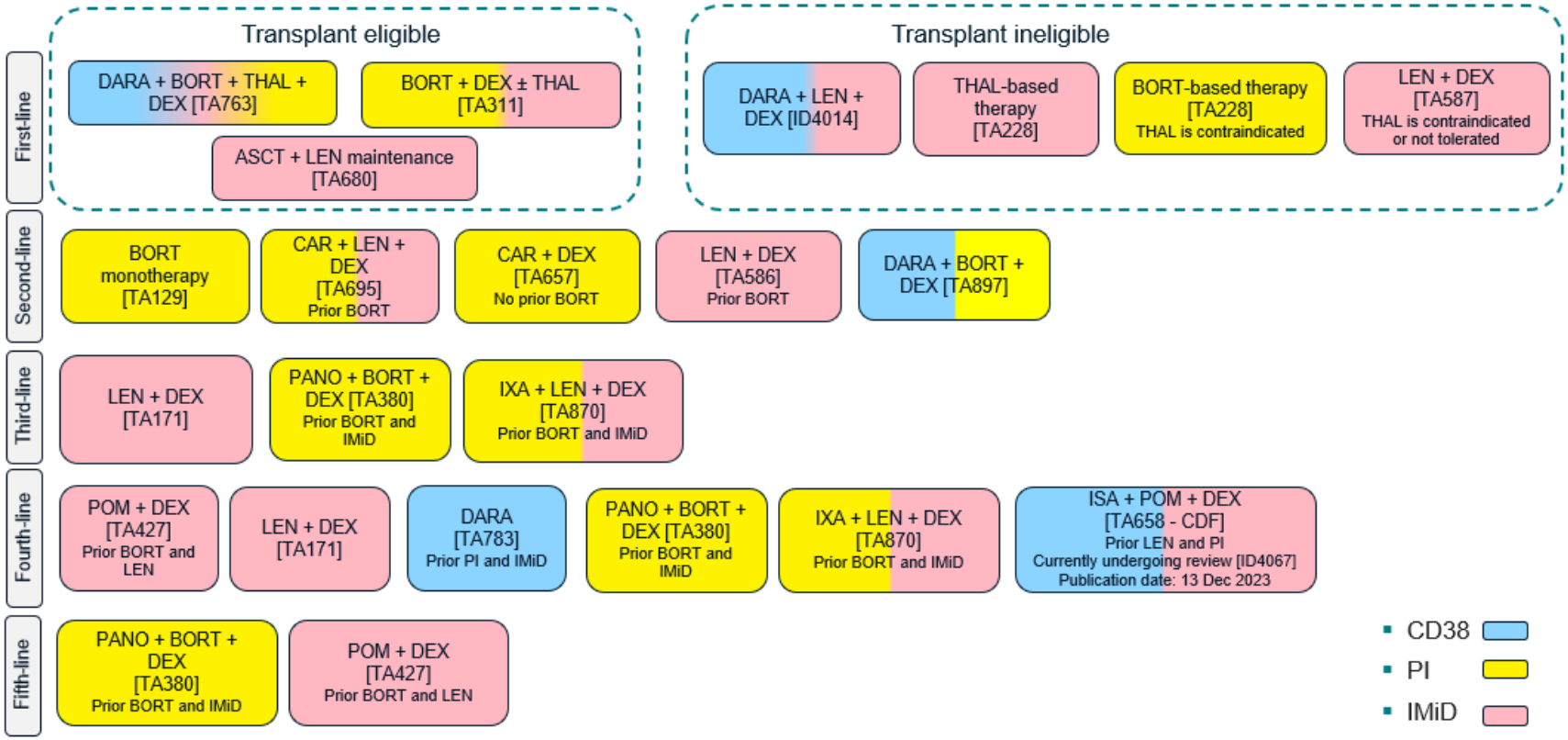
B.1.3.3. Current pathway of care

Figure 2 shows the current clinical pathway of care for MM in England, as recommended by NICE, as of October 2023. This section covers NICE approved therapies (including those recommended for use within a managed access agreement) and assumes that patients enter the pathway in the current reimbursement climate. However, this account is not exhaustive as there are additional therapies in use that do not appear on the pathway. In addition, patients can access care through other routes such as clinical trials and expanded access schemes.

Patients are treated with combinations of drugs from the PI (BORT, CAR, ixazomib [IXA]), IMiD (THAL, lenalidomide [LEN], pomalidomide [POM]), anti-CD38 mAb (daratumumab [DARA], isatuximab [ISA]), corticosteroid (dexamethasone [DEX], prednisolone), histone deacetylase inhibitor (panobinostat [PANO]) and/or alkylator agent (cyclophosphamide [CYC], bendamustine, melphalan) classes.

Therapies have specific eligibility criteria relating to factors such as fitness for transplant, toxicities, the number of prior therapies and the pattern of disease refractoriness. This results in significant variation in treatment sequencing between patients and heterogenous routes through the treatment pathway.

Figure 2: NICE-approved therapies for the treatment of multiple myeloma



Key: ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, Carfilzomib; CDF, Cancer Drugs Fund; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PANO, panobinostat; PI, proteasome inhibitor; POM, pomalidomide; THAL, thalidomide.
Notes: Colours indicate the use of anti-CD38s, IMiDs, and PIs within the treatment pathway. Blue indicates the use of anti-CD38s, green indicates the use of PIs, and red indicates the use of IMiDs.
Source: Adapted from Pfizer, 2023[1]; NICE [NG35], 2018[54]; NICE [TA763], 2022[23]; NICE [TA311], 2014[66]; NICE [TA680], 2021[9]; NICE [ID4104], 2023[8]; NICE [TA228], 2011[67]; NICE [TA129], 2007[68]; NICE [TA587], 2019[53]; NICE [TA695], 2021[11]; NICE [TA657], 2020[69]; NICE [TA586], 2019[12]; NICE [TA897], 2023[10]; NICE [TA171], 2019[7]; NICE [TA380], 2016[70]; NICE [TA870], 2023[71]; NICE [TA427], 2017[72]; NICE [TA783], 2022[5]; NICE [TA658], 2020.[4]

B.1.3.3.1. First-line

Newly diagnosed MM patients are stratified, based on their suitability for intensive treatment, into transplant-eligible and transplant-ineligible cohorts (Figure 2). The current standard of care (SoC) for transplant-eligible patients is induction therapy with a fixed-duration of DARA in combination with BORT, THAL and DEX (DARA+BORT+THAL+DEX), followed by myeloablative conditioning with high-dose melphalan and autologous stem cell transplant (ASCT),[23] some patients also receive 2 cycles of consolidation after ASCT. Patients then receive maintenance therapy with LEN until disease progression.[9]

DARA in combination with LEN and DEX (DARA+LEN+DEX) has recently been approved for use in transplant-ineligible patients, which continues until disease progression.[8] Patients may also receive fixed-duration THAL or BORT in combination with an alkylating agent and a corticosteroid (i.e. CYC+THAL+DEX), or LEN in combination with DEX (LEN+DEX), which is given until progressive disease.[53, 54]

B.1.3.3.2. Second line

At second-line, patients (unless DARA refractory or BORT intolerant/refractory) can receive DARA in combination with BORT and DEX (DARA+BORT+DEX; Figure 2).[10]

Patients who are LEN refractory and unsuitable for an anti-CD38mAb containing regimen (e.g. transplant ineligible patients after DARA+LEN+DEX) can instead receive either BORT monotherapy or CAR in combination with DEX (CAR+DEX).[68, 69]

Alternatively, patients who remain LEN sensitive can receive CAR in combination with LEN and DEX (CAR+LEN+DEX) or LEN+DEX.[12]

B.1.3.3.3. Third line

Decision-making at third line can be challenging owing to drug refractoriness and limited NICE approved options (Figure 2). IXA in combination with LEN and DEX (IXA+LEN+DEX) and LEN+DEX are available.[7, 71] However, as patients must be LEN sensitive to qualify for these regimens, those who received an ASCT or

DARA+LEN+DEX at first-line will not be eligible.[8, 9] This leaves PANO in combination with BORT and DEX (PANO+BORT+DEX)[71], a combination not favoured by clinicians due to its limited efficacy and poor side-effect profile (as confirmed through Committee conclusions in TA658 and TA783).[4, 5]

As outlined above there is a cohort of patients who lack efficacious options in the third line, referred to as the "third-line gap" by healthcare professionals. This gap necessitates the use of drugs/combinations, which lack robust efficacy data, as "bridging therapies" to access more effective treatments in the fourth-line.[3] The use of therapies such as CYC in combination with DEX or melphalan at third-line identified in the Pfizer sponsored burden of disease (BoD) study is indicative of this practice.[6] As newer therapies are approved and reimbursed in earlier treatment lines, options at third-line may become even more challenging. This lends further weight to the rationale for approving therapies indicated by class-sensitivity and not line-of-therapy.

B.1.3.3.4. Fourth line

UK clinicians confirm that there is no SoC from fourth-line.[1] Of the routinely reimbursed therapies, POM in combination with DEX (POM+DEX) is currently the most used therapy for patients who have received 3 prior therapies, including a PI, an IMiD and an anti-CD38 mAb (Figure 2).[6, 73] PANO+BORT+DEX and IXA+LEN+DEX or LEN+DEX (in LEN sensitive patients) can also be used in patients naïve to these combinations.[7, 70, 71] DARA monotherapy[5] or ISA in combination with POM+DEX (ISA+POM+DEX; via the Cancer Drugs Fund [CDF])[4], are available, however the majority of patients will be anti-CD38 mAb refractory following treatment with DARA+LEN+DEX at first-line or DARA+BORT+DEX at second-line, making these treatment options unsuitable.[8, 10] Furthermore, UK clinicians have confirmed that re-challenging with this drug class in a refractory patient would be unsuitable.[1, 4]

B.1.3.3.5. Fifth line

UK RWE indicates substantial heterogeneity of treatments given in the fifth line.[6, 73] This speaks to the lack of a SoC and the complexity of decision making in these patients. PANO+BORT+DEX and POM+DEX are available in patients naïve to these

combinations; however, patients may receive other therapies including cytotoxic chemotherapy combinations.[72]

B.1.3.3.6. Positioning of elranatamab within the treatment pathway

Elranatamab is anticipated to be indicated as “monotherapy for the treatment of adult patients with relapsed and refractory MM, who have received at least three prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy.”

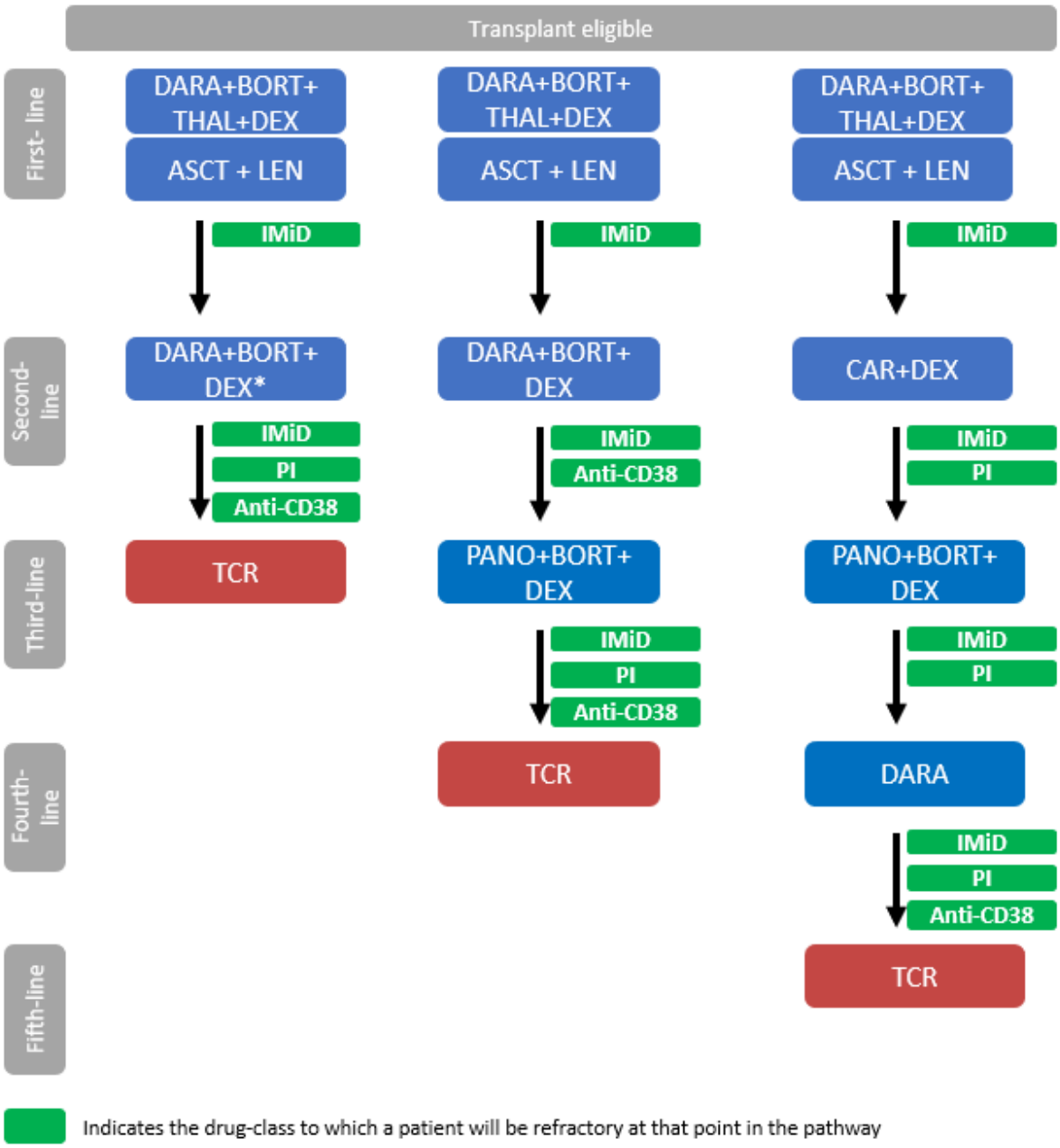
The MagnetisMM-3 study population was, per its eligibility criteria (see Section B.2.3.1), a TCR cohort. Whilst the anticipated label indication is broader than this, most UK patients eligible per the label will in fact be TCR. This is due the use of multi-drug combination therapies early in the pathway, and that most of these therapies are given to progressive disease. Consequently, UK clinicians have stated that the MagnetisMM-3 data is generalisable to the anticipated label population in the real world.[1-3]

Due to the complex and evolving nature of the myeloma therapy landscape, describing elranatamab positioning by line-of-therapy may not be appropriate. Therefore, the following section describes how patients become TCR in UK clinical practice and thus eligible for treatment with elranatamab.

Route to eligibility in the current NICE treatment pathway

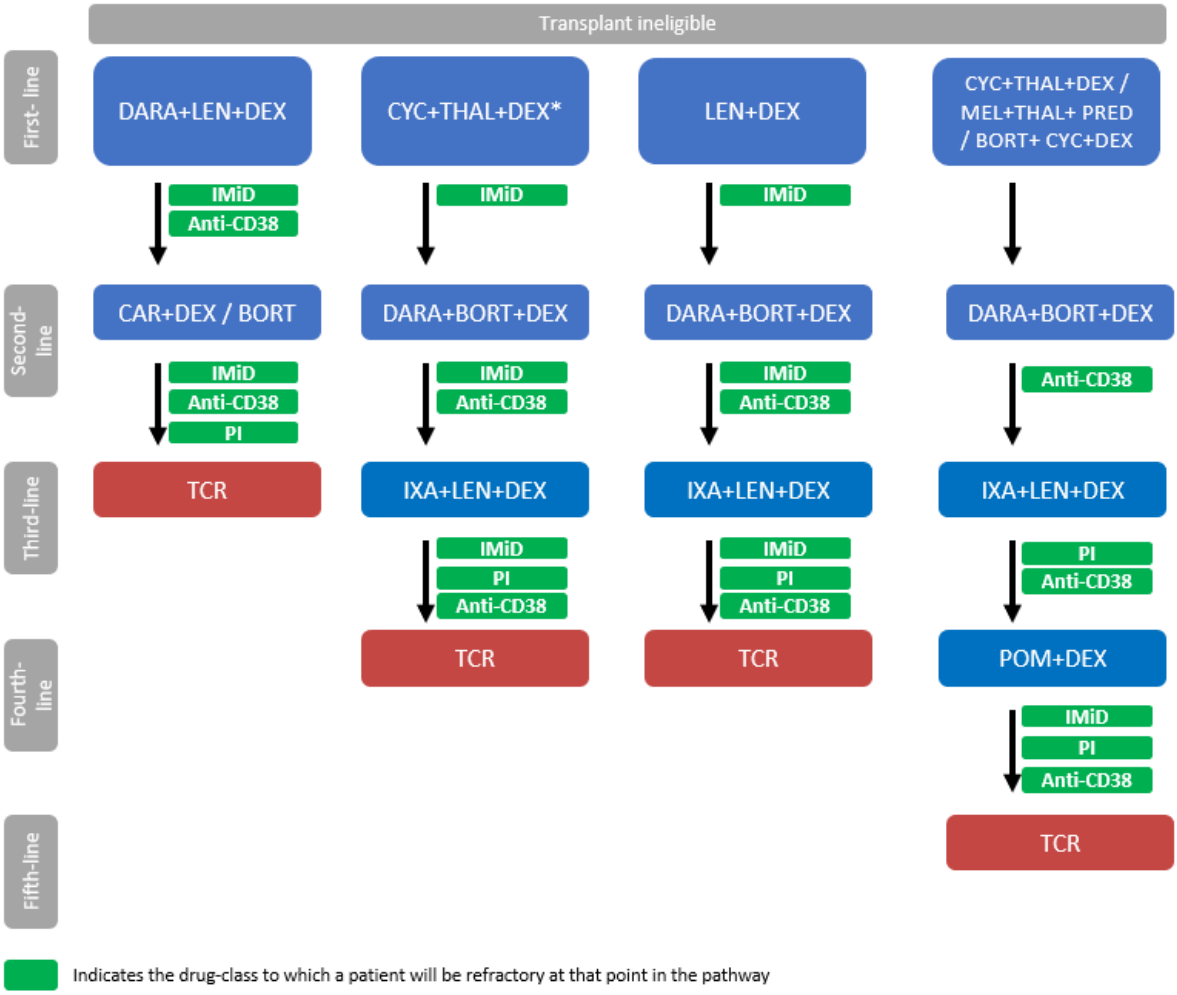
Figure 3 and Figure 4 display routes that transplant-eligible and transplant-ineligible patients can take to become TCR, therefore being eligible for treatment with elranatamab, in the current treatment pathway. These figures are not exhaustive as many therapy combinations/pathway routes are possible. To be considered refractory to a drug/class a patient must have an inadequate response or disease progression whilst on treatment or within 60 days of the most recent treatment, as defined by the International Myeloma Working Group (IMWG) criteria.[74]

Figure 3: Potential routes to eligibility in transplant eligible patients in the NICE pathway



Key: Anti-CD38, anti-CD38 monoclonal antibody; ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, carfilzomib; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; LEN, lenalidomide; NICE, National Institute for Health and Care Excellence; PANO, Panobinostat; PI, proteasome inhibitor; TCR, triple class refractory; THAL, thalidomide.
Notes: *Relapse within 10-months of DARA+BORT+THAL+DEX initiation.
This diagram illustrates potential routes through the NICE pathway to becoming TCR, it is not exhaustive.
Owing to fixed-duration induction therapy, patients are typically only lenalidomide refractory after first line. Patients treated with daratumumab in combination with bortezomib and dexamethasone in second line are not typically bortezomib refractory, however they can be if they relapse early in treatment (within 10-months of starting).
Source: Pfizer data on file, 2023.[75]

Figure 4: Potential routes to eligibility in transplant ineligible patients in the NICE pathway



Key: Anti-CD38, anti-CD38 monoclonal antibody; BORT, bortezomib; CAR, carfilzomib; CYC cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; IXA, ixazomib; LEN, lenalidomide; MEL, melphalan; NICE, National Institute for Health and Care Excellence; PI, proteasome inhibitor; POM, pomalidomide; PRED, prednisolone; TCR, triple class refractory; THAL, thalidomide; TI, transplant ineligible.
Notes: *Early relapse on CYC+THAL+DEX.
This diagram illustrates potential routes through the NICE pathway to becoming TCR, it is not exhaustive. Note that not all patients relapsing after front-line therapy will be class-refractory owing to fixed-duration therapies. However, patients with aggressive disease may relapse early (as depicted with cyclophosphamide with thalidomide and dexamethasone) thus becoming refractory.
Source: Pfizer data on file, 2023.[75]

Refractoriness at first line of therapy

Transplant-eligible patients receiving DARA+BORT+THAL+DEX induction therapy become triple class exposed (TCE) in their first LoT (Figure 3).[23] However, this regimen is fixed-duration so patients will usually relapse on the post-ASCT LEN maintenance, thus only being IMiD refractory at first relapse.[9]

The recent approval of DARA+LEN+DEX in transplant-ineligible patients will result in the majority of patients thus treated being refractory to an IMiD and an anti-CD38 mAb at first relapse (Figure 4).[8]

Patients treated with LEN+DEX (which is given continuously until disease progression) will be IMiD refractory.[12] The remaining front-line therapies for transplant-ineligible patients are fixed-duration, therefore patients can be IMiD or PI refractory at first relapse, if they are primary refractory or relapse on-treatment. However, the majority will relapse off-treatment: these patients will not be drug/class refractory at first relapse.

Refractoriness at second line of therapy

DARA+BORT+DEX is given until disease progression in the second LoT (Figure 3 and Figure 4). However, as the BORT component is only given for 8 cycles, patients will usually only be anti-CD38 mAb refractory at relapse. Patients with aggressive disease who experience relapse within 60-days of the last BORT dose will also be PI refractory. Therefore, the majority of these patients will only be refractory to IMiDs (from the first LoT) and anti-CD38 mAbs.[10]

Patients receiving BORT (given for 8 cycles), CAR+DEX or CAR+LEN+DEX in this LoT can be PI refractory at relapse but will not be anti-CD38 mAb refractory. Patients on CAR+LEN+DEX only receive 18 cycles of CAR in this combination. Therefore, patients on this regimen who relapse more than 60-days after the last CAR dose will not be PI refractory.[11, 69]

Transplant-ineligible patients who received DARA+LEN+DEX at first line (IMiD and anti-CD38 mAb refractory) will only be eligible for CAR+DEX or BORT monotherapy

at second line (Figure 4**)**. Following treatment, most of these patients will also become PI refractory and therefore TCR at second relapse.

TCR status at third and fourth lines of therapy

Due to the recent approval of DARA+LEN+DEX at first-line in transplant-ineligible patients, going forward the proportion of patients who are TCR by third-line will increase significantly (see Figure 3 and Figure 4). These patients have no effective treatment options and will be given bridging therapies to access more effective treatments in the fourth-line.[3] However, transplant-eligible or transplant-ineligible patients who did not receive DARA+LEN+DEX, will usually remain PI sensitive at third line.

By fourth line the majority of patients in the current pathway will be TCR, having relapsed on IXA+LEN+DEX or PANO+BORT+DEX at third-line, thus gaining PI refractoriness (see Figure 3 and Figure 4).[70, 71] Patients who received BORT, CAR+DEX or CAR+LEN+DEX at second-line, may still be anti-CD38 mAb sensitive; these patients can receive DARA monotherapy[5] (or indeed ISA+POM+DEX via the CDF[4]), thus becoming TCR in fifth-line. However, due to the increased use of DARA+LEN+DEX at first line and DARA+BORT+DEX at second line, the proportion of patients who will still be CD38 mAb sensitive in fourth line is expected to substantially fall.

Comparators

In a Pfizer advisory board (May 2023) clinical experts indicated that the majority of patients will be TCR, and therefore eligible for elranatamab, from fourth-line onwards.[1] A small cohort of patients will become TCR at third-line; these patients currently have no effective treatment options. Following the recent approval of DARA+LEN+DEX in first-line transplant-ineligible patients, the number of patients becoming TCR earlier in the treatment pathway is expected to rise.[8]

As described in Section B.1.1, POM+DEX is considered the only relevant comparator to elranatamab. This aligns with Committee conclusions from previous NICE MM appraisals (TA783, TA658) where POM+DEX was accepted as the

relevant comparator.[4, 5] The ongoing appropriateness of this comparator was reiterated by practicing clinicians at a Pfizer advisory board (May 2023)[1] and the HTA Access Forum meeting (July 2023).[2] Pfizer also undertook a national BoD study using the Systemic Anti-Cancer Therapy (SACT) database to examine the demographic and clinical characteristics of patients diagnosed with MM in England, their treatment patterns and clinical outcomes (OS and time to next treatment).[6] This study found POM+DEX to be the most frequent subsequent therapy after patients had received a PI, IMiD, and anti-CD38 mAb, supporting findings from a separate study using the SACT database over an earlier study period.[35]

B.1.3.4. Unmet need

The introduction of novel combination therapies early in the treatment pathway has resulted in a cohort of patients becoming TCR earlier in their treatment. Outcomes are particularly poor for these patients for whom there are no effective reimbursed options (See Section B.1.3.1).[34, 36, 73] Furthermore, TCR MM and its treatment has a significant impact on both patient and carer quality of life (See Sections B.1.3.2.1 to Section B.1.3.2.4).

RWE has demonstrated substantial heterogeneity in subsequent therapies received by TCR MM patients, indicating the lack of a SoC.[34, 36, 73, 76, 77] LocoMMotion, a prospective real-world study of outcomes in TCE patients (73.8% were TCR), identified 92 varied regimens for patients within this heavily pre-treated population.[34] Given the lack of a SoC, these patients are often prescribed regimens containing drugs or classes to which they have previously been exposed or have become refractory.[3] Due to the recent approval of DARA+LEN+DEX for first-line transplant-ineligible patients, the number of patients becoming TCR earlier in the treatment pathway, who have no suitable treatment options available to them, will likely rise significantly.[8]

B-cell maturation antigen (BCMA) is a novel treatment target for MM due to its highly selective expression in malignant plasma cells. BCMA-targeted therapies include bispecific antibodies (e.g., elranatamab), antibody–drug conjugates (ADCs), and chimeric antigen receptor T-cell therapies (CAR-T therapies). Some of these modalities have achieved remarkable clinical responses in TCR patients, increasing

treatment options for heavily pre-treated patients.[78-81] However, no BCMA-targeted therapies are currently reimbursed in the UK, and at the time of writing, elranatamab is the only BCMA-targeting therapy undergoing a NICE submission for the treatment of TCR patients.

In summary, there is a clear unmet need for novel therapies for TCR MM patients which can extend remission, improve life expectancy, and improve HRQL in both patients and carers, while also having a manageable safety profile and reducing the administration burden.

B.1.4. Equality considerations

As described in Section B.1.3.3, based on the current treatment pathway in England, the majority of patients will become TCR from fourth-line onwards.[1] However, a decision to restrict reimbursement by line of treatment as opposed to receipt and/or refractory status to previous therapies will create inequalities in access, particularly for patients who become TCR earlier in the treatment pathway (i.e., third-line or earlier). Recent approvals are expected the exacerbate this inequality.[8] Consequently, clinicians would be forced to use drugs/combinations that lack robust efficacy data, as “bridging therapies” to enable these patients to access elranatamab at fourth line.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

Appendix D provides full details of the systematic literature review (SLR) used to identify and select clinical evidence relevant to this submission. A broad, global SLR was conducted to identify evidence on the relative efficacy and safety of elranatamab and relevant comparators in people with RRMM. The SLR was subsequently filtered to select evidence to match the final NICE scope, in order to identify evidence for elranatamab and relevant comparators in adults with RRMM after at least 3 prior therapies (Table 1). A total of 14 unique trials (summarised across 33 publications) were identified. Of these studies, one trial reported on elranatamab (MagnetisMM-3),

and 6 trials reported evidence for POM+DEX, the comparator of interest in the submission (See Section B.1.1 and Section B.1.3).

The SLR was then further restricted to match the decision problem addressed in the company submission, in order to identify evidence for elranatamab and POM+DEX in adults with RRMM who have received at least three prior therapies including an IMiD, PI and anti-CD38 antibody and have demonstrated disease progression on the last therapy (Table 1). When restricting further, only the MagnestisMM-3 study (reported across 7 publications) of elranatamab was identified in the relevant patient population.[82-84]

The six POM+DEX studies reporting data in adults with RRMM after at least 3 prior therapies were either published before the introduction of anti-CD38 mAbs, excluded patient's refractory to anti-CD38 mAbs, or began recruiting before the introduction of anti-CD38 mAbs so included very limited data (See Section Appendix D). Thus, it is likely that patients enrolled in the POM+DEX clinical trials will generally have disease that is less refractory and easier to treat than the patients enrolled in MagnetisMM-3 – the pivotal study for elranatamab. This poses a challenge for providing comparative efficacy assessments because data on the effect of POM+DEX are not available in a population similar to MagnestisMM-3. Of the six POM+DEX trials, MM-003 was considered the most relevant and subsequently used to inform the unanchored matching-adjusted indirect comparison (MAIC) described in Section B.2.9.It has been used as efficacy data for the POM+DEX arm in the base case economic analysis (See Section B.3.3.3 - B.3.3.4).[85] MM-003 was selected from the six POM+DEX studies, as it included the most comparable population to elranatamab according to baseline characteristics including median lines of prior treatments.

To provide an additional source of comparative evidence in a population aligned with the decision problem addressed in the company submission, Pfizer have conducted an external control arm (ECA) study.[73] Exploratory analyses within this study were undertaken on data from [redacted] UK patients who had received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy (i.e. RRMM) treated with POM+DEX who had a

median of ▌ prior lines of treatment. Data from the ECA study have been used to inform an unadjusted direct comparison described in Section B.2.9 and have been used as alternative efficacy data for the POM+DEX arm in the economic analysis (See Section B.3.3.1 and appendix O).

B.2.2. List of relevant clinical effectiveness evidence

Details of the elranatamab clinical effectiveness evidence are provided in Table 4.

The pivotal regulatory evidence to support elranatamab, and the focus of this submission, is MagnetisMM-3; an ongoing, Phase II, open-label, multicentre, non-randomised study.[82, 83, 86] This pivotal trial informs the economic model presented in Section B.3.

Supportive evidence is provided by the earlier MagnetisMM-1 trial, a Phase I trial designed to assess the safety and tolerability at increasing dose levels of elranatamab in patients with RRMM to determine the maximum tolerated dose and select the recommended Phase II dose.[87] Evidence is available in 55 patients with RRMM (90.9% were TCR) who received single-agent elranatamab subcutaneously ≥215 μg kg^{-1}. Of these patients, 23.6% had received prior BCMA targeted therapy. This trial provides more mature PFS and OS data in a sicker, more heavily pre-treated cohort of patients who received a lower dose of elranatamab compared with patients in Cohort A of MagnetisMM-3 and to what will be used in clinical practice. This study has been used to validate model assumptions.

Table 4: Clinical effectiveness evidence

Study	MagnetisMM-3 (NCT04649359)	MagnetisMM-1 (NCT03269136)
Study design	Phase II, open-label, multicentre, non-randomised study	Phase I, open label, multi dose, multi centre, dose escalation, safety, pharmacokinetic and pharmacodynamic study
Population	Adult patients with RRMM who were refractory to at least one PI, one IMiD, and one anti-CD38 mAb and who were relapsed or refractory to their most recent regimen	Adult patients with RRMM who were refractory to at least one PI, one IMiD, and one anti-CD38 mAb
Intervention(s)	Elranatamab (n = 187)	Elranatamab ≥215 μg/kg^{-1} (n

Study	MagnetisMM-3 (NCT04649359)	MagnetisMM-1 (NCT03269136)
	• Cohort A (BCMA-naïve) (n = 123) • Cohort B (BCMA-exposed) (n = 64)	= 55)
Comparator(s)	Not applicable	Not applicable
Indicate if study supports application for marketing authorisation	Yes	No
Indicate if study used in the economic model	Yes	No
Rationale if study not used in the model	Not applicable	Not applicable
Reported outcomes specified in the decision problem	• **Overall survival** • Progression-free survival • Response rate • Adverse events of treatment • Health-related quality of life	• **Overall survival** • Progression-free survival • Response rate • Adverse events of treatment
All other reported outcomes	• Time to response • Minimal residual disease negativity rate • Pharmacokinetics • Immunogenicity	• Time to response • Minimal residual disease negativity rate • Pharmacokinetics • Immunogenicity

Key: BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteasome inhibitor; RRMM, relapsed or refractory multiple myeloma.
Notes: Bolded outcomes are those used in the economic modelling.
Source: Bahlis et al. 2022[82]; Mohty et al. 2023[83]; MagnetisMM-3 Clinical Study Report[86]; Bahlis et al. 2023.[87]

Full details of the pivotal trial (MagnestisMM-3) are provided in Sections B.2.3 to B.2.6 of this submission. Relevant outcomes of the supportive trial (MagnestisMM-1) are provided in Section B.2.6.2; details of the methods, population and safety data are provided in Appendix M.6.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. MagnetisMM-3 study design

MagnetisMM-3 is a Phase II, open-label, multicentre study designed to evaluate the efficacy and safety of elranatamab monotherapy in patients with RRMM who are refractory to at least one PI, one IMiD, and one anti-CD38 mAb and who have relapsed or refractory to their most recent regimen.[82, 83, 86] The study is ongoing and is being conducted at 76 sites in 10 countries, with one site in the UK.[88] The MagnetisMM-3 trial design is presented in Figure 5, and a summary of the trial methodology is presented in Appendix M.1.

To determine the effects of prior BCMA-targeted therapy on the response to elranatamab, MagnetisMM-3 enrolled two independent parallel cohorts[83, 86]:

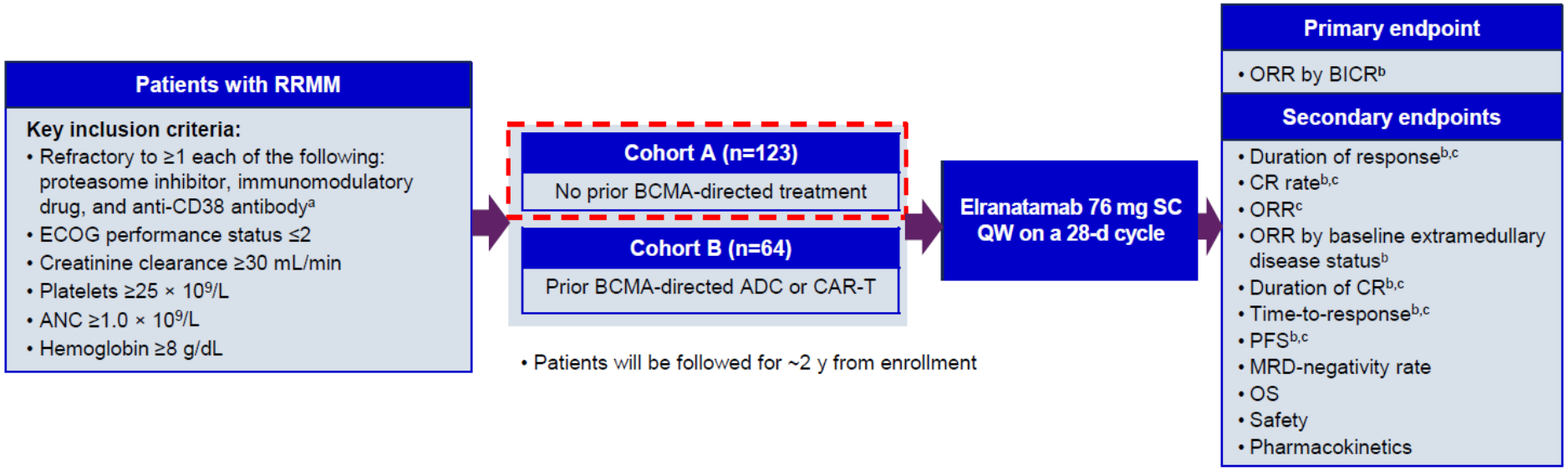
- Cohort A: Patients who had not received any prior BCMA-directed therapy (BCMA-naïve; n = 123)
- Cohort B: Patients who had previously received BCMA-directed ADC or BCMA-directed CAR-T therapy, either approved or investigational (BCMA-exposed; n = 64)

For inclusion in MagnetisMM-3, patients were ≥ 18 years of age with RRMM who were refractory to at least one PI, one IMiD, and one anti-CD38 mAb, and who were relapsed or refractory to their most recent regimen.[83, 86] Eligible patients had measurable disease according to the IMWG criteria and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Both Cohorts A and B had the same inclusion–exclusion criteria, except for the prior BCMA-directed therapy exposure, which was used for cohort assignment.

The primary efficacy endpoint of MagnetisMM-3 in Cohort A and Cohort B is objective response rate (ORR) by blinded independent central review (BICR), as per the IMWG criteria.[83, 86] The key secondary endpoint in Cohort A is ORR, by BICR, according to baseline extramedullary disease (EMD) status, as per the IMWG criteria. Other secondary endpoints include PFS and OS. Details of all other secondary endpoints are provided in Figure 5 and Appendix M.1.

No BCMA-targeted therapies are currently reimbursed for use in the UK; therefore, Cohort A (BCMA-naïve) is the most relevant patient population and is the focus of this submission. Efficacy and safety data for Cohort B and the total population are presented in Appendix M.4 and M.5, respectively for completeness.

Figure 5: Study design of MagnestisMM-3



Key: ADC, antibody–drug conjugate; ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; BICR, blinded independent central review; CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; ECOG, Eastern Cooperative Oncology Group; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QW, once weekly; SC, subcutaneous.
Notes: [a] Refractory is defined as having disease progression while on therapy or within 60 days of the last dose in any line, regardless of response. MM with measurable disease as defined by IMWG criteria. Patients with active or clinically significant bacterial, fungal, or viral infection, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), and those who received a stem cell transplant within 12 weeks prior to enrolment were excluded. [b] By BICR assessment per IMWG response criteria. [c] By Investigator assessment per IMWG response criteria. * If a patient achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval could be changed from once weekly (QW) to once every 2 weeks (Q2W).
Source: Mohty et al. 2023.[83]

B.2.3.2. Patient characteristics

The baseline characteristics for patients in Cohort A in the MagnetisMM-3 trial are presented in Table 5.[82, 83, 86]

The median age of patients was 68.0 years, 55.3% were male, and the majority (94.3%) had an ECOG performance status of either 0 or 1.[82, 83, 86] Patients had a median of five prior LoTs, 96.7% of patients were TCR, and 42.3% were penta-refractory. Over two-thirds of patients (70.7%) had at least one poor prognostic feature including EMD at baseline, high-risk cytogenetics, bone marrow plasma cell involvement, International Staging System (ISS) Stage III disease, and an ECOG performance status of 2.[83, 86]

Table 5: Patients demographics and baseline disease characteristics in MagnetisMM-3

Characteristic	Cohort A, n (%) (n = 123)
Age, years, mean (SD)	67.1 (9.45)
Age, years, median (range)	68.0 (36.0–89.0)
Sex n (%)	
Male	68 (55.3)
Female	55 (44.7)
Race, n (%)	
White	72 (58.5)
Black or African American	9 (7.3)
Asian	16 (13.0)
Primary diagnosis and duration	
Time since the first diagnosis[a], months, mean (SD)	[redacted]
Time since onset of current relapse[b], months, mean (SD)	[redacted]
EMD by BICR, per the IMWG criteria, n (%)	
Yes	39 (31.7)
Target EMD	37 (30.1)
Non-target EMD only	2 (1.6)
No	84 (68.3)
Non-target bone lesions only	43 (35.0)
No lesion	41 (33.3)
ECOG PS, n (%)	
0	45 (36.6)
1	71 (57.7)

Characteristic	Cohort A, n (%) (n = 123)
2	7 (5.7)
R-ISS disease stage, n (%)	
I	28 (22.8)
II	68 (55.3)
III	19 (15.4)
Unknown	8 (6.5)
Cytogenetic risk, n (%)	
Standard risk	83 (67.5)
High-risk[c]	31 (25.2)
Missing	9 (7.3)
Baseline bone marrow plasma cells, n (%)	
< 50%	89 (72.4)
≥ 50%	26 (21.1)
Missing	8 (6.5)
Patients with ≥ 1 poor prognosis feature[d], n (%)	87 (70.7)
Prior anticancer therapy	
Number of prior anticancer LoTs, median (range)	5.0 (2, 22)
Patients who were TCE[e]	123 (100.0)
Patients who were TCR[f]	119 (96.7)
Patients who were penta-drug exposed[g]	87 (70.7)
Patients who were penta-drug refractory[h]	52 (42.3)
Refractory to the last LoT	118 (95.9)
Prior BCMA-targeted treatment	0 (0.0)

Key: ADC, antibody–drug conjugate; BCMA, B-cell maturation antigen; BICR, blinded independent central review; CAR-T therapy, chimeric antigen receptor T-cell therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; IMWG, International Myeloma Working Group; LoT, line of treatment; R-ISS, Revised International Staging System; SD, standard deviation; TCE, triple-class exposed; TCR, triple-class refractory.
Notes: [a] Duration since first diagnosis is from Date of Initial Diagnosis to date of first dose. [b] Time since onset of current relapse, defined as (date of first dose of study intervention – date of onset of current episode). [c] 'High-Risk' if any of the following 3 chromosomal abnormalities in interest is 'YES': T(4;14), T(14;16), DEL (17P). [d] 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%. [e] Triple-class exposed refers to having received at least 1 PI, 1 IMiD and 1 anti-CD38. [f] Triple-class refractory refers to refractory to at least 1 PI, 1 IMiD and 1 anti-CD3. [g] Penta-drug exposed refers to having received at least 2 PIs, 2 IMiDs and 1 anti-CD38. [h] Penta-drug refractory refers to refractory to at least 2 PIs, 2 IMiDs and 1 anti-CD38.
Source: Bahlis et al. 2022[82]; Mohty et al. 2023[83]; MagnetisMM-3 15-month data-cut, 2023.[89]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Trial populations

Definitions of the patient populations for each analysis set in the MagnetisMM-3 clinical trial are presented in Appendix M.2.

Efficacy and safety analyses were based on the safety analysis set, which included all enrolled patients in the respective cohort who received one or more doses of elranatamab.[86] For patient-reported outcomes (PROs), HRQL analyses were based on the patient PRO analysis set, defined as all patients in the safety analysis set who completed a baseline PRO assessment and one or more post-baseline PRO assessments. Given the proposed positioning for elranatamab, only data for Cohort A are presented in the main submission.

B.2.4.2. Statistical analysis

The hypothesis and associated statistical analysis methods in the MagnetisMM-3 are summarised in Appendix M.2.

An interim analysis for both (non-binding) futility and efficacy was to be conducted using ORR by BICR based on the first 90 and 30 participants enrolled and treated in Cohort A and B, respectively.[86] 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 three post-baseline assessments) among the participants to be included have had their responses confirmed.

The final analysis of each cohort for the primary endpoint of ORR by BICR was planned once all patients had at least two post-baseline response assessments or otherwise discontinued response assessments within the first 2 months of treatment.[86] Cohort A crossed the efficacy boundary at the interim analysis based on the initial [redacted] patients dosed and a data cut-off of [redacted]. For Cohort B, it was determined that no interim analysis would be performed as not enough participants had adequate follow-up, since Cohort B has a higher incidence of EMD at baseline

compared with Cohort A. Cohort B crossed the efficacy boundary at the final analysis based on a data cut-off of [redacted].

The primary efficacy analyses evaluated the null hypothesis that the ORR by BICR was ≤ 30% for Cohort A and an ORR by BICR of ≤ 15% for Cohort B, with a 1-sided significance level of 0.025.[86]

B.2.4.3. Patient disposition

Between 09 February 2021 and 07 January 2022, a total of 187 patients were enrolled in MagnetisMM-3, including 123 in Cohort A.[83, 84, 86, 89] At the 15-month data cut-off (14 March 2023), 66.7% of patients in Cohort A discontinued elranatamab treatment; the most frequent reasons were disease progression (41.4%) followed by AEs (13.8%) and death (7.3%).[83, 84, 89]

See Appendix D.2 for full details of the number of participants eligible to enter the MagnetisMM-3 study and the CONSORT diagram presenting patient disposition.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

MagnetisMM-3 was conducted in accordance with the ethical principles of Good Clinical Practice (GCP) and is considered to be a good-quality study. The quality assessment of the MagnetisMM-3 study was conducted using the Downs and Black checklist, which is recommended for use with non-randomised controlled trials.[90] The overall risk of bias was considered to be low – full results of this assessment are presented in Appendix D.3.

B.2.6. Clinical effectiveness results of the relevant trials

In this section, efficacy results are presented for MagnetisMM-3 from the data-cut of 14 March 2023, after a median follow-up of approximately 15 months.[83, 84, 89] As described previously, data are presented for Cohort A (BCMA-naïve) throughout this section. Key results observed for Cohort B (BCMA-exposed) and the total population are presented in Appendix M.4. Efficacy results are also presented for MagnetisMM-1, a phase I trial of elranatamab in RRMM.[87]

B.2.6.1. MagnetisMM-3

B.2.6.1.1. Primary efficacy endpoint: ORR by BICR per IMWG criteria

After a median follow-up of approximately 15 months, the primary endpoint was met, with a significant and high ORR of 61.0% (95% confidence interval [CI]: 51.8, 69.6; p < 0.0001) achieved in Cohort A as assessed by BICR per the IMWG criteria (Table 6) and responses deepened over time (Figure 6).[83, 84, 89]

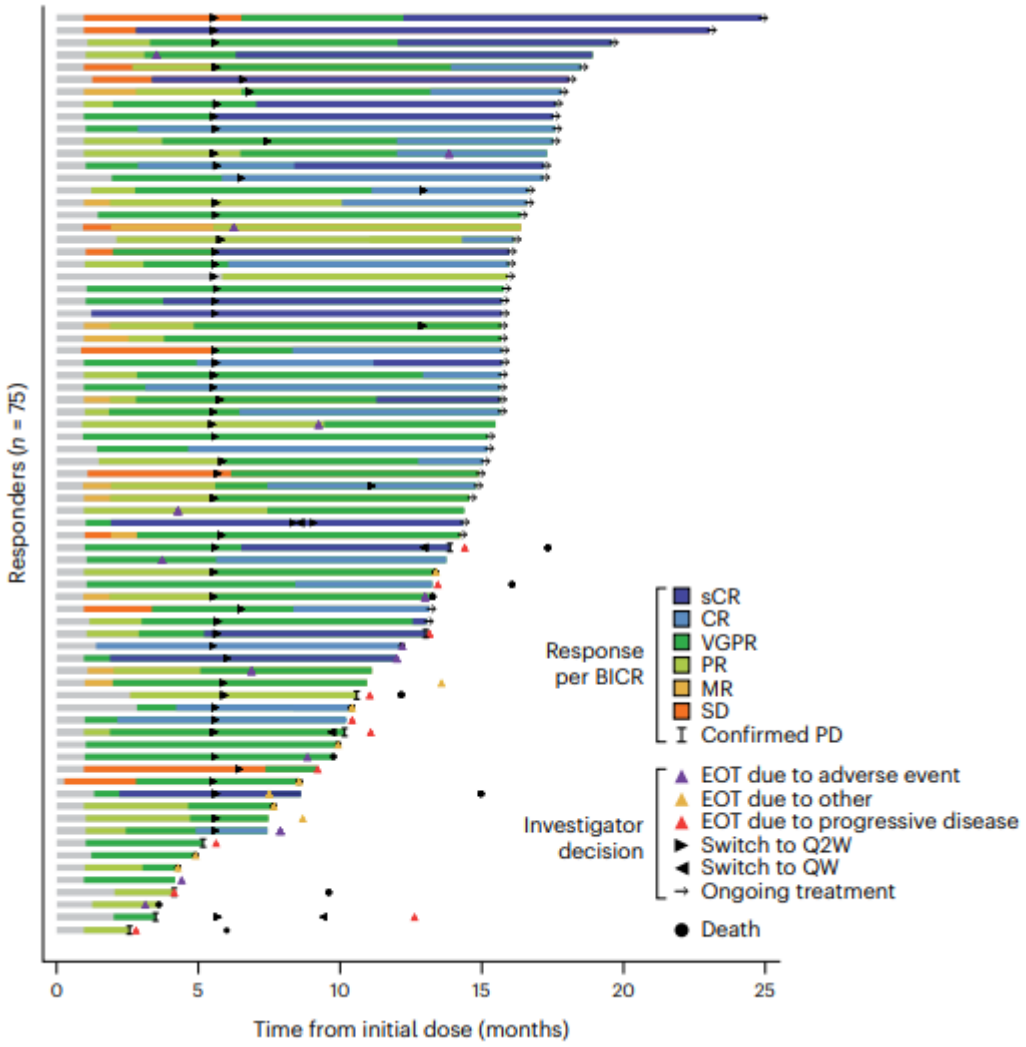
Table 6: Summary of best overall response by BICR in Cohort A of MagnetisMM-3

	Cohort A, n (%) (n = 123)
Best overall response[a], n (%)	
Stringent complete response	19 (15.4)
Complete response	24 (19.5)
Very good partial response	26 (21.1)
Partial response	6 (4.9)
Minimal response	0
Stable disease	21 (17.1)
Progressive disease	22 (17.9)
Not evaluable	5 (4.1)
ORR (sCR+CR+VGPR+PR), n (%) (95% CI[b]; p-value)	75 (61.0) (51.8–69.6; p < 0.0001)
CRR (sCR+CR), n (%) (95% CI[b])	43 (35.0) (26.6–44.1)
VGPR or better (sCR+CR+VGPR), n (%) (95% CI[b])	69 (56.1) (46.9–65.0)
CBR (sCR+CR+VGPR+PR+MR), n (%) (95% CI[b])	75 (61.0) (51.8–69.6)
Patients with ongoing response[c]	50 (66.7)
Patients 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	9 (7.3)

Key: BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CRR, complete response rate; MR, minimal response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Notes: For Cohort A: 1-sided efficacy boundary p-value ≤ 0.0202 (≥ 48 responders) for H0: ORR ≤ 30. [a] Responses defined per the modified IMWG criteria 2016.[24] [b] Clopper–Pearson method was used. [c] Only for patients with a best overall response of objective response.
Source: Lesokhin et al. 2023[84]; Mohty et al. 2023[83]; MagnetisMM-3 15-month data cut, 2023.[89]

Figure 6: Swimmer plot showing responses over time in responders



Key: EOT, end of treatment; MR, minimal response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.
Notes: Responses were assessed by BICR, whereas treatment decisions, including switch to Q2W dosing, were made by the investigator.
Source: Lesokhin et al. 2023.[84]

Of the 75 patients in Cohort A who achieved a response, 50 had at least a partial response and switched to once every 2 weeks (Q2W) dosing after 6 cycles.[83, 89] Among responders who switched to Q2W dosing, 40 (80.0%) maintained/improved their response at least 6-months after the switch. Of these patients, [redacted] ([redacted]%) maintained their response after the switch ([redacted] in very good partial response [VGPR], [redacted]

in complete response [CR], and [redacted] in stringent complete response [sCR]) and [redacted] ([redacted]%) improved (deepened) their response after the switch to Q2W dosing ([redacted] to VGPR, [redacted] to CR, and [redacted] to sCR).[89]

B.2.6.1.2. Secondary efficacy endpoints

The results for all secondary efficacy endpoints consistently support the results of the primary efficacy endpoint and confirm the treatment benefit of elranatamab in patients in Cohort A.[83, 84, 89]

B.2.6.1.2.1. ORR by BICR baseline EMD status per IMWG criteria

At baseline, 31.7% of patients in Cohort A had EMD as assessed by BICR as per the IMWG criteria.[84, 89] At the 15-month data cut-off, confirmed ORR by BICR by baseline EMD status for Cohort A was significant for patients both without baseline EMD (71.4%; 95% CI: 60.5, 80.8; $p < 0.0001$) and with baseline EMD (38.5%; 95% CI: 23.4, 55.4; $p < 0.0001$).[84, 89]

B.2.6.1.2.2. Confirmed ORR by investigator per IMWG criteria

At the 15-month data cut-off, the confirmed ORR by the investigator was 59.3% (95% CI: 50.1, 68.1) in Cohort A (Table 7), consistent with the confirmed ORR by BICR (Section B.2.6.1.1).[84, 89]

Table 7: Summary of best overall response by investigator in Cohort A of MagnetisMM-3

	Cohort A, n (%) (n = 123)
Best overall response, n (%)	
Stringent complete response	12 (9.8)
Complete response	30 (24.4)
Very good partial response	22 (17.9)
Partial response	9 (7.3)
Minimal response	1 (0.8)
Stable disease	24 (19.5)
Progressive disease	19 (15.4)
Not evaluable	6 (4.9)
ORR (sCR+CR+VGPR+PR), n (%) (95% CI[a])	73 (59.3) (50.1–68.1)

	Cohort A, n (%) (n = 123)
CRR (sCR+CR), n (%) **(95% CI[a])**	42 (34.1) (25.8-43.2)
VGPR or better (sCR+CR+VGPR), n (%) **(95% CI[a])**	64 (52.0) (42.8–61.1)
CBR (sCR+CR+VGPR+PR+MR), n (%) **(95% CI[a])**	74 (60.2) (50.9–68.9)
Patients still on treatment without progression and confirmed response	1 (0.8)
Responders still on treatment without progression and confirmed VGPR	1 (0.8)
Responders still on treatment without progression and confirmed CR	9 (7.3)

Key: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CRR, complete response rate; IMWG, International Myeloma Working Group; MR, minimal response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
Notes: [a] Clopper–Pearson method was used.
Source: Lesokhin et al. 2023[84]; MagnetisMM-3 15-month data-cut, 2023.[89]

B.2.6.1.2.3. Complete response rate by BICR and investigator per IMWG criteria

The complete response rate (CRR) analysis by BICR (Table 6) and by the investigator (Table 7) as per the IMWG criteria demonstrated deep responses in Cohort A.[84, 89] At the time of the 15-month data cut-off, 7.3% of patients with a confirmed CR by BICR were still receiving elranatamab monotherapy and without disease progression. Overall, 15.4% of patients achieved an sCR and 19.5% achieved a CR, leading to a CRR by BICR of 35.0% (95% CI: 26.6, 44.1).[83, 84, 89] The results of the investigator assessment were consistent with the BICR assessment (Table 7).

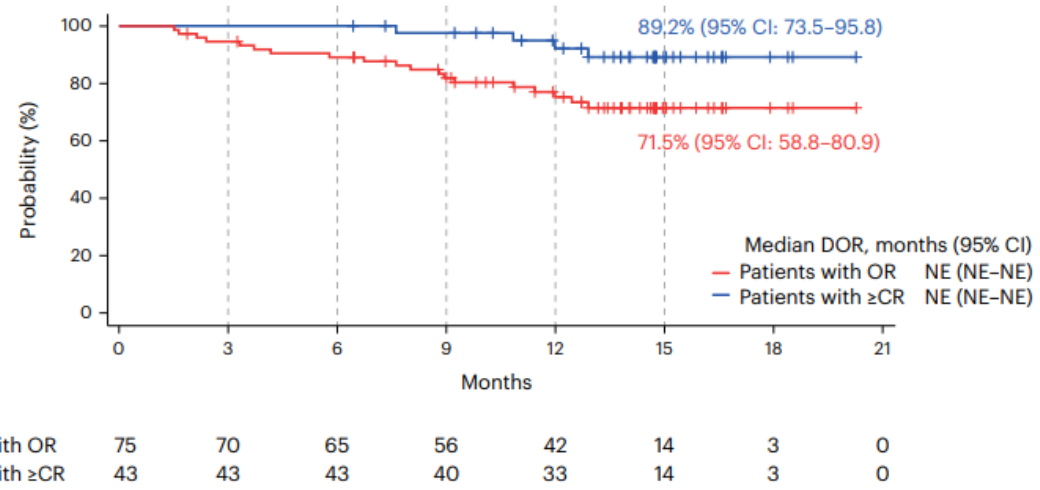
B.2.6.1.2.4. Duration of response by BICR and investigator per IMWG criteria

In patients in Cohort A with a confirmed objective response, as assessed by the BICR and investigator as per the IMWG criteria, durable responses which deepened over time were achieved with elranatamab monotherapy.[83, 84, 89] At the 15-month data cut-off, median duration of response (DoR) by BICR was not yet reached (95% CI: not evaluable [NE], NE). Figure **7** presents the Kaplan–Meier curve of DoR

assessed by BICR. Overall, 71.5% of patients treated with elranatamab had ongoing responses at 15 months and responses deepened over time (Figure 7).

Elranatamab is a bispecific BCMA-directed T-cell engaging antibody. BCMA is highly expressed on malignant plasma cells and thus making it an effective target for anti-myeloma therapies.[87] This mechanism of action redirects cytotoxic T lymphocytes against the myeloma cells, forming an immune synapse which results in T-cell activation, tumour cell lysis, and T-cell proliferation.[91, 92] The cytotoxic effect is independent of MHC co-stimulation and thus permits immune stimulation in the context of the immunosuppressive myeloma environment.[93, 94] This novel mechanism of action would explain the observed deep and durable responses seen with elranatamab in a heavily pre-treated population.

Figure 7: Duration of response and duration of complete response by BICR in Cohort A of MagnetisMM-3



Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; OR, objective response.
Source: Lesokhin et al. 2023.[84]

The results of the investigator assessment were consistent with the BICR assessment (see Appendix M.3).[83, 84, 89]

B.2.6.1.2.5. Duration of complete response by BICR and investigator per IMWG criteria

At the 15-month data cut-off, the median duration of CR by BICR was not yet reached (95% CI: NE, NE) in Cohort A.[83, 84, 89] Figure 7 presents the Kaplan–Meier

curve of duration of CR assessed by BICR. Among those who achieved a CR, 89.2% of patients treated with elranatamab were still on treatment without an event at 15 months and responses deepened over time (Figure 6).

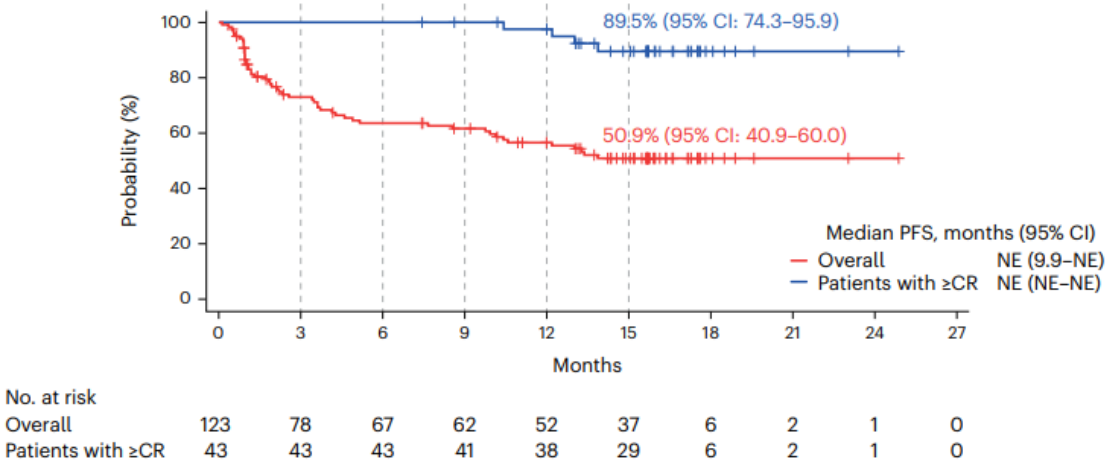
The results of the investigator assessment were consistent with the BICR assessment (see Appendix M.3).[83, 89]

B.2.6.1.2.6. Progression-free survival by BICR and investigator per IMWG criteria

At the 15-month data cut-off, median PFS by BICR was not reached (95% CI: 9.9 months, NE) in Cohort A.[83, 84, 89] Figure 8 presents the Kaplan–Meier curve of PFS assessed by BICR. The probability of being progression-free at 15 months when treated with elranatamab was 50.9%. Among those who achieved a CR, 89.5% of patients treated with elranatamab were progression-free at 15 months.

As described in Section B.2.6.1.2.4, elranatamab's novel mechanism of action would explain the observed deep and durable responses seen with elranatamab in a heavily pre-treated population.

Figure 8: Kaplan–Meier curve of progression-free survival by BICR in Cohort A of MagnetisMM-3



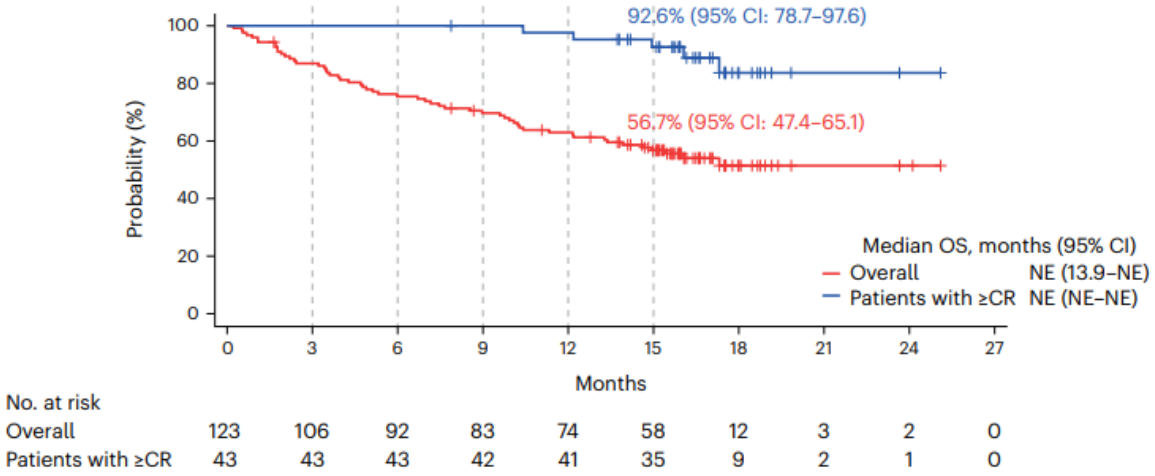
Key: BICR, blinded independent central review; CI, confidence interval; CR, complete response; NE, not evaluable; PFS, progression-free survival.
Source: Lesokhin et al. 2023.[84]

Results of the investigator assessment were consistent with the BICR assessment (see Appendix M.3).[83, 84, 89]

B.2.6.1.2.7. Overall survival

At the 15-month data cut-off, OS data were not mature in Cohort A; median OS was not reached (95% CI: 13.9, NE) and 44.7% of patients had died.[83, 84, 89] Figure 9 presents the Kaplan–Meier curve for OS. The probability of patients surviving at 15 months was 56.7% when treated with elranatamab. Among those who achieved a CR, the probability of patients surviving at 15 months was 92.6%.[83, 84]

Figure 9: Kaplan–Meier curve for overall survival in Cohort A of MagnetisMM-3



Key: CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival.
Source : Lesokhin et al. 2023.[84]

B.2.6.1.2.8. Time to response by BICR and investigator per IMWG

Among patients who achieved an objective response, response to elranatamab therapy occurred within the first 2 months of treatment in Cohort A.[83, 84, 89] Of the 75 responders, the median time to response, as assessed by BICR, was 1.2 months (Table 8).

Table 8: Time to response by BICR in Cohort A of MagnetisMM-3

	Cohort A (n = 75)
TTR (months)	
n	75
Mean (SD)	
Q1	
Median (range)	1.2 (0.9–7.4)
Q3	
Time to VGPR or better (months)	

	Cohort A (n = 75)
n	[redacted]
Mean (SD)	[redacted]
Q1	[redacted]
Median (range)	[redacted]
Q3	[redacted]
Time to CR or better (months)	
n	[redacted]
Mean (SD)	[redacted]
Q1	[redacted]
Median (range)	6.05 (1.22–14.29)
Q3	[redacted]
Time to best response (months)	
n	[redacted]
Mean (SD)	[redacted]
Q1	[redacted]
Median (range)	[redacted]
Q3	[redacted]

Key: BICR, blinded independent central review; CR, complete response; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; TTR, time to response; VGPR, very good partial response.
Source : Lesokhin et al. 2023[84]; Mohty et al. 2023[83]; MagnetisMM-3 15-month data-cut, 2023.[89]

Results of the investigator assessment were consistent with the BICR assessment (see Appendix M.3).

B.2.6.1.2.9. Minimal residual disease negativity rate

Minimal residual disease (MRD) rate (by central lab) was a secondary endpoint in MagnetisMM-3. This was assessed using next generation sequencing (NGS) of a bone marrow aspirate: NGS detects patient-specific DNA sequences of the malignant clone and gives an indication of the frequency within the sample. MRD at the sensitivity threshold of 10^{-5} was used in MagnetisMM-3, meaning the ability to detect one myeloma cell in 100,000 cells. MRD negativity was achieved by 21.1% of patients in Cohort A at a sensitivity level of 10^{-5}.[89] In addition, MRD negativity in complete responders (sCR/CR) was achieved in the majority of patients (89.7%) (Table 9).[83, 84, 89]

Table 9: Minimal residual disease negativity rate by threshold in Cohort A of MagnetisMM-3

	Cohort A (n = 123)
By threshold 10^{-5}	
MRD negative, n (%) [95% CI][a]	26 (21.1) [redacted]
sCR/CR population	[redacted]
MRD negative and sCR/CR, n (%) [95% CI][a]	[redacted]
Evaluable population	29
MRD negative and sCR/CR, n (%) [95% CI][a]	26 (89.7) [72.65, 97.81]

Key: CI, confidence interval; MRD, minimal residual disease; sCR/CR, stringent complete response/complete response.
Notes: [a] 95% CIs using the Clopper–Pearson method.
Source: Lesokhin et al. 2023[84]; Mohty et al. 2023[83]; MagnetisMM-3 15-month data-cut, 2023.[89]

B.2.6.1.3. Health-related quality of life

In MagnetisMM-3, HRQL was an exploratory endpoint. Data for PROs are based on the 15-month data-cut (cut-off date of 14 March 2023).[89] At baseline, [redacted]% of patients in Cohort A had completed the EORTC QLQ questionnaires.[89] Over the course of treatment, completion rates for the EORTC QLQ questionnaire, based on at least one question being answered, ranged between [redacted]% (end of treatment) and [redacted]% (Cycle 8 Day 8).

Overall, treatment with elranatamab demonstrated improvements in QoL in heavily pre-treated patients with TCR MM.[89]

B.2.6.1.3.1. EORTC QLQ-C30

Patients treated with elranatamab reported significant reductions in global health status (GHS) and pain based on the EORTC QLQ-C30 questionnaire.[89] In Cohort A, a transient early decrease (i.e. worsening) in the EORTC QLQ-C30 GHS score was observed from baseline through to Cycle 2 Day 15, with a least square mean (LSM) change from baseline of [redacted] (95% CI: [redacted]; Figure 10), followed by an improvement to baseline levels from Cycle 3 Day 1. Scores continued to increase through Cycle 15 Day 1 (LSM change from baseline: [redacted] [95% CI: [redacted], [redacted]), except for a transient non-significant decrease at Cycle 13 Day 1 (Figure 10).

Figure 10: LSM change from baseline in EORTC QLQ-C30 GHS score in Cohort A of MagnetisMM-3

Key: BL, baseline; C, Cycle; D, Day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer Core 30; GHS, global health status LSM, least square mean; QoL, quality of life.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Higher scores in the EORTC-QLQ-C30 GHS domain indicate better health. * p < 0.05.
Source: MagnetisMM-3 15-month data-cut, 2023.[89]

A significant decrease (i.e. improvement) in EORTC QLQ-C30 pain scores was observed from Cycle 4 Day 1, with an LSM change from baseline of [redacted] (95% CI: [redacted]; Figure 11).[89] This was maintained through Cycle 15 Day 1, except for a transient and non-significant increase at Cycle 9 Day 1 and Cycle 18 Day 1 (Figure 11).

Figure 11: LSM change in baseline in EORTC-QLQ-C30 pain scores in Cohort A of MagnetisMM-3

Key: BL, baseline; C, Cycle; D, Day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer Core 30; LSM, least square mean.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Lower scores in the EORTC QLQ-C30 pain domain indicate a decrease or improvement in pain * p < 0.05.
Source: MagnetisMM-3 15-month data-cut, 2023.[89]

Similar to the EORTC QLQ-C30 GHS, there was a transient decrease (worsening) in the domain scores for physical functioning, fatigue, nausea/vomiting, and appetite loss, followed by an improvement to baseline levels (or beyond).[89] Scores for the other domains, such as emotional functioning, cognitive functioning, dyspnoea, insomnia, constipation, diarrhoea, and financial difficulties, were generally maintained over time (see Appendix M.3).

B.2.6.1.3.2. EORTC QLQ-MY20

Patients treated with elranatamab reported significant reductions in MM disease symptoms based on the EORTC Multiple Myeloma Quality of Life Questionnaire (EORTC QLQ-MY20) questionnaire.[89] In Cohort A, a significant decrease (i.e. improvement) from baseline QLQ-MY20 disease symptom domain scores was observed starting at Cycle 5 Day 1, with LSM change from baseline of [redacted] (95% CI: [redacted]; Figure 12). This was maintained through Cycle 12 Day 1 and beyond (Figure 12). The domain scores for body image were maintained over time, and there was a rapid and significant improvement from baseline in future perspectives domain scores.

Figure 12: LSM change from baseline in EORTC QLQ-MY20 disease symptom scores in Cohort A of MagnetisMM-3

Key: BL, baseline; C, Cycle; D, Day; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Multiple Myeloma Quality of Life Questionnaire; GHS, global health status; LSM, least square mean; QoL, quality of life.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Lower scores in the QLQ-MY20 disease symptom domain indicate an improvement in symptoms. * $p < 0.05$.
Source: MagnetisMM-3 15-month data-cut, 2023.[89]

B.2.6.1.3.3. EQ-5D-3L

Patients treated with elranatamab reported significant improvements in generic HRQL over time based on the EQ-5D-3L.[89] The EQ-5D-3L index scores (using a UK value set) showed a trend similar to the EORTC-QLQ GHS. In Cohort A, there was a transient and early non-significant decrease from baseline in EQ-5D-3L scores (i.e. worsening), followed by an improvement in scores over time starting at Cycle 4 Day 1 and becoming significantly greater than baseline values at Cycle 11 Day 1, with LSM change from baseline of [redacted] (95% CI: [redacted]; Figure 13) at Cycle 11 Day 1 and [redacted] (95% CI: [redacted]; Figure 13) at Cycle 12 Day 1.

Figure 13: LSM change from baseline in EQ-5D index scores in Cohort A of MagnetisMM-3

Key: BL, baseline; C, Cycle; D, Day; LSM, least square mean; PRO, patient-reported outcomes; QoL, quality of life.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Higher scores in the EQ-5D disease symptom domain indicate an improvement in symptoms. * $p < 0.05$.
Source: MagnetisMM-3 15-month data-cut, 2023.[89]

The EQ-5D VAS scores followed a similar trend to EQ-5D-3L index scores. In Cohort A, there was a transient decrease from baseline EQ-5D VAS scores followed by an increase in scores over time starting at Cycle 6 Day 1; this reflected an improvement in general HRQL, with an LSM change from baseline of [redacted] (95% CI: [redacted]) at Cycle 15 day 1.

B.2.6.1.3.4. Patient global impression of change

Patients treated with elranatamab reported rapid improvements in their overall disease state based on the Patient Global Impression of Change (PGI-C) Questionnaire. In Cohort A, approximately [redacted]% of patients reported their clinical

status as either ‘a little better’ or ‘much better’ compared with baseline as early as Cycle 1 Day 15. This increased to more than [redacted]% by Cycle 7 Day 1 (Figure 14).

Figure 14: Distribution of Patient Global Impression of Change in Cohort A of MagnetisMM-3

Key: C, cycle; D, day.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment.
Source: MagnetisMM-3 15-month data-cut, 2023.[89]

B.2.6.1.4. Subsequent therapies

Amongst the 36 patients in Cohort A with progressive disease assessments, [redacted] received subsequent anti-cancer therapy following treatment with elranatamab. A summary of the subsequent treatments given to these patients is provided in Table 10. Further details are presented in Section B.3.5.1.1.

Table 10: Summary of subsequent therapy in Cohort A

Subsequent treatment	**Cohort A, n (%) (n = 36)**
Any subsequent anticancer medication, n (%)	[redacted]
Bortezomib, Cyclophosphamide, Dexamethasone	[redacted]
Carfilzomib, Cyclophosphamide, Dexamethasone	[redacted]

Subsequent treatment	Cohort A, n (%) (n = 36)
Carfilzomib, Daratumumab, Dexamethasone	[redacted]
Antineoplastic mAb	[redacted]
Bortezomib, Cisplatin, Cyclophosphamide, Dexamethasone, Etoposide	[redacted]
Bortezomib, Dexamethasone, Eftozanermin Alfa	[redacted]
Bortezomib, Dexamethasone, Selinexor	[redacted]
Carfilzomib, Dexamethasone, Selinexor	[redacted]
Daratumumab, Pomalidomide, Talquetamab	[redacted]
Belantamab Mafodotin	[redacted]
Bortezomib, Dexamethasone	[redacted]
Carfilzomib, Selinexor	[redacted]
Carfilzomib, Daratumumab, Dexamethasone, Pomalidomide	[redacted]
Carfilzomib, Dexamethasone, Lenalidomide	[redacted]
Cisplatin, Cyclophosphamide, Dexamethasone, Doxorubicin, Etoposide	[redacted]
Combinations of antineoplastic agents	[redacted]
Cyclophosphamide, Dexamethasone, Doxorubicin, Etoposide	[redacted]
Cyclophosphamide, Dexamethasone, Pomalidomide	[redacted]
Cyclophosphamide, Fludarabine	[redacted]
Cyclophosphamide, Fludarabine, Idecabtagene vicleucel	[redacted]
Daratumumab, Dexamethasone, Lenalidomide, Melphalan, Stem cells nos	[redacted]
Daratumumab, Dexamethasone, TTI 622	[redacted]
Dexamethasone, Isatuximab	[redacted]
Dexamethasone, Isatuximab, Pomalidomide	[redacted]
Dexamethasone, Lenalidomide, Talquetamab	[redacted]
Dexamethasone, Pomalidomide, Venetoclax	[redacted]
Dexamethasone, Thalidomide	[redacted]
Dexamethasone, Pomalidomide	[redacted]
Idecabtagene vicleucel	[redacted]
Investigational drug	[redacted]
Investigational drug, Zimberelimab	[redacted]
TAK 573	[redacted]
Talquetamab	[redacted]

Key: nos, not otherwise specified; mAb, monoclonal antibody.
Source: MagnetisMM-3 15-month data-cut, 2023.[89]

B.2.6.2. MagnetisMM-1

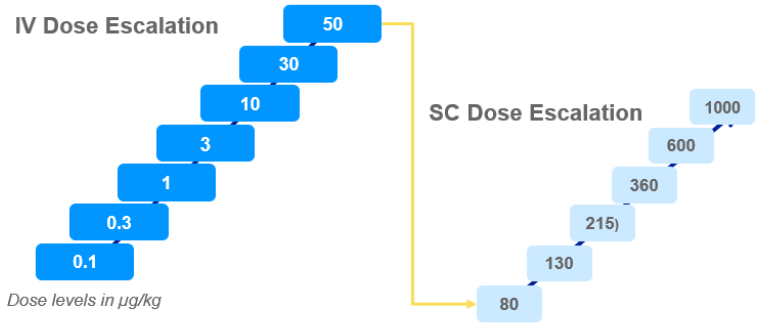
MagnetisMM-1 was the first in human phase I, open-label, multi-centre, dose escalation study of elranatamab monotherapy in patients with RRMM.[87] The objective of the study was to identify dose limiting toxicities, to evaluate the anti-

myeloma activity of elranatamab, to identify treatment-emergent adverse event (TEAE), to assess the pharmacokinetic and dynamic profile, and to identify the recommended phase 2 dose.

Eligibility criteria were similar to those of MagnetisMM-3: Adult patients (>18 years) with RRMM which had progressed on therapies which includes PI, IMiD and anti-CD39mAb.[87] Patients could be ECOG 0 or 1, with absolute neutrophil count (ANC) ≥1,000/mm^3, platelet count ≥25,000/mm^3, haemoglobin ≥8.0 g/dL and serum creatinine ≤2.5 mg/dL.

Between November 2017 and April 2021, 101 patients were enrolled in the study and received at least one dose.[87] Of the 101 patients, 88 received elranatamab monotherapy, following the IV dose escalation, 65 patients went on to receive SC therapy. Of these, 10 patients received sub-efficacious doses of <215µg kg^{-1} which were not associated with partial responses or better per the IMWG response criteria.[74] Overall, 55 patients received efficacious SC elranatamab of between 215µg kg^{-1} and 1000µg kg^{-1}.[87]

Figure 15: Dose escalation in the MagnetisMM-1 study



Key: IV, intravenous; SC, subcutaneous.
Source: Bahlis et al. 2023.[87]

Data are presented for 55 patients with RRMM who received single-agent elranatamab subcutaneously at efficacious doses ≥215µg kg^{-1}.[87] The median age was 64, 90.9% were ECOG<2, 20% were Revised ISS (R-ISS) 3, 29.1% has high risk cytogenetics, 30.9% had EMD, median prior lines was 5, 90.9% were TCR, 23.6% had received prior BCMA targeted therapy.

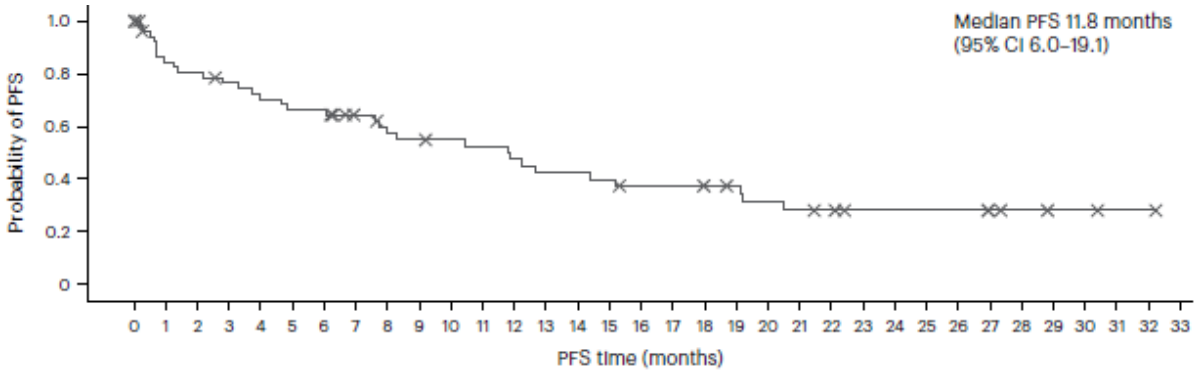
PFS and OS data are presented here with ORR and DOR data presented in Appendix M.6. The median duration of follow-up for the 55 patients presented below was 12.0 months (range, 0.3–32.3).[87]

This cohort of patients were therefore more heavily pre-treated than those in Cohort A of MagnetisMM-3. In addition, this cohort contains patients who received a range of elranatamab doses, most of which being lower than that given to Cohort A of MagnetisMM-3 and to what will be used in clinical practice.

B.2.6.2.1. Progression-free survival

Figure 16 presents the Kaplan–Meier curve of PFS. Median PFS was 11.8 months (95% CI: 6.0–19.1) in a sicker, more heavily pre-treated cohort of patients who received a lower dose of elranatamab.[87] The longer-term follow-up in MagnetisMM-1 demonstrates that the probability of being progression-free at 2 years when treated with elranatamab in this sicker, more heavily pre-treated cohort of patients is approximately 40% (Figure 16).

These data support the PFS observed for elranatamab in the most recent analysis of the MagnetisMM-3 trial and the observed deep and durable responses (see Section B.2.6.1.2.6), but likely under estimate the long term outcomes of elranatamab due to the inclusion of BCMA treated patients, as well as most patients receiving a lower doses of elranatamab that was used in MagnetisMM-3.**Figure 16: Kaplan–Meier curve of progression-free survival in MagnetisMM-1**

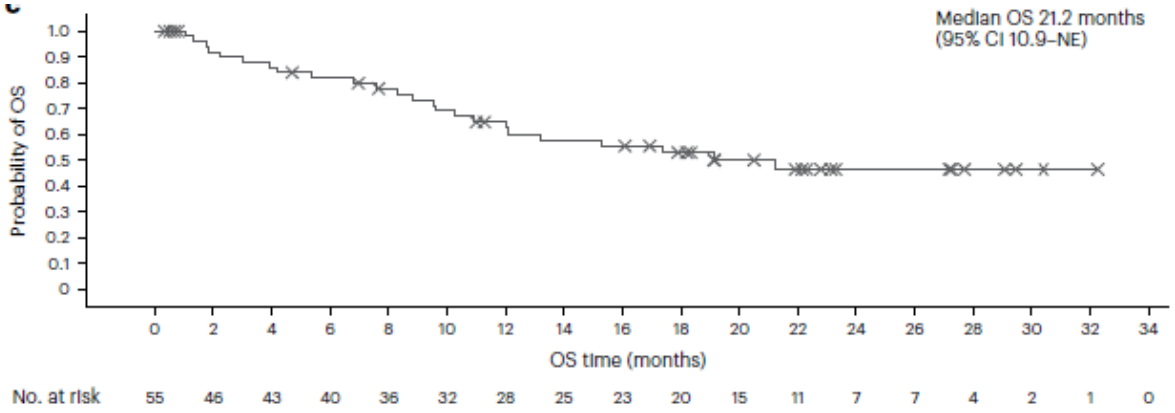


Key: CI, confidence interval; PFS, progression-free survival.
Source: Bahlis et al. 2023.[87]

B.2.6.2.2. Overall survival

Figure 17 presents the Kaplan–Meier curve of OS. Median OS was 21.2 months (95% CI: 10.9–NE) in a sicker more heavily pre-treated cohort of patients who received a lower dose of elranatamab.[87] The longer-term follow-up in MagnetisMM-1 demonstrates that the 2-year survival rate when treated with elranatamab for this sicker, more heavily pre-treated cohort of patients is approximately 50% (Figure 17).

Figure 17: Kaplan–Meier curve of overall survival in MagnetisMM-1



Key: CI, confidence interval; OS, overall survival.
Source: Bahlis et al. 2023.[87]

B.2.7. Subgroup analysis

In MagnestisMM-3, pre-specified subgroup analyses were conducted for ORR and CRR as per the Independent Review Charter (IRC) assessment in the elranatamab-treated population based on the following factors[84, 86]:

- Baseline cytogenetics (high risk, standard risk)
- Baseline extramedullary disease (yes, no)
- Baseline bone marrow plasma cells (< 50%, > 50%)
- Prior SCT (yes, no)
- Disease stage (1–2, 3)
- Number of prior lines (≤ 5, > 5)
- Type of myeloma (immunoglobulin G [IgG], non-IgG, light chain only)
- Age (< 65, ≥ 65, < 75, ≥ 75)
- Sex (male, female)
- Race (White, others)

- Region (North America, Europe, Asia, other)
- Renal function (creatinine clearance ≤ 60 mL/min, creatinine clearance > 60 mL/min)
- Liver function (normal, impaired)
- Refractory to last therapy (yes, no)
- Penta-refractory (yes, no)
- ECOG (0, 1–2)

After a median follow-up of approximately 15 months (data cut-off: 14 March 2023), a consistent ORR benefit as assessed by BICR was observed across prespecified subgroups in Cohort A.[84, 89] Despite the ORRs in patients with poor prognostic features being lower than the overall population, including those with EMD at baseline, multiple prior LoTs (> 5), R-ISS Stage III disease, high-risk cytogenetics, and penta-refractory disease, response rates in these subgroups Cohort A were still high. Further details on subgroup analyses are presented in Appendix E.

B.2.8. Meta-analysis

Meta-analysis is not applicable to this submission, as a single study provides data for elranatamab.

B.2.9. Indirect and mixed treatment comparisons

As detailed in Appendix D, when the clinical SLR was restricted to match the decision problem addressed in the company submission, only one trial of elranatamab (reported across 7 publications) was identified in the relevant patient population.[82-84]

Six trials with a POM+DEX arm were identified in the SLR. However, available clinical trial data for POM+DEX were either published before the introduction of anti-CD38 mAbs, excluded patient's refractory to anti-CD38 mAbs, or began recruiting before the introduction of anti-CD38 mAbs so included very limited data (See Appendix D), no data were available in the relevant patient population. Thus, it is likely that patients enrolled in the POM+DEX clinical trials will generally have disease that is less refractory and easier to treat than the patients enrolled in MagnetisMM-3 – the pivotal study for elranatamab. This poses a challenge for providing robust

comparative efficacy assessments because data on the effect of POM+DEX are not available in a population similar to MagnestisMM-3. Of the six trials, MM-003 has been used to inform the unanchored MAIC presented in Section B.2.9.1, as this trial includes the most comparable population to elranatamab according to baseline characteristics including median lines of prior treatments.[85] This analysis has been used as efficacy data for the POM+DEX arm in the base case economic analysis (See Section B.3.3.4). However, as patients in MM-003 were not TCR, efficacy outcomes from this trial will provide upper bound estimates of efficacy outcomes, given that true TCR patients will have worse outcomes.

To address some of the challenges and provide an additional source of comparative evidence to address potential uncertainty, Pfizer conducted an ECA study using real-world, patient-level data collected from the Arcturis UK dataset of four National Health Service (NHS) centres in the UK covering over 5,500 MM patients (Appendix D.1.3.1.2).[73] The aim of the ECA study was to estimate the treatment effect of real world treatments, including POM+DEX, in patients who have received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy (e.g. TCR MM) in UK clinical practice compared with patients treated with elranatamab in MagnestisMM-3. Of the patients included in the ECA study, [redacted] patients were treated with POM+DEX who had a median of [redacted] prior lines of treatment. Data from the ECA study have been used to inform the unadjusted direct comparison described in Section B.2.9 and have been used as scenario efficacy data for the POM+DEX arm in the economic analysis (See Section B.3.11.3).

B.2.9.1. Matching-adjusted indirect comparison versus POM+DEX trial

Full details of the design of MagnetisMM-3 are provided in Section B.2.3 and details of MM-003 are provided in Appendix D.

To explore how best to provide an indirect comparison between elranatamab and POM+DEX, the company sought to explore key differences between trials that might need to be considered. The designs of MagnetisMM-3 and MM-003 have some differences which have been explored in Table 11.

There are key differences in the patient populations between the two trials. MM-003 included patients with RRMM who had failed at least two previous treatments with BORT and LEN, no patients were anti-CD38 mAb exposed or refractory. In MagnetisMM-3, 96.7% of patients were TCR and were 42.3% penta-class refractory. MM-003 excluded patients who were previously treated with POM, while MagnetisMM-3 did not. Differences in the proportion of previous exposure to POM (81% of patients in MagnetisMM-3 were treated with POM) was identified as a considerable limitation in adjustment, as adjusting for this in the MAIC could lead to a very small sample size.

Table 11: Comparative summary of studies considered for MAIC

	MagnetisMM-3	**MM-003**
Study design	Phase II, open label, multicentre, non-randomised single arm study	Phase III randomised, open-label, multicentre study
Population	Adult patients with RRMM who were refractory to at least one PI, one IMiD, and one anti-CD38 mAb and who were relapsed or refractory to their most recent regimen	Adult patients with RRMM patients who have received at least 2 lines of lenalidomide and bortezomib, alone or in combination
Intervention	Elranatamab monotherapy (n = 123)	POM+DEX (n = 302)
Comparator	N/A	DEX monotherapy (n = 153)
Primary endpoint	ORR	PFS
Median follow-up duration	14.7 months (range: 0.2–25.1)	10.0 months (IQR 7.2–13.2)
Definition of PFS	Time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause	Time from randomisation until documented disease progression, or death, whichever occurred earlier
Definition of OS	Time from the date of first dose until death due to any cause	Time from randomisation to death

Key: DEX, Dexamethasone; IMiD, immunomodulatory drug; mAb, monoclonal antibody; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed refractory multiple myeloma.
Source: Lesokhin et al. 2023[84]; Miguel et al. 2013.[85]

Table 12 provides an overview of the baseline characteristics of patients enrolled in the MagnetisMM-3 and MM-003 clinical trials, based on the list of identified

prognostic variables (PVs) and treatment effect modifiers (EMsEMs). Out of the identified PVs and EMs, high-risk cytogenetics, extramedullary disease, penta-exposed and penta-refractory reported in the MM-003 data and therefore adjustment could not be made for them in the MAIC. The exclusion of high-risk cytogenetics and extramedullary disease leads to bias of the results, as these variables were identified as key PV/EMs based on clinical opinion.

Table 12: Patient characteristics at baseline for studies considered for MAIC

Characteristics		**MagnetisMM-3 Cohort A (n = 123)**	**MM-003 (n = 302)**
Age	Median	68	64
	> 75	21 (17)	24 (8)
Male		68 (55)	181 (60)
Time since diagnosis (year, median)		6.1	5.3
Type of myeloma, n (%)	IgG	65 (53)	-
	Non-IgG	45 (37)	-
ECOG, n (%)	0	45 (37)	110 (36)
	1	71 (58)	138 (46)
	2	7 (6)	52 (17)
Number of prior lines	Median	5	5
	> 2	[redacted]	285 (94)
ISS disease stage, n (%)	I–II	82 (67)	197 (65)
	III	24 (20)	93 (31)
Cytogenetic risk, n (%)	High-risk	31 (25)	-
	Standard-risk	83 (67)	-
	Missing	9 (7)	-
Creatinine clearance, n (%)	< 60	37 (30)	95 (31)

Key: ECOG, Eastern Cooperative Oncology Group; IgG, immunoglobulin G; ISS, The International Staging System.
Source: Lesokhin et al. 2023[84]; Miguel et al. 2013.[85]

A comparative summary of the outcomes from MM-003 versus MagnetisMM-3 is summarised in Table 13. As the definitions of OS and PFS were similar between the two trials, they were able to be compared as endpoints in the indirect comparative analysis (Table 11).

Table 13: Summary of outcomes used for clinical studies considered for MAIC

	MagnetisMM-3 Cohort A (n = 123)	**MM-003 (n = 302)**
OS	Median OS at 15-months:	Median OS:

	MagnetisMM-3 Cohort A (n = 123)	MM-003 (n = 302)
	• Not reached (95% CI: 13.9, NE)	• POM+DEX: 11.9 months (95% CI: 10.4, 15.5) • DEX: 7.8 months (95% CI: 6.4–9.2)
PFS	Median PFS at 15-months: • Not reached (95% CI: 9.9, NE)	Median PFS: • POM+DEX: 4.0 months (95% CI: 3.6, 4.7) • DEX: 1.9 months (95% CI: 1.9–2.2)
Key: CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; ISA, isatuximab; NE, not evaluable; OS, overall survival; PFS, progression-free survival; POM, pomalidomide. **Source**: Lesokhin et al. 2023[84]; Miguel et al. 2013.[85]		

B.2.9.1.1. Methods

Unanchored MAICs were used to indirectly compare the treatment effect of elranatamab to the POM+DEX arm of the MM-003 trial. Full details of the methods adopted for MAIC are provided in Appendix D. In summary, each patient in the elranatamab arm was given an MAIC weight so that in aggregate the elranatamab arm resembled the POM+DEX arms on selected baseline characteristics.

Exploration and identification of PVs and treatment EMs (via Cox proportional hazards models, an SLR, previous indirect treatment comparison (ITCs) and clinical opinion) is detailed in Appendix D; the final list of PVs and EMs is presented in Table 14.

Table 14: Prognostic variables and effect modifiers identified based on the SLR and clinical opinion

	PFS	OS
Prognostic variables and effect modifiers	• Age • Time since initial diagnosis • R-ISS or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • ECOG performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)	• Age • Sex • Time since initial diagnosis • R-ISS or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • ECOG performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)
Key: ECOG, Eastern Cooperative Oncology Group; EM, effect modifiers; OS, overall survival; PFS, progression-free survival; PV, Prognostic variables; R-ISS, Revised International Staging System. **Note:** R-ISS was prioritised as a PV/EM if it was reported in the comparator's trial.		

For the unanchored MAIC, MagnetisMM-3 data were reweighted to the aggregated data from MM-003, based on the identified PVs and EMs (Table 14). The adjusted PVs and EMs in this analysis were age (>75 years), sex, median time since initial diagnosis, ISS disease stage, number of prior lines (>2 lines), ECOG status, and creatinine clearance. Weights were generated so that the distributions of these variables for elranatamab were the same as those reported for POM+DEX in the MM-003 study.

Baseline characteristics of the MagnetisMM-3 trial before and after adjustment are provided in Appendix D.

B.2.9.1.2. Results

Results of the naïve comparison and the unanchored MAIC adjusting for MagnetisMM-3 versus MM-003 for PFS and OS are summarised in Table 15.

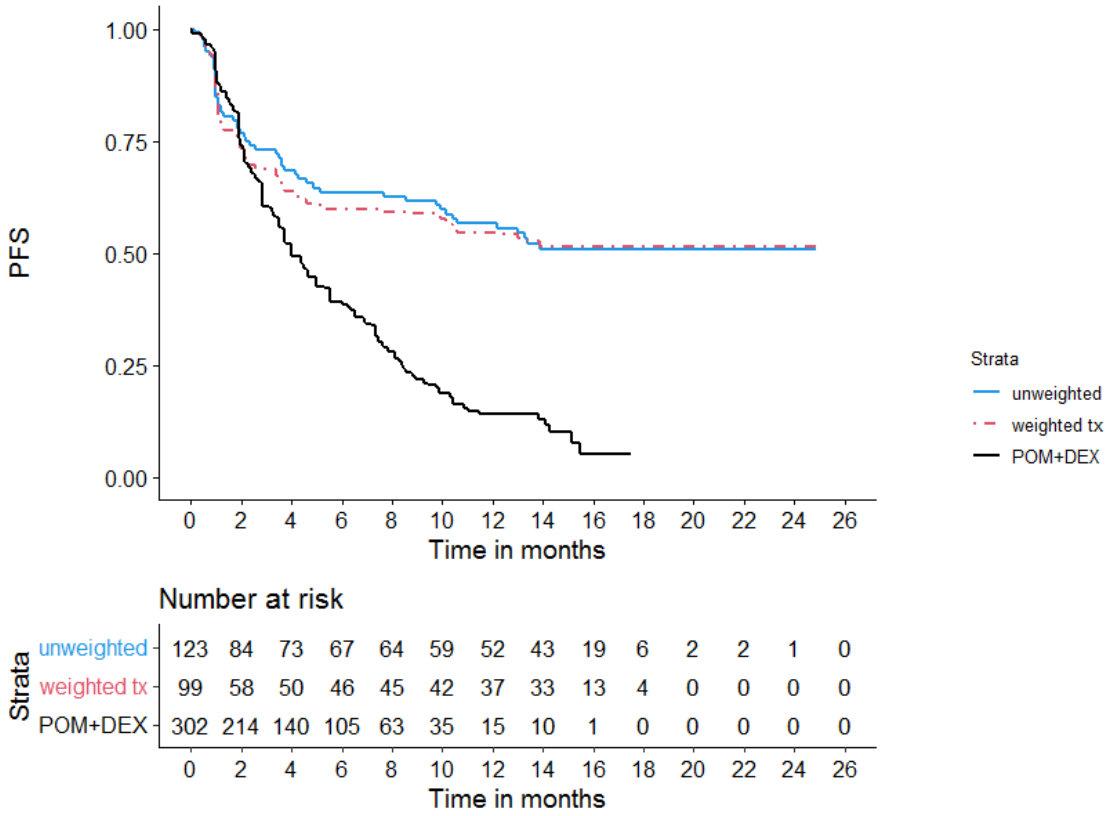
Table 15: Unanchored MAIC: MagnetisMM-3 versus MM-003

Outcome and analysis	ESS	HR (95% CI) (Elranatamab vs POM+DEX)	p-value
PFS – Naïve comparison	123	0.359 (0.263, 0.490)	0.000
PFS – Unanchored MAIC	76	0.386 (0.253, 0.589)	0.000
OS – Naïve comparison	123	0.655 (0.477, 0.900)	0.009
OS – Unanchored MAIC	75	0.705 (0.494, 1.007)	0.054

Key: CI, confidence interval; DEX, dexamethasone; ESS, estimated sample size; HR, hazard ratio;PFS, progression-free survival; POM, pomalidomide.

Figure 18 presents the Kaplan–Meier curves from the naïve comparison and the unanchored MAIC of PFS for MagnetisMM-3 versus MM-003. Elranatamab treatment led to significant improvements in PFS compared to POM+DEX across all analyses. Limited emphasis should be placed on the p-values given the diverging curves indicate the proportional hazard (PH) assumption required for this test is flawed. However, the diverging curves themselves alongside the notable gap in the Kaplan-Meier data, indicate a longer time in progression-free for patients treated with elranatamab versus POM+DEX.

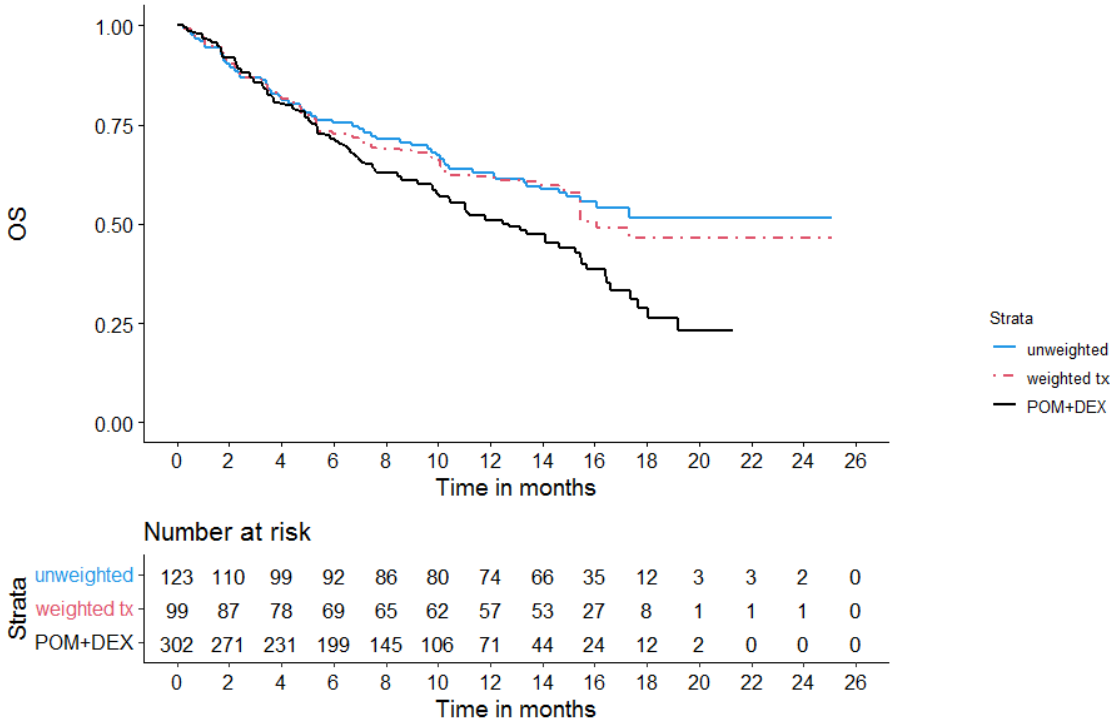
Figure 18: Kaplan–Meier of PFS for the unanchored MAIC: MagnetisMM-3 versus MM-003



Key: DEX, dexamethasone; PFS, progression-free survival; POM, pomalidomide.

Figure 19 presents the Kaplan–Meier curves from the naïve comparison and the unanchored MAIC of OS for MagnetisMM-3 versus MM-003. Elranatamab treatment led to significant improvements in OS compared to POM+DEX in the naïve comparison. In the adjusted unanchored MAIC, elranatamab treatment was associated with numerically more favourable OS results compared to POM+DEX, but statistical significance was not reached (p = 0.054). However, as it is questionable whether the PHs assumption holds when clinical trial differences were adjusted for and, as shown in Figure 18 the curves are diverging, limited focus should be given to the p-values. The more favourable OS suggests a longer survival time for patients treated with elranatamab versus POM+DEX. These results are observed despite the inability of the MAIC to fully account for differences in each cohort's exposure to prior therapies – a bias that would likely lead to the treatment benefit of elranatamab being underestimated.

Figure 19: Kaplan–Meier of OS for the unanchored MAIC: MagnetisMM-3 versus MM-003



Key: DEX, dexamethasone; OS, overall survival; POM, pomalidomide.

B.2.9.2. Unadjusted direct comparison versus the ECA study

To understand the generalisability of findings to a real-world UK setting, an ECA study was conducted aligned with the decision problem. The study was developed due to expected limitations of unanchored MAICs. This was a retrospective RWE study using individual patient data (IPD) from electronic health records from four UK centres and provides an alternative source of comparative efficacy data.

A comparative summary of the methods, key patient characteristics and outcomes from this study versus MagnetisMM-3 is summarised in Table 16, **Table 17** and Table 18, respectively. At the time of submission only an unadjusted analysis could be provided for the POM+DEX cohort given small patient numbers and insufficient time to incorporate additional data for further analyses. Full details of the design of MagnetisMM-3 are provided in Section B.2.3 and details of the ECA study are provided in Appendix D.

Table 16: Comparative summary of MagnetisMM-3 and the ECA study

	MagnetisMM-3	ECA study
Study design	Phase II, open label, multicentre, non-randomised single arm study	Retrospective, real-world evidence study using IPD from EHRs extracted from fourArcturis UK dataset NHS centres
Population	Adult patients with RRMM who were refractory to at least one PI, one IMiD, and one anti-CD38 mAb and who were relapsed or refractory to their most recent regimen	Adult patients with RRMM who had received at least one PI, one IMiD, and one anti-CD38 mAb and are refractory to the last therapy based on documented disease progression (according to the IMWG definition) within 60-days of the last dose, or during treatment with that drug class
Intervention	Elranatamab monotherapy (n = 123)	POM+DEX (n = [redacted])
Comparator	N/A	N/A
Primary endpoint	ORR	PFS
Median follow-up duration	14.7 months (range: 0.2–25.1)	N/A
Definition of PFS	Time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause	Time (in days) from index date to the first recorded progression event, as defined by IMWG (with IgA being an acceptable substitute for quantified serum paraprotein if serum paraprotein values are unmeasurable), or death, within the approximately 25-month period following index date
Definition of OS	Time from the date of first dose until death due to any cause	Time (in days) from index date to date of death, irrespective of cause, within the approximately 25-month period following index date

Key: DEX, Dexamethasone; EHR, electronic healthcare record; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IPD, individual patient data; mAb, monoclonal antibody; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed refractory multiple myeloma.
Source: Lesokhin et al. 2023[84]; Pfizer data on file, 2023.[73]

Table 17: Patient characteristics of MagnetisMM-3 and the ECA study

Characteristics		MagnetisMM-3 Cohort A (n = 123)	ECA study (n = [redacted])
Age	Mean (SD)	67.07 (9.45)	
Male		68 (55.28)	
MM Duration, months (Mean (SD))		78.71 (45.87)	
ECOG, n (%)	0	45 (36.59)	
	1	71 (57.72)	
	2	7 (5.69)	
	Missing	0	
Median (range) number of prior lines		5 (4, 6)	
Type of prior therapy - Contains PI, n (%)		54 (43.90)	
Type of prior therapy - Contains IMiD, n (%)		38 (30.89)	
Type of prior therapy – Contains anti-CD38 mAb, n (%)		47 (38.21)	
Type of prior therapy – Other, n (%)		22 (17.89)	
ISS disease stage, n (%)	I	35 (28.46)	
	II	47 (38.21)	
	III	24 (19.51)	
	Missing	17 (13.82)	
Cytogenetic risk, n (%)	High-risk	83 (67.48)	
	Standard-risk	31 (25.20)	
	Missing	9 (7.32)	

Key: ECOG, Eastern Cooperative Oncology Group; IgG, immunoglobulin G; ISS, The International Staging System.
Source: Lesokhin et al. 2023[84]; Pfizer data on file, 2023.[73]

Table 18: Summary of outcomes of MagnetisMM-3 and the ECA study

	MagnetisMM-3 Cohort A (n = 123)	ECA study (n = [redacted])
OS	Median OS at 15-months: • Not reached (95% CI: 13.9, NE)	• Median OS: [redacted] months (95% CI: [redacted])
PFS	Median PFS at 15-months: • Not reached (95% CI: 9.9, NE)	• Median PFS: [redacted] months (95% CI: [redacted])

Key: CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; ISA, isatuximab; NE, not evaluable; OS, overall survival; PFS, progression-free survival; POM, pomalidomide.
Source: Lesokhin et al. 2023[84]; Miguel et al. 2013[85] ; Pfizer data on file, 2023.[73]

B.2.9.2.1. Methods

For each cohort and for each outcome, an unadjusted Kaplan–Meier curve was produced and visualised with associated 95% confidence intervals presented. Additionally, the median survival for each outcome was obtained using the unadjusted Kaplan–Meier curve. Due to time constraints, no adjustments were made. Full details of the methods used in the ongoing ECA study are provided in Appendix D.

B.2.9.2.2. Results

Results of the unadjusted direct comparison of MagnetisMM-3 versus the ECA study are summarised in Table 19.

Table 19: Unadjusted direct comparison: MagnetisMM-3 versus ECA

		Description	Effect Estimate	95% Confidence Intervals	
				Lower Bound	Upper Bound
PFS (INV)	Unadjusted Analysis	**Cox Regression (HR)**			
		ECA	REF	-	-
		MagnetisMM-3	[redacted]	[redacted]	[redacted]
		RMST (Months)			
		Difference	[redacted]	[redacted]	[redacted]
		Schoenfeld Residual Test	[redacted]		
PFS (BICR)	Unadjusted Analysis	**Cox Regression (HR)**			
		ECA	REF	-	-
		MagnetisMM-3	[redacted]	[redacted]	[redacted]
		RMST (Months)			
		Difference	[redacted]	[redacted]	[redacted]
		Schoenfeld Residual Test	[redacted]		
OS	Unadjusted Analysis	**Cox Regression (HR)**			
		ECA	REF	-	-
		MagnetisMM-3	[redacted]	[redacted]	[redacted]
		RMST (Months)			
		Difference	[redacted]	[redacted]	[redacted]
		Schoenfeld Residual Test	[redacted]		

Key: BICR, blind independent central review; ECA, external control arm; HR, hazard ratio; INV, investigator; OS, overall survival; PFS, progression free survival; REF, reference; RMST, Restricted Mean Survival Time.
Source: Pfizer data on file, 2023.[73]

Figure 20 presents the Kaplan–Meier curves from the unadjusted direct comparison of PFS assessed by investigator for MagnetisMM-3 versus the ECA study. Analysis using Cox proportional hazard models indicated that elranatamab treatment led to significant improvements in investigator assessed PFS compared to POM+DEX (HR 0.37 95%: CI 0.25–0.56). The more favourable PFS suggests a longer time without progression for patients treated with elranatamab versus POM+DEX. Divergence in the curves undermines the assumption of PHs required for this test. As such the p-values should be treated with caution. However, the notable difference in the Kaplan-Meier curves, and the fact the space between the curves seems to be widening over time is suggestive of a notable treatment benefit.

Figure 20: Kaplan–Meier of PFS assessed by investigator for the unadjusted direct comparison: MagnetisMM-3 versus ECA

Key: ECA, external control arm; PFS, progression free survival.
Source: Pfizer data on file, 2023.[73]

Figure 21 presents the Kaplan–Meier curves from the unadjusted direct comparison of PFS assessed by BICR for MagnetisMM-3 versus the ECA. Analysis using Cox proportional hazard models indicated that elranatamab treatment led to significant improvements in PFS assessed by BICR compared to POM+DEX (HR 0.34 95% CI: 0.22–0.51). Divergence in the curves again undermines the assumption of proportional hazards required for this test. As such the p-values should again be treated with caution. However, the notable difference in the Kaplan-Meier curves,

and the fact the space between the curves seems to be widening over time is suggestive of a notable treatment benefit.

Figure 21: Kaplan–Meier of PFS assessed by BICR for the unadjusted direct comparison: MagnetisMM-3 versus ECA

Key: BICR, blind independent central review; ECA, external control arm; PFS, progression free survival.
Source: Pfizer data on file, 2023.[73]

Figure 22 presents the Kaplan–Meier curves from the unadjusted direct comparison of OS for MagnetisMM-3 versus the ECA. Analysis using Cox proportional hazard models indicated that elranatamab treatment led to significant improvements in OS compared to POM+DEX (HR 0.51 95% CI: 0.33–0.78). Divergence in the curves again undermines the assumption of proportional hazards required for this test. As such the p-values should again be treated with caution. However, the notable difference in the Kaplan-Meier curves, and the fact the space between the curves seems to be widening over time is suggestive of a notable treatment benefit.

Figure 22: Kaplan–Meier of OS for the unadjusted direct comparison: MagnetisMM-3 versus ECA

Key: ECA, external control arm; OS, overall survival.
Source: Pfizer data on file, 2023.[73]

B.2.9.3. Uncertainties in the indirect and mixed treatment comparisons

B.2.9.3.1. Uncertainties in the matching-adjusted indirect comparison versus MM-003

There was heterogeneity across MagnetisMM-3 and MM-003 with regard to trial design and patient populations, for example:

- Patients in MM-003 were not previously treated with anti-CD38 therapies, while this was an inclusion criterion for MagnetisMM-3. As such patients in MagnetisMM-3 have a poorer prognosis than the population of MM-003. These differences cannot be adjusted in a MAIC and may cause bias
- Patients previously treated with POM were excluded from MM-003, while in MagnetisMM-3, 81% of patients were treated with POM previously. These differences cannot be adjusted in a MAIC and may cause bias
- Patients in MM-003 werenot TCR MM, therefore, efficacy outcomes from this trial will provide upper bound estimates of efficacy outcomes, given that true TCR patients will have worse outcomes

Additionally, PHs were assessed in the MAIC. The PHs assumption did not hold in the comparison of PFS and OS outcomes, when clinical trial differences were adjusted for. Given the gap is widening through time between the PFS and OS elranatamab and POM+DEX Kaplan-Meier data the p-values based on the PHs assumption will underestimate the true treatment benefit.

In summary, every attempt has been made to provide a robust MAIC for the comparison of elranatamab to POM+DEX from the MM-003 trial, despite limitations in the comparability of the populations, data availability, maturity, and heterogeneity. However, the MAIC analyses suggest that elranatamab provides longer PFS and OS compared to POM+DEX.

B.2.9.3.2. Uncertainties in the unadjusted direct comparison versus the ECA

Compared to the MM-003 data the ECA cohort is: 1) more comparable to the MagnetisMM-3 cohort, 2) directly relevant to the population in the decision problem and 3) more generalisable given it consists of UK patients who received treatment during the same time period as MagnetisMM-3 and up until 2023. However, uncertainty remains in the results of the direct comparison using the ECA because:

- The cohort is relatively small ([redacted] patients),
- For some patients, data are missing on prognostic covariates (of which some are not routinely collected in UK clinical practice),),
- At the time of submission, it has only been possible to provide an unadjusted direct comparison versus the ECA

In summary, as a result of the sample size, missing covariate information and insufficient time to incorporate additional data to increase the sample size, it was not feasible to provide an analysis which attempts to adjust for any imbalances between the ECA and MagnetisMM-3 patient cohorts. Despite these uncertainties, the results of the unadjusted direct comparison suggest that elranatamab provides longer PFS and OS compared to POM+DEX in a more generalisable cohort of patients.

B.2.10. Adverse reactions

B.2.10.1. MagnetisMM-3

In this section, safety data are reported for MagnetisMM-3 from the data-cut of 14 March 2023 after a median follow-up of approximately 15 months.[84, 89] As described previously, data are presented for Cohort A (BCMA-naïve) throughout this section. Key results observed in Cohort B (BCMA-exposed) are presented in Appendix M.5.

B.2.10.1.1. Extent of exposure to study treatment

The median (range) duration of treatment in Cohort A was [redacted] months.[89] A total of [redacted] patients ([redacted]%) received treatment for more than 6 months and [redacted] ([redacted]%) received treatment for more than 12 months. The median (range) relative dose was [redacted]% ([redacted]). Further details on extent of exposure are presented in Appendix M.5.

B.2.10.1.2. Treatment-emergent adverse events

A summary of the most common TEAE occurring in ≥ 10% of patients and corresponding Grade 3/4 TEAEs in Cohort A is provided in Appendix M.5. All patients in Cohort A had at least one TEAE.[82, 84, 89] The most commonly reported TEAEs were cytokine release syndrome (CRS), which occurred in 57.7% of patients, followed by anaemia (48.8%), neutropenia (48.8%), diarrhoea (42.3%), fatigue (36.6%), decreased appetite (33.3%), thrombocytopenia (30.9%), pyrexia (30.1%), lymphopenia (26.8%), nausea (26.8%), injection site reaction (26.8%), hypokalaemia (26.0%), cough (25.2%), headache (23.6%), and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) test positive ([redacted]%).[83, 84]

Grade 3/4 TEAEs were reported in 70.7% of patients in Cohort A.[83, 84, 89] The most commonly reported Grade 3/4 TEAEs were neutropenia (48.8%), anaemia (37.4%), lymphopenia (25.2%), and thrombocytopenia (23.6%). No patients experienced Grade 3/4 CRS. Among patients who switched to Q2W dosing, the incidence of Grade 3/4 TEAEs decreased by > 10% after the change to dosing frequency – from 58.6% in the 3 months before switching to 46.6% in the 3 months after switching.[83, 84]

B.2.10.1.3. Treatment-related adverse events

A summary of the most common TRAE occurring in ≥ 10% of patients and corresponding Grade 3/4 TRAEs in Cohort A is provided in Appendix M.5. A total of [redacted]% of patients in Cohort A experienced a treatment-related adverse event (TRAE).[89] The most commonly reported TRAEs were CRS (57.7%), neutropenia ([redacted]%), injection site reaction (26.8%), anaemia ([redacted]%), lymphopenia ([redacted]%), and thrombocytopenia ([redacted]%).

Grade 3/4 TRAEs were reported in [redacted]% of patients in Cohort A.[89] The most commonly reported Grade 3/4 AEs were neutropenia ([redacted]%) and lymphopenia ([redacted]%). [redacted] patients experienced Grade 3/4 CRS.

B.2.10.1.4. Serious adverse events

Serious adverse events (SAEs) were reported in [redacted]% of patients in Cohort A.[89] The most commonly reported SAE (≥ 5% of patients) was coronavirus disease-19 (COVID-19) pneumonia ([redacted]%). Other commonly reported SAEs were CRS ([redacted]%), pneumonia ([redacted]%), and sepsis ([redacted]%).

B.2.10.1.5. Adverse events of special interest

B.2.10.1.5.1. Cytokine release syndrome

CRS was the most commonly reported adverse event (AE) among patients treated with elranatamab.[89] Any-grade CRS was reported in 57.7% of patients in Cohort A.[83, 84] This included [redacted] of the [redacted] patients who received one step-up dose of 44/76 mg of elranatamab and [redacted] of the [redacted] patients ([redacted]%) who received the 12/32 mg step-up regimen. CRS events occurred early, with the majority limited to the step-up doses; [redacted]% of CRS events occurred with the first three doses and [redacted]% occurred with the 12/32 mg step-up doses. All CRS events were Grade 1 and Grade 2, with 39.8% of patients in Cohort A experiencing a Grade 1 event, and 17.9% of patients experiencing a Grade 2 event.[83] No patients experienced Grade 3 or above CRS, and no patients permanently discontinued treatment with elranatamab as a result of CRS.

In patients who received the 12/32 mg step-up regimen, the median (range) time to onset of CRS was 2.0 days (1.0, 9.0) from the most recent dose of elranatamab.[83, 89]

Events were transient and resolved after a median of 2.0 days (1.0, 19.0). Overall, 27 (40.3%) patients who developed CRS were managed with tocilizumab or siltuximab treatment and a further 14.9% were managed with corticosteroids.

B.2.10.1.5.2. Immune-effector cell-associated neurotoxicity syndrome

Less than 5% of patients developed immune effector cell-associated neurotoxicity syndrome (ICANS) in Cohort A ([redacted]%), all of which were Grade 1 ([redacted]%) and Grade 2 ([redacted]%).[89] This included [redacted] of the [redacted] patients ([redacted]%) who received one step-up dose of 44/76 mg of elranatamab and [redacted] of the [redacted] patients ([redacted]%) who received the 12/32 mg step-up regimen. No patients experienced Grade 3 or above ICANS, and no patients permanently discontinued treatment with elranatamab as a result of ICANS.

In patients who received the 12/32 mg step-up regimen, the median (range) time to onset of ICANS following the most recent dose of elranatamab was 2.5 days (1.0, 4.0); all ICANS events resolved after a median (range) of 2.0 days (1.0, 6.0).[83, 89] In 3 ([redacted]%) patients who received the 12/32 mg step-up regimen, ICANS events were managed with support care, with 2 ([redacted]%) receiving tocilizumab, 2 ([redacted]% receiving dexamethasone, and 1 ([redacted]%) receiving levetiracetam.

B.2.10.1.5.3. Infections

Infections were reported in 69.9% of patients in Cohort A, of which 39.8% of patients experienced a Grade 3/4 infection and 6.5% of patients experienced a Grade 5 infection.[83, 84, 89] The MagnetisMM-3 trial ran during the COVID-19 pandemic, likely leading to a higher infection rate. Indeed, MM patients have been found to be at increased risk of COVID-19 infection and severe disease[95, 96]. The median time to onset of infections was [redacted] days; all infections resolved after [redacted] days. Treatment discontinuations due to infections were reported in [redacted]% of patients.[89]

The most frequently (≥ 5%) reported infections of any grade were pneumonia (16.3%), upper respiratory tract infection (16.3%), COVID-19 pneumonia ([redacted]%), sinusitis (10.6%), urinary tract infection (9.8%), sepsis (6.5%), bacteraemia (5.7%), COVID-19 ([redacted]%), and cytomegalovirus infection reactivation (5.7%).[83, 84, 89] The

following Grade 5 infections occurred (n=8, 6.5%, events could co-occur): COVID-19 pneumonia (n = 2), septic shock (n = 3), adenoviral hepatitis (n = 1), adenovirus infection (n = 1), pneumonia adenoviral (n = 1), pneumonia pseudomonal (n = 1), failure to thrive (n = 1).[89]

Treatment-related infections were reported in [redacted]% of patients, with the most commonly reported being pneumonia ([redacted]%), upper respiratory tract infection ([redacted]%), COVID-19 pneumonia ([redacted]%), and sinusitis ([redacted]%).[89]

Overall, 53 (43.1%) patients in Cohort A received intravenous immunoglobulin (IVIG) therapy.[84] Of these patients, [redacted] ([redacted]%) received IVIG as prophylaxis but did not go on to develop a bacterial infection. However, as described in Appendix M.3, UK patients cannot receive prophylactic IVIG in the current commissioning landscape.[3, 97] A further [redacted] patients received IVIG as treatment for COVID-19 but did not develop a bacterial infection. Overall, [redacted] ([redacted]%) patients received IVIG either because of a bacterial infection or developed one whilst on IVIG for a different indication. The median duration of IVIG use in this cohort was [redacted] months, mean was [redacted] months. See Appendix M.3.2.4 for further details.

B.2.10.1.6. Deaths

Death occurred in 44.7% of patients (n = 55) in Cohort A.[84] The primary cause of death was due to MM (30.1% of patients). Deaths related to elranatamab were reported in [redacted]% of patients (n = [redacted]).[89]

B.2.10.1.7. Discontinuation and dose modifications

Permanent discontinuation of elranatamab occurred in [redacted]% of patients in Cohort A due to TEAEs.[89] The majority of TEAEs leading to discontinuation occurred in [redacted] patient each, and therefore no trend was observed. Some of the more common TEAEs leading to discontinuation (≥ 1%) were neutropenia ([redacted]%), septic shock ([redacted]%) and sepsis ([redacted]%).

TEAEs leading to dose interruption of elranatamab were reported in 77.2% of patients in Cohort A, and TEAEs leading to dose reduction were reported in 28.5% of patients.[84, 89] The most common AEs leading to dose reduction (≥ 1%) were

neutropenia (15.4%), asthenia ([redacted]%), CRS ([redacted]%), thrombocytopenia ([redacted]%), fatigue ([redacted]%), leukopenia ([redacted]%), and peripheral sensory neuropathy ([redacted]%).[84, 89]

B.2.10.1.8. Safety overview

The safety data from MagnetisMM-3 showed that elranatamab monotherapy had a manageable safety profile in patients with TCR MM that was consistent with its mode of action and previous studies.[83, 84, 89]

Following treatment with elranatamab, all patients in Cohort A experienced a TEAE, with 70.7% of patients experiencing a Grade 3/4 AE.[84, 89] The most commonly reported TEAEs in Cohort A were CRS (57.7%), anaemia (48.8%), neutropenia (48.8%), diarrhoea (42.3%), fatigue (36.6%), decreased appetite (33.3%), thrombocytopenia (30.9%), and pyrexia (30.1%). The most commonly reported Grade 3/4 TEAEs were neutropenia (48.8%), anaemia (37.4%), lymphopenia (25.2%), and thrombocytopenia (23.6%).[83, 84]

No Grade 3/4 CRS events were reported, and all events were manageable with appropriate intervention, with the majority occurring with early onset.[83, 84, 89] ICANS occurred in [redacted]% of patients, and all events were Grade 1 or Grade 2. Infections were reported in [redacted]% of patients, [redacted]% were Grade 3/4, and [redacted]% of patients discontinued due to infections. Clinicians stated that infections following mAbs is well known, and they are used to managing this in clinical practice.[1]

B.2.10.2. MagnetisMM-1

A summary of safety data from MagnetisMM-1 are provided in Appendix M.6. These data were broadly consistent with those observed during the MagnetisMM-3 trial.

B.2.11. Ongoing studies

MagnetisMM-3 is currently ongoing, with an estimated study completion of December 2025. Another interim data-cut will be available in [redacted], and the final data-cut will take place in [redacted].

MagnestisMM-5 is an ongoing, 3-arm study comparing the efficacy of elranatamab monotherapy and elranatamab in combination with DARA against DARA in combination with POM and DEX in patients with RRMM. Eligible patients had

received at least three prior LoT, including lenalidomide and a PI. Patients could have previously received an anti-CD 38 mAb if this treatment had stopped > 6 months prior to enrolment and are not refractory. As such, some patients within this MagnetisMM-5 will have TCR MM, although this number is capped at ~25%. MagnetisMM-5 may therefore provide additional evidence for TCR MM patients treated with elranatamab monotherapy in the next 12 months.

Further UK specific RWE evidence plans are currently under consideration.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the clinical evidence

Elranatamab has been studied in MagnetisMM-3, an open-label, multi-centre, non-randomised Phase II study, in a heavily pre-treated TCR population in whom outcomes would be expected to be poor.[83, 84, 89] In patients with no prior BCMA-directed therapy exposure (Cohort A), the median age of patients was 68.0 years. Patients had a median of five prior LoTs; 96.7% of patients were TCR, and 42.3% were penta-refractory. In addition, over two-thirds of patients (70.7%) had at least one poor prognostic feature including EMD at baseline, high-risk cytogenetics, bone marrow plasma cell involvement, ISS Stage III disease, and ECOG performance status of 2. [83, 84, 89]

B.2.12.1.1. Elranatamab efficacy

Elranatamab provided patients in Cohort A of MagnetisMM-3 with a deep and durable response[83, 84, 89] After a median follow-up of approximately 15 months (data cut-off: 14 March 2023), the primary endpoint was met, with a significant and high ORR of 61.0% ($p < 0.0001$) achieved in Cohort A. Overall, 71.5% of responders had ongoing responses at 15 months (median DoR not reached). Furthermore, deepened and/or sustained responses were observed in the majority (80.0%) of responders who switched to Q2W dosing at 6 months. Median PFS was not reached (95% CI: 9.9, NE), and the probability of being progression-free at 15 months when treated with elranatamab was 50.9%. Furthermore, median OS was not reached (95% CI: 13.9, NE), and the probability of patients surviving at 15 months was

56.7%. Among those who achieved a CR, 89.5% of patients were progression-free at 15 months, and the probability of patients surviving was 92.6%. In addition, MRD negativity (at the threshold of 10^{-5}) was achieved in the majority of patients who achieved a CR (89.7%).[83, 84, 89]

Elranatamab demonstrated meaningful and consistent ORR benefit across prespecified subgroups in Cohort A of MagnetisMM-3 (see Section B.2.6.1).[84, 89] Despite the ORRs in patients with poor prognostic features being lower than the overall population – including those with EMD at baseline, multiple prior LoTs (more than five), R-ISS Stage III disease, high-risk cytogenetics, and penta-refractory disease – response rates in these subgroups in Cohort A were still high.

The MagnetisMM-1 trial provides supportive evidence of the longer-term benefit of elranatamab in RRMM patients (90.0% TCR), demonstrating a 2-year survival rate of 50% in a sicker, more heavily pre-treated cohort of patients who received a lower dose of elranatamab compared to patients in Cohort A of MagnetisMM-3 and to what will be used in clinical practice.[87]

B.2.12.1.2. Elranatamab quality of life

Overall, treatment with elranatamab demonstrated improvements in QoL in heavily pre-treated patients with TCR MM.[89] Patients treated with elranatamab in Cohort A of MagnetisMM-3 reported significant reductions in pain and MM disease symptoms based on the EORTC QLQ-C30 and QLQ-MY20 questionnaires.[89] A significant decrease (i.e. improvement) in EORTC QLQ-C30 pain scores was observed from Cycle 4 Day 1, which was maintained through Cycle 15 Day 1, except for a transient and non-significant increase at Cycle 9 Day 1 and Cycle 18 Day 1. A significant decrease (i.e., improvement) from baseline QLQ-MY20 disease symptom domain scores was observed starting at Cycle 5 Day 1 and was maintained through Cycle 12 Day 1 and beyond.

Patients treated with elranatamab in Cohort A of MagnetisMM-3 reported significant improvements in generic HRQL over time, based on the EQ-5D-3L.[89] There was a transient and early non-significant decrease from baseline in EQ-5D-3L scores (i.e. worsening), followed by an improvement in scores over time starting at Cycle 4 Day

1 and becoming significantly greater than baseline values at Cycle 11 Day 1. The EQ-5D VAS scores followed a similar trend to the EQ-5D-3L index scores. There was a transient decrease from baseline EQ-5D VAS scores followed by an increase in scores over time starting at Cycle 6 Day 1, reflecting an improvement in general HRQL.

Patients treated with elranatamab in Cohort A of MagnetisMM-3 reported rapid improvements in their overall disease state based on the PGI-C.[89] Assessment of patient-reported clinical status on the PGI-C scale showed that as early as Cycle 1 Day 15, approximately [redacted]% of patients reported their clinical status as either 'a little better' or 'much better' compared with baseline, which increased to more than [redacted]% by Cycle 7 Day 1.

B.2.12.1.3. Elranatamab safety

The safety data from MagnetisMM-3 and MagnetisMM-1 showed that elranatamab monotherapy had a manageable safety profile in patients with TCR MM that was consistent with its mode of action and previous studies.[84, 87, 89]

Following treatment with elranatamab, the most commonly reported TEAEs in Cohort A of MagnetisMM-3 were CRS (57.7%), anaemia (48.8%), neutropenia (48.8%), diarrhoea (42.3%), fatigue (36.6%), decreased appetite (33.3%), thrombocytopenia (30.9%), and pyrexia (30.1%).[83, 84, 89] The most commonly reported Grade 3/4 TEAEs were neutropenia (48.8%), anaemia (37.4%), lymphopenia (25.2%), and thrombocytopenia (23.6%). No events of Grade 3/4 CRS were reported, and all events were manageable with appropriate intervention, with the majority occurring with early onset. ICANS occurred in [redacted]% of patients, and all events were Grade 1 or Grade 2. Infections were reported in 69.9% of patients; 39.8% of infections were Grade 3/4, and [redacted]% of patients discontinued due to infections.[83, 84, 89] Clinicians stated that infections following mAbs are well known, and they are used to managing this in clinical practice.[1]

B.2.12.1.4. Summary of elranatamab findings

The anticipated indication is broader than the MagnetisMM-3 study population which was, as per its eligibility criteria (see Section B.2.3.1), a TCR cohort. However, the

majority of UK patients, as per the anticipated label indication, will in fact be TCR. In addition, UK clinicians have stated that the MagnetisMM-3 data is generalisable to the anticipated label population in the real world.[1-3] Therefore, the efficacy and safety data from MagnetisMM-3 supports a positive benefit–risk ratio for elranatamab in patients with relapsed and refractory MM, who have received at least three prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy, for whom no established SoC exists.[1, 16]

B.2.12.1.5. Clinical benefit of elranatamab relative to current comparator treatments

In the MAIC using the POM+DEX arm from MM-003, elranatamab treatment led to substantial improvements in PFS compared to POM+DEX across all analyses, suggesting patients treated with elranatamab will spend a longer time being progression-free compared to those treated with POM+DEX. Elranatamab treatment led to favourable OS results compared to POM+DEX in the adjusted unanchored MAIC. Statistical significance was not reached. However, as discussed in Section B.2.9.1.2, the diverging elranatamab and POM+DEX OS Kaplan-Meier curves both undermine the assumption of proportional hazards required for this test and indicate that its results will underestimate the treatment benefit of elranatamab.

In the unadjusted direct comparison using data for POM+DEX TCR patients from the ECA study, elranatamab treatment led to substantial improvements in both PFS and OS compared to POM+DEX, suggesting longer time in progression-free and survival times for patients treated with elranatamab versus POM+DEX.

B.2.12.2. Strengths and limitations of the evidence base

In MagnetisMM-3, elranatamab demonstrated significant antimyeloma activity in patients with heavily pre-treated, highly refractory TCR MM who would otherwise have a poor prognosis.[86, 89] This study is considered to be a good-quality study and is being conducted in accordance with the ethical principles of Good Clinical Practice, and the overall risk of bias is considered to be low (Section B.2.5).

MagnetisMM-3 enrolled 123 patients in Cohort A from 76 sites across 10 countries, including one site in the UK that enrolled [redacted] patient.[86, 89] UK clinicians agreed that

the patients treated in the study were generalisable to UK patients seen in clinical practice, and the outcomes measured in the trial are considered clinically important in routine practice in NHS England.[1]

A key limitation of the MagnetisMM-3 study is that it does not provide head-to-head data comparing elranatamab with POM+DEX. In the absence of head-to-head trial data, an ITC analysis, in accordance with NICE technical support guidance, has been conducted to provide an estimate of elranatamab compared with POM+DEX in the relevant patient population. However, as mentioned in Section B.2.9, the only clinical trial data available for POM+DEX were either published before the introduction of anti-CD38 mAbs, excluded patient's refractory to anti-CD38 mAbs, or began recruiting before the introduction of anti-CD38 mAbs so included very limited data. Therefore, the patient populations do not closely match the target patient population considered in this submission, as patients from the POM+DEX trials did not have TCR MM. This causes bias in the relative estimation of elranatamab's efficacy, as patients in MM-003 were not TCR, meaning efficacy outcomes from this trial will provide upper bound estimates, given that true TCR patients will have worse outcomes. To address some of these uncertainties, data from the ECA study for [redacted] UK patients with TCR MM who were treated with POM+DEX have been used as alternative efficacy data, as these patients are more comparable to the MagnetisMM-3 cohort and relevant to the decision problem.[73]

Another potential limitation of the MagnetisMM-3 study is the maturity of the survival data, as both PFS and OS have not yet been met in Cohort A. In recognition of the uncertainty within the current evidence base and the immaturity of data from the MagnetisMM-3 study, elranatamab may be considered as a candidate for managed access with the CDF. The company are developing a UK RWEstrategy for elranatamab which could inform any data collection and are considering the development of a managed access proposal. Therefore, should any identified uncertainty be resolvable through data collection, the company would consider this option at that time to allow earlier access to patients.

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

A broad, global SLR was conducted in October 2022 and updated 30 May 2023 to identify evidence on the cost-effectiveness of elranatamab and relevant economic evaluations of treatments for patients with RRMM. The SLR was subsequently filtered to select evidence to match the final NICE scope, i.e., RRMM after at least three prior therapies. The inclusion criteria for the SLR on published cost-effectiveness studies were not further restricted beyond the final NICE scope. The search identified seven unique published cost-effectiveness studies that met the inclusion criteria relevant to this submission (listed in Appendix G). In summary, none of these seven identified studies directly address the target indication of TCR. Therefore, no prior cost-effectiveness analyses exist for patients with RRMM who have received at least three prior treatments (including a PI, an IMiD and an anti-CD38 mAb) and have demonstrated disease progression on the last therapy (see Section B.1.3).[36, 48, 98] Despite the limited cost-effectiveness analyses published for the TCR patient population directly relevant to this submission, the identified studies detailed in Appendix G include models with similar partitioned survival model (PSM) structures and are in line with the longer time horizon. A detailed description of the methods, full results and quality assessment of the identified studies are reported in Appendix G.

Additional information sources informing model development for this indication included previous NICE appraisals for adults with RRMM. These appraisals are summarised in Table 20 and include the following:

- TA658[4] – Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma
- TA427[72] – Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib
- TA783[5] – Daratumumab monotherapy for treating relapsed and refractory multiple myeloma

- TA870[71] – Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma
- TA380[70] – Panobinostat for treating multiple myeloma after at least 2 previous treatments

Whilst not all of the previous NICE appraisals mentioned above are directly relevant to the patient population or comparators in this submission, the structure and approach to modelling MM has been drawn on and used to inform such key issues and assumptions for elranatamab.

Table 20: Previous NICE TAs

NICE TA:	TA380 Panobinostat for treating multiple myeloma after at least 2 previous treatments[70]	TA427 Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib[72]	TA658 Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma[4]	TA783 Daratumumab monotherapy for treating relapsed and refractory multiple myeloma[5]	TA870 Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma[71]
Year	2016	2016	2020	2022	2023
Summary of model	3-state PSM (PF, PD, death)	Semi-Markov PSM – PF (on treatment), PF (off-treatment), PD, death	4-state PSM – PF (on treatment), PF (off-treatment), PD, death	4-state PSM – PF (on treatment), PF (off-treatment), PD, death.	3-state PSM (PF, PD, death)
Patient population	Adults with RRMM who have had 2 previous treatments	Adults with RRMM who have had 3 previous treatments	Adults with RRMM who have had 3 previous treatments	Adults with RRMM who have had 3 previous treatments	Adults with RRMM who have had 2 or 3 previous treatments
Average age (years)	63	67	67	63	66
Time horizon	25 years (lifetime)	15 years (lifetime)	15 years (lifetime)	15 years (lifetime)	25 years (lifetime)
Source of efficacy data	PANORAMA-1, MM-009 and MM-010	MM-010, PANORAMA-2, MM-003, MM-002, MUK-1, supplemented Gooding and Tarant studies	ICARIA-MM, PANORAMA 2	MMY2002, MM-003, PANORAMA-2, additional evidence RWE SACT dataset available after CDF approval.	TMM1, SACT
Source of utilities	PANORAMA-1	MM-003 trial	ICARIA-MM trial	Palumbo et al. (2013)	TMM1
Source of costs	NHS reference costs	NHS reference costs	NHS reference costs	NHS reference costs	NHS reference costs

NICE TA:	TA380 Panobinostat for treating multiple myeloma after at least 2 previous treatments[70]	TA427 Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib[72]	TA658 Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma[4]	TA783 Daratumumab monotherapy for treating relapsed and refractory multiple myeloma[5]	TA870 Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma[71]
QALYs (intervention, comparator)	Redacted	Redacted	Redacted	Redacted	Redacted
Costs (currency, intervention, comparator)	Redacted	Redacted	Redacted	Redacted	Redacted
FAD outcome	Recommended	Recommended	Recommended CDF	Recommended	Recommended CDF

Key: CDF, Cancer Drugs Fund; FAD, final appraisal determination; NHS, National Health Service; PD, progressed disease; PF, progression-free; PSM, partitioned survival model; QALY, quality-adjusted life year; SACT, systemic anti-cancer therapy; TA, technology appraisal.

B.3.2. Economic analysis

A de novo four-health-state PSM was developed to evaluate the cost-effectiveness of elranatamab versus POM+DEX in patients with RRMM who have received at least three prior treatments (including a PI, an IMiD and an anti-CD38 mAb) and who have demonstrated disease progression on the last therapy, from the perspective of the UK NHS.

The model structure was informed by the review of existing models in this indication and is consistent with those used in previous NICE technology appraisals – including TA658[4] and TA783[5], which both used PSMs to directly capture key clinical outcomes of PFS, OS and time to treatment discontinuation (TTD) from pivotal trial data (see model structure; Section B.3.2.2).

B.3.2.1. Patient population

In line with the anticipated marketing authorisation, the cost-effectiveness analysis evaluated elranatamab for the treatment of adult patients with RRMM who have received at least three prior therapies, including one PI, one IMiD and one anti-CD38 mAb (see Section B.2.3 for a full description of the technology under evaluation).

Data from patients who received no prior BCMA-directed therapy are used to inform model clinical outcomes. This corresponds to Cohort A of the prospective, open-label MagnetisMM-3 trial.[99] As discussed in Section B.2.3, no BCMA-targeted therapies are currently reimbursed for use in the UK; therefore, Cohort A (BCMA-naïve) is the most relevant patient population and is the focus of this submission, in line with the decision problem.

Baseline patient characteristics are presented in Table 21 (for full model inputs relating to patient characteristics, refer to Section B.2.3.1). All baseline characteristics are based on information derived from patients receiving elranatamab from MagnetisMM-3.

Table 21: Summary of patient characteristics

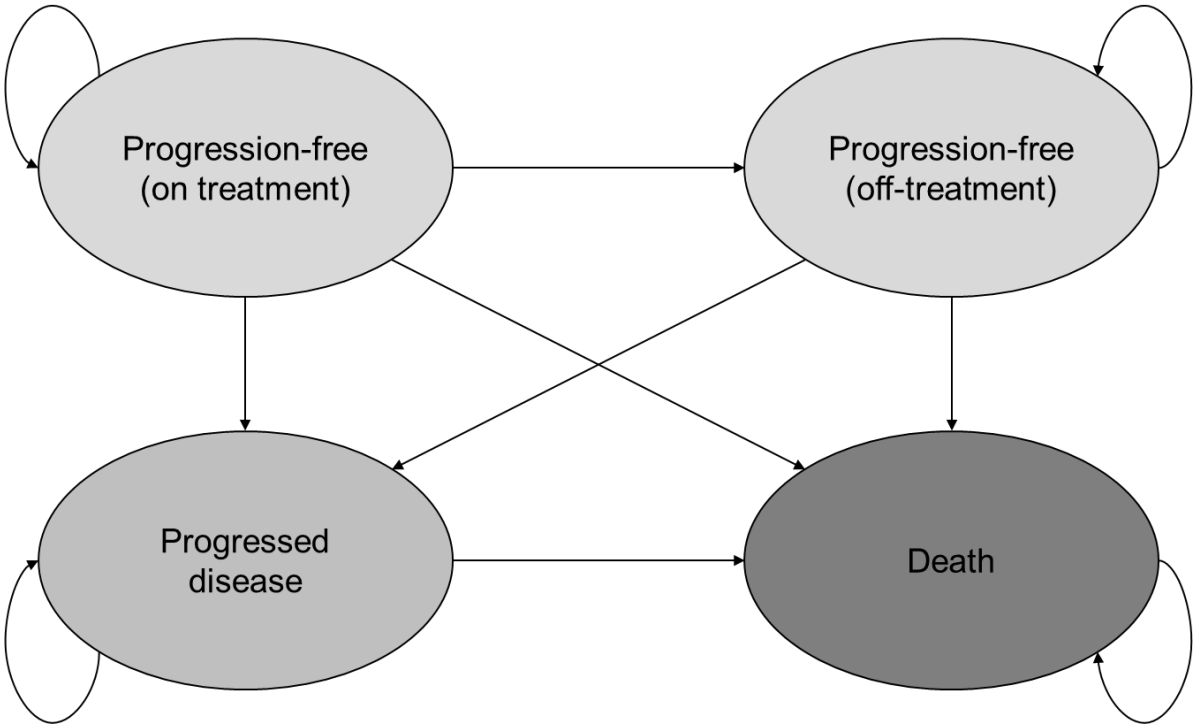
Characteristic	Cohort A (n = 123)	Source
Age, years, mean (SD)	67.1 (9.45)	MagnetisMM-3, 15-month data. CSR Table 14.1.2.1.
Percentage male, %	55.3%	
Weight, kg	74.05	
Height, cm	166.47	
Body surface area, m²	1.85	
Key: CSR, clinical study report; SD, standard deviation.		

B.3.2.2. Model structure

The economic model developed to assess the cost-effectiveness of elranatamab in this indication follows a partitioned survival approach. PSMs are widely used in oncology modelling, and previous NICE appraisals in MM have included similar area-under-the-curve approaches to capture treatment benefits in terms of both delaying time to disease progression and improving survival. TA427, TA658 and TA783 included four health states: progression-free (PF; one state for on treatment and one state for off treatment), post-progression (progressed disease [PD]) and death, whereby treatment-specific utilities were implemented in the pre-progression states. However, we assume pre-progression utility to be equal in the base case. The model allows for the possibility that patients might stop therapy before disease progression and thus a similar four-state model has been implemented, with different utility options for on and off treatment explored under scenario analysis (see Section B.3.11.3).[4, 5, 70-72]

Four health states (including PF on treatment, PF off treatment, PD and dead) were informed for the three time-to-event endpoints, PFS, TTD and OS, which were derived directly from the MagnetisMM-3 trial for elranatamab and ITCs for POM-DEX (Section B.3.3). Figure 23 illustrates the health states and possible transitions in each model treatment arm. The health states capture disease progression status (PF or PD) and treatment status (on or off treatment). Treatment-dependent costs and health outcomes associated with each arm are captured within each mutually exclusive health state.

Figure 23: Economic model structure



Patients with RRMM enter the model in the PF (on treatment) state and are assumed to be on treatment. In each model cycle:

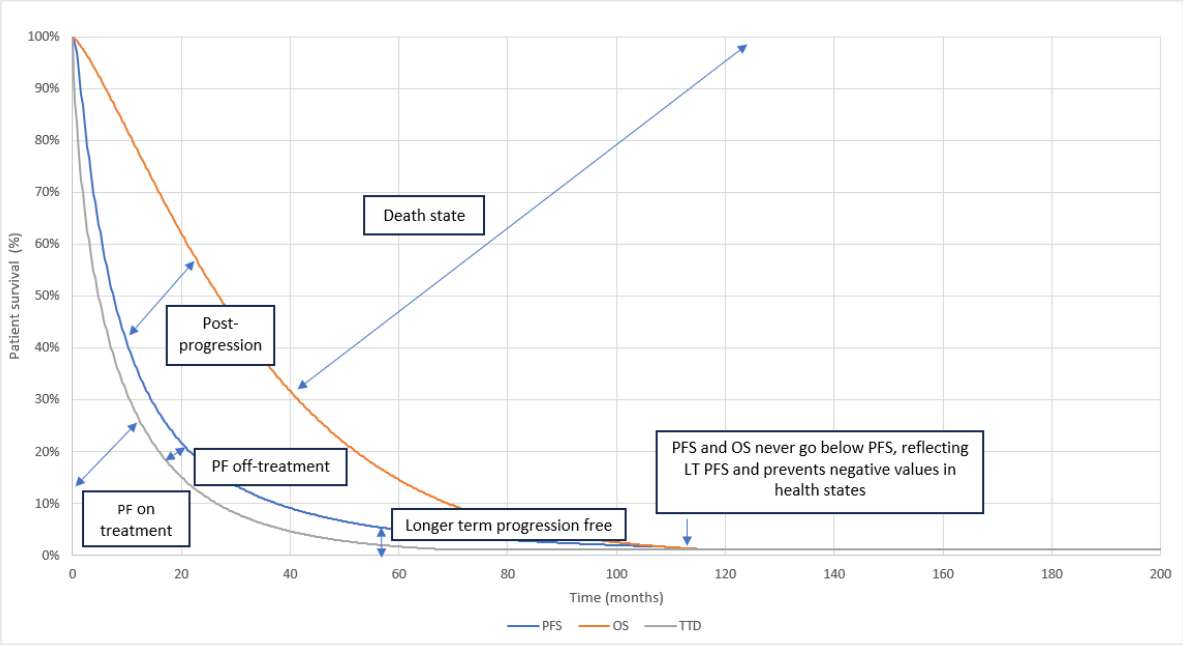
- Those in the PF (on treatment) state can either remain in the PF (on treatment) state or move into the PF (off treatment) state, PD state or death state
- Those in the PF (off treatment) state can remain in the PF (off treatment) state or move into the PD state or death state
- Those in the PD state can remain in the PD state or move into the death state
- Death is included as an absorbing health state

The four health states in the model are mutually exclusive and fully exhaustive; patients can only occupy one of the states at any given point in time.

As outlined in the NICE Decision Support Unit (DSU) review of partitioned survival analysis (NICE DSU Technical Support Document [TSD] 19), the partitioned survival method uses PFS and OS curves to directly estimate the proportion of patients occupying each state over time.[100] The proportion of patients occupying the PF (on treatment) state is estimated directly from the cumulative survival probabilities for TTD; the proportion of patients occupying the PF (off treatment) state is estimated

from the cumulative survival of PFS minus the cumulative survival of TTD; and the proportion of patients occupying the PD state is estimated from the cumulative survival of OS minus the cumulative survival of PFS. The death health state captures patient deaths from both cancer- and non-cancer-related causes; the proportion of patients occupying the death state is estimated as one minus the cumulative survival of OS. Note: As discussed in B.3.3.5.2, where evidence demonstrates patients may be on-treatment post-progression, the TTD curve is modelled independently. An illustration of the partitioned survival calculation method is presented in Figure 24.

Figure 24: Illustration of the partitioned survival calculation



Key: LT, long term; overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

Several adjustments were implemented to ensure consistency in logic and reasoning over a long-term time perspective:

- Patient mortality risks were aligned with the mortality risk of the general population, sourced from the latest available Office for National Statistics Life Tables[101]
- Given that patients face significantly higher mortality risks compared with the general population and patients in earlier stages of RRMM, a time-varying

standardised mortality ratio (SMR) was applied to the mortality risk of the general population (see Section B.3.3.2.3). A constant SMR is explored under scenario analysis (see Section B.3.11.3)

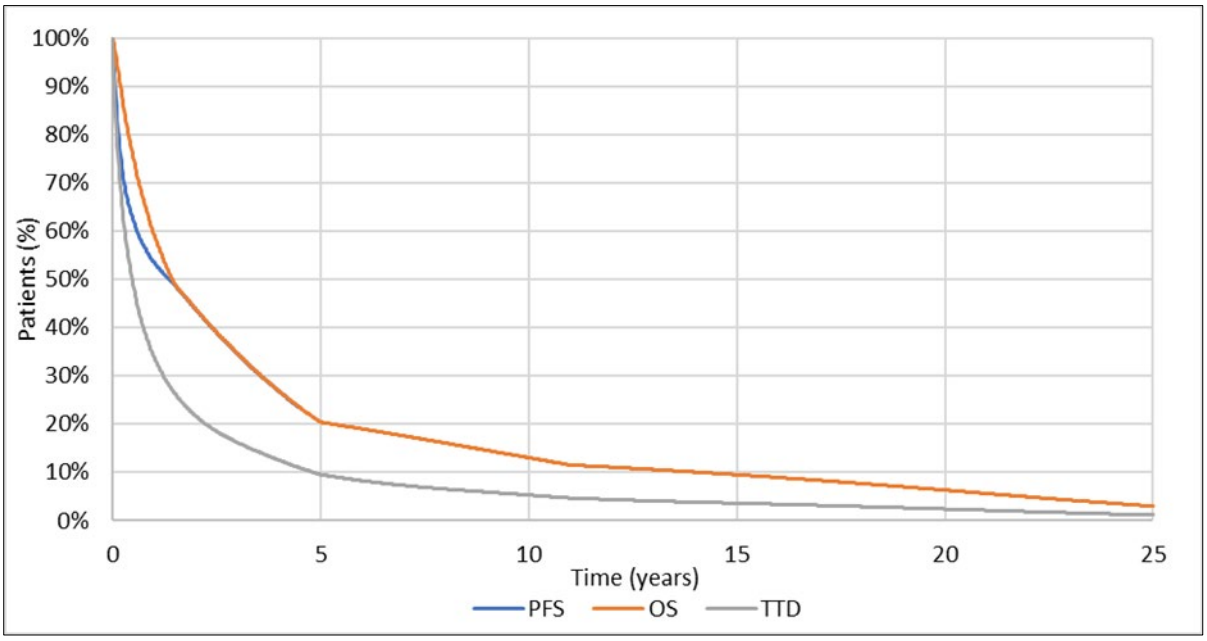
In the following sections (B.3.3.2 to B.3.3.5.3.), economic analyses use the survival inputs derived from an ITC based on an MAIC analysis comparing MagnetisMM-3 (Cohort A) with the efficacy of POM+DEX from MM-003. Typical assumptions of partitioned survival modelling consider independence of PFS and OS curves, along with trends in hazards over trial periods that are generalisable over the extrapolation period (see NICE TSD 19).[100] However, as will be discussed, neither assumption holds when extrapolating OS and PFS outcomes for elranatamab from Cohort A of the MagnetisMM-003 trial.

Section B.3.3.2.3 illustrates the OS and PFS Kaplan–Meier curves for elranatamab from Cohort A of MagnetisMM-3. The curves are very close to each other nearer the end of the available trial follow-up after 18 months. This may be explained by the greater number of events in the PFS curve which, unlike the OS Kaplan–Meier curve, has had time to plateau during trial follow-up. The converging OS and PFS Kaplan–Meier curves mean that, when using the traditional logic (of the OS extrapolation dominating the PFS extrapolation), extrapolated curves rapidly cross (see Figure 36), violating the key assumptions underpinning partitioned survival modelling mentioned in NICE TSD 19.[100] Assuming traditional extrapolation methods also ignores the PFS evidence from MagnetisMM-3 and MagnetisMM-1 in which a proportion of patients enter a deep and durable response as evidenced in Section B.2.6.1.2.3 and B.2.6.2.

To avoid the eventual convergence of the curves and give precedence to PFS evidence, which gives more plausible long-term extrapolations, Section B.3.2.2 discusses a switch in the logic applied in the decision model, whereby drawing on the approach adopted by the York External Assessment Group (EAG) in TA559 [102], we give priority to the extrapolation of the PFS data rather than the OS data. The plateauing PFS cohort are interpreted as the group with a deep and durable response. When extrapolating the PFS data beyond the trial follow-up period, this group is assumed to progress or die according to whichever hazard is higher of the

best-fitting parametric distribution (discussed further in Section B.3.3) and the SMR-adjusted general population mortality rate. See Figure 25 for PSM calculations for elranatamab, based on the above assumptions.

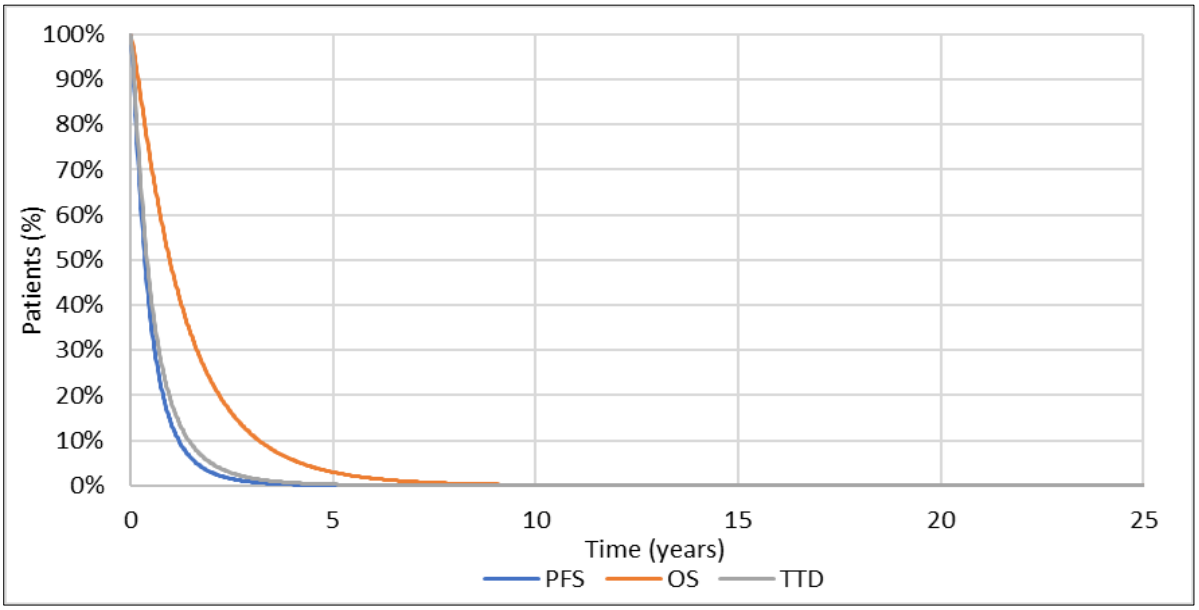
Figure 25: Partitioned survival illustration for elranatamab



Key: OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

In section B.3.3.3 we outline how a traditional extrapolation approach is adopted for POM+DEX to ensure that PFS cannot exceed OS. The reasoning for selecting different assumptions for elranatamab and POM+DEX is because the issues of curve convergence between OS and PFS do not appear for POM+DEX, and there is no evidence of a deep and durable response from the MAIC or ECA data (Figure 26). Therefore, this directly opposed the curve trends observed for elranatamab, thus the assumption of PFS dominated OS is superfluous for the POM+DEX arm in the economic model as PFS has never exceeded OS.

Figure 26: Partitioned survival illustration, PFS and OS, for POM+DEX (MM-003)



Key: OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; TTD, time to treatment discontinuation.

B.3.2.2.1. General settings

The cohort model structure appropriately captures survival and HRQL implications for patients, and cost and resource use implications for the NHS (as reported in Sections B.3.4 and B.3.5, respectively), in line with the NICE reference case.[103]

The model includes costs for medications, medication administration and dispensing costs, follow-up, monitoring, terminal care costs, and costs of treatment of AEs, all of which were based on published sources. Utility values for the different health states in the model were also based on data from MagnetisMM-3.[99] For POM+DEX, estimates were based on a MAIC from the MM-003 trial. These analyses are further supported via the POM+DEX-treated patients from the ECA study (Section B.3.3).

All outcomes were evaluated over a 25-year time horizon, beginning with the start of treatment, in line with the models included in TA380[70] and TA870[71]. A shorter time horizon of 15 year was utilised in TA427[72], TA658[4] and TA783[5], however, a small proportion of patients would be expected to survive up to 25 years, in line with clinical expert opinion. Therefore to sufficiently approximate all patients over a lifetime projection in the populations of interest 25 years was utilised in the base-

case analysis.[3] Both 20-year and 15-year time horizons are explored under scenario analyses (see Section B.3.11.3).

A 1-week cycle length is considered sufficiently short enough to accurately capture key clinical outcomes and dosing regimens. Given the short cycle length, a half-cycle correction is not applied to any cost or health outcomes. Both costs and effects were discounted at a rate of 3.5% per year, in line with the NICE reference case.[103]

Table 22 summarises key features of the de novo economic analysis. Sources of utilities and costs are discussed further in Section B.3.4 and Section B.3.5, respectively.

Table 22: Features of the economic analysis

Factor	Chosen values	Justification
Population and comparators	3L+ TCR POM+DEX	See Section B.1.3.3.6
Model structure	Four-state PSM	In line with the NICE reference case, which is a partitioned survival structure used in most oncology submissions.[103]
Health states	PF (on treatment), PF (off-treatment), PD, Death	
Time horizon	25 years (lifetime)	NICE reference case recommends a lifetime time horizon[103] and accepted by NICE in TA380[70] and TA870[71]
Model cycle length	1 week	This allows the model to capture the differences in treatment cycle length across elranatamab and POM+DEX. In addition, a short cycle length captures the rapid progression of RRMM.
Source of utilities	Utility data sourced from MagnetisMM-3 and MM-003 trial[99, 104]	NICE reference case.[103]
Source of costs	Conventional sources relevant to the NHS (e.g., MIMS, NHS reference costs, BNF) as well as other oncology submissions.	NICE reference case.[103]

Key: 3L+, third-line or later; BNF, British National Formulary; DEX, dexamethasone; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; POM, pomalidomide; PSM, partitioned survival model; RRMM, relapsed/refractory multiple myeloma; TCR, triple class refractory.

B.3.2.3. Intervention technology: elranatamab

The intervention, elranatamab, is implemented within the model as per its marketing authorisation and given according to the recommended dosing regimen.
Elranatamab is administered SC once per week (after a two-dose step-up regimen in the first week) based on the following schedule:

- Elranatamab 12 mg on Day 1, Week 1
- Elranatamab 32 mg on Day 4, Week 1
- Followed by a full treatment dose of elranatamab 76 mg weekly, from Week 2 to Week 24, given by SC injection[16]
- For patients who have received at least 24 weeks of treatment with elranatamab, and who have achieved a response, the dosing interval should transition to a Q2W schedule
- Treatment with elranatamab should be continued until disease progression or unacceptable toxicity

The MagnetisMM-3 protocol states that after the initial first cycle step-up dosing, once weekly (QW) dosing should be given for at least 24 weeks (6 dosing cycles). For patients who have received at least 24 weeks of treatment with elranatamab and have achieved a response (partial response or better) persisting for at least 2 months, the dose interval will be changed from QW to Q2W. The SmPC will state that, after at least 24 weeks, if patients have achieved a response they should switch to Q2W dosing[16]. Thus the SmPC criteria is more permissive, with regards to the Q2W de-escalation, than the MagnetisMM-3 protocol.

B.3.2.3.1. Elranatamab premedication

As described in Section B.2.3.1, premedication should be used before the first three doses of elranatamab infusion to reduce the risk and severity of CRS. In line with the SmPC[16], patients should be monitored for signs and symptoms of CRS and ICANS for 48 hours after administration of each of the two step-up doses, and instructed to remain within the proximity of a healthcare facility. The following pre-treatment medicinal products should be administered approximately 1 hour prior to

elranatamab in the dosing schedule, which includes step-up Dose 1, step-up Dose 2, and the first full treatment dose[16]:

- Paracetamol 500 mg orally (or equivalent)
- Dexamethasone 20 mg orally or intravenously (or equivalent)
- Diphenhydramine 25 mg orally (or equivalent)

B.3.2.4. Comparator: pomalidomide in combination with dexamethasone (POM+DEX)

As outlined in Section B.1.3.3.6, the relevant comparator is POM+DEX which is modelled as per its marketing authorisation and licensed dosing regimen until the end of the TTD period (Section B.3.3.5).

The treatment dosing is as follows:

- Dexamethasone 40 mg (or 20 mg if the patient is ≥ 75 years old), administered orally or intravenously, on Days 1, 8, 15 and 22
- Pomalidomide 4 mg orally, on Days 1 to 21 in a 28-day cycle

The comparator in the model base case is consistent with the NICE scope[15] for the evaluation of elranatamab in RRMM, and is the treatment that is most likely to be replaced by the introduction of elranatamab.

B.3.3. Clinical parameters and variables

Data from the pivotal Phase II MagnetisMM-3 trial were used to inform clinical outcomes for elranatamab. As MagnetisMM-3 is an ongoing study, the model has used clinical evidence from the latest data-cut on 14 March 2023 (median on-study follow-up 15 months for Cohort A).

A summary of the modelled baseline patient characteristics for Cohort A is presented in Section B.3.2.1. The baseline characteristics used to inform model calculations are presented in Table 5.

The following clinical outcomes are included in the economic model:

- PFS

- OS
- TTD
- HRQL
- AEs

B.3.3.1. Data sources

As noted in Section B.2.3.1, data from Cohort A of the MagnetisMM-3 trial were used to inform clinical outcomes for elranatamab. For patients with a confirmed objective response, as assessed by the BICR and investigator as per the IMWG criteria, deep and durable responses were achieved with elranatamab monotherapy.[83, 89] However, survival data from the trial were not mature, with median PFS and median OS not reached.

As MagnetisMM-3 was a single-arm trial (with two cohorts), ITCs were conducted to compare the efficacy of elranatamab – as observed in MagnetisMM-3 (Cohort A)[99] – with the efficacy of POM+DEX from MM-003, an open-label, Phase III, randomised controlled trial used to compare POM+DEX with dexamethasone alone (Section B.2.9).[104]

The MM-003 study was chosen for the analysis as it provides data from the relevant patient population, with a patient population comparable to MagnetisMM-3, both with median prior five lines of treatment. Additionally, the definitions of OS and PFS were similar between the two trials; therefore, they could be compared as endpoints in the indirect comparative analysis and be included in the economic analysis. Finally, as discussed in Section B.2.9, the analysis was able to adjust for as many as possible PV and EM variables as identified by experts, to provide as robust a comparison as possible. See Appendix D for further details on ITCs.

Given the limitations within the MAIC described in Section B.2.9.3.1, an alternative approach is provided by the ECA (described in Section B.2.9.2 and Appendix D). Overall, [redacted] patients treated with POM+DEX were included in the analysis. Table 23 summarises all the data sources considered in the economic model both as base-case and under scenario analysis.

Table 23: Summary of comparator data sources

Model	Source	Study design	Population	Sample size	Median follow up	Data available	Methodology	Justification
Base case	MM-003	RCT	RRMM pts received at least 2 lines of lenalidomide and bortezomib, alone or in combination	POM+DEX arm n = 302	Median follow-up 10.0 months	PFS and OS	MAIC	Provides the most relevant comparator population from an RCT
Scenario	ECA	Retrospective RWE study of 4 NHS centres in the UK	RRMM patients who received at least three prior treatments, including a PI, an IMiD, and an anti-CD38 mAb and demonstrated disease progression on the last therapy	POM+DEX arm n=[redacted]	8.01 months (range: 0.03-25.1)	PFS, OS and TTD	Unadjusted direct comparison	Provides a real-world comparator population

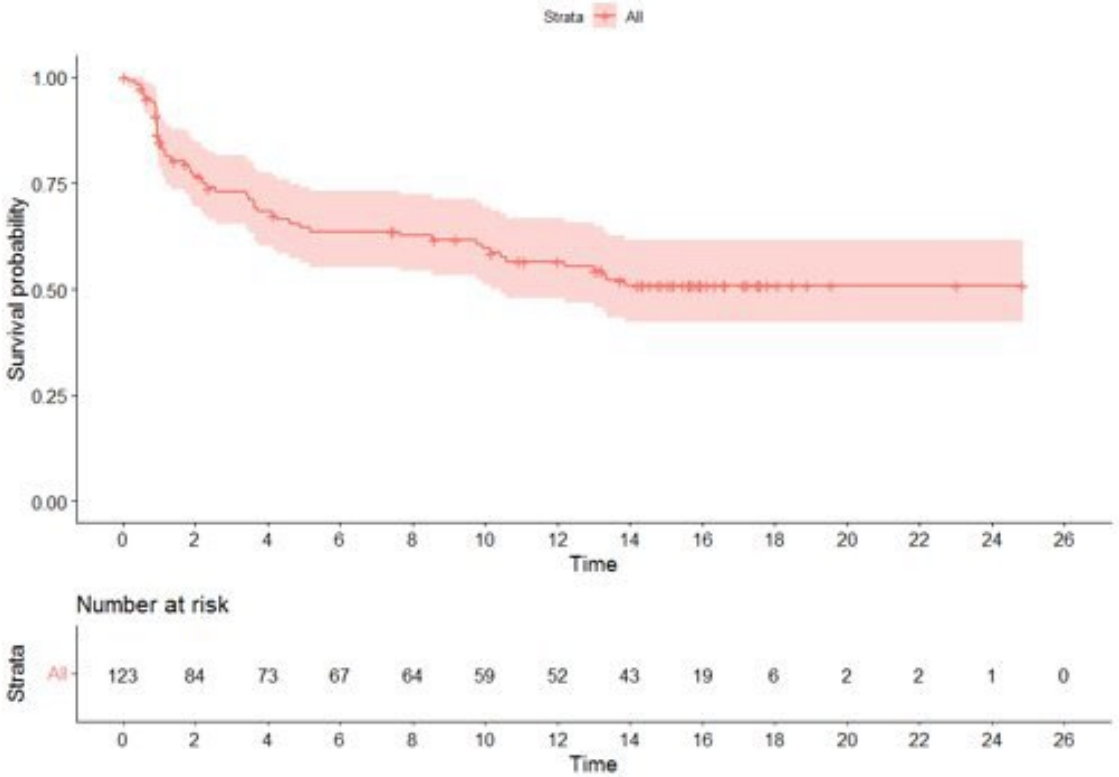
Key: DEX, dexamethasone; ECA, external control arm; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; POM, pomalidomide; RCT, randomised controlled trial; RRMM, relapsed/refractory multiple myeloma; RWE, real world evidence; TTD, time to discontinuation.

B.3.3.2. Elranatamab efficacy

B.3.3.2.1. Elranatamab progression-free survival

The following section describes the PFS by BICR outcome (defined in MagnetisMM-3 as the time from the date of first dose until confirmed PD per IMWG criteria, or death due to any cause). The PFS Kaplan–Meier data in Figure 27Figure 27 are based on the 15-month data cut-off Cohort A patients in MagnetisMM-3 and display the corresponding underlying number of patients at risk over time. The Kaplan–Meier curve shows that median PFS was not met. As noted in Section B.2.6.1.2.5, among those who achieved a CR, 89.5% of patients treated with elranatamab were progression-free at 15 months.

Figure 27: Kaplan–Meier plot curve of PFS by BICR in Cohort A of MagnetisMM-3 15-month data-cut (Safety Analysis Set)

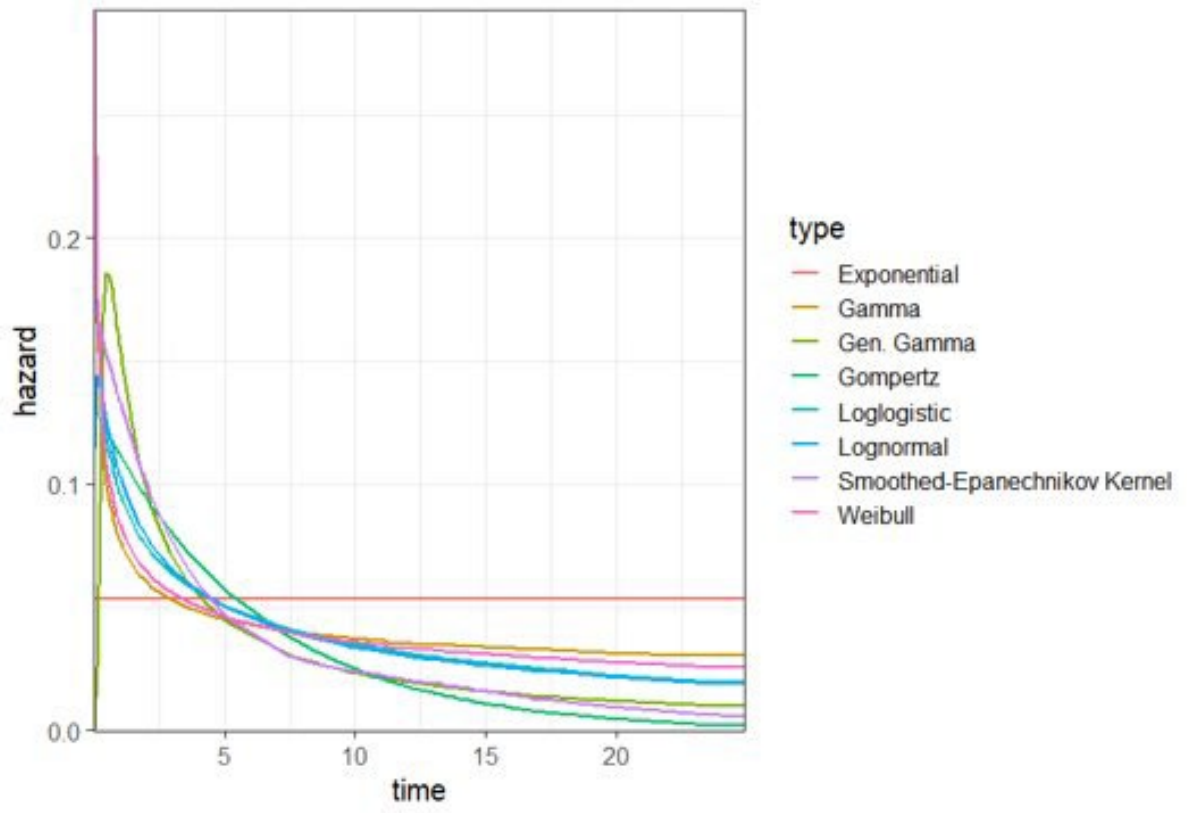


Key: BICR, blinded independent central review; PFS, progression-free survival.

Extrapolation of PFS

The PFS data suggest that treatment with elranatamab is associated with durable and sustained long-term PFS l for a proportion of patients. Such sustained response represents a deviation from the monotonic hazards function over time and the standard parametric distributions may not accurately reflect this expected survival profile. Smoothed-Epanechnikov Kernel plots were fitted to determine the hazard plots over the trial period (Figure 28Figure 28). The smoothed-Epanechnikov Kernel hazard shows a small reduction in hazards between Months 6–8, which are suggestive of the deep and durable response. However, exploration of more complex parametric distributions, with the first step assessing splines, yielded no improvement in statistical fit. Therefore, the use of splines (and more advanced methods) cannot be justified and was not explored any further. The generalised gamma curve hazard is the parametric curve which visually fits the smoothed-Epanechnikov Kernel hazard the best.

Figure 28: Elranatamab hazard function for PFS-fitted parametric models



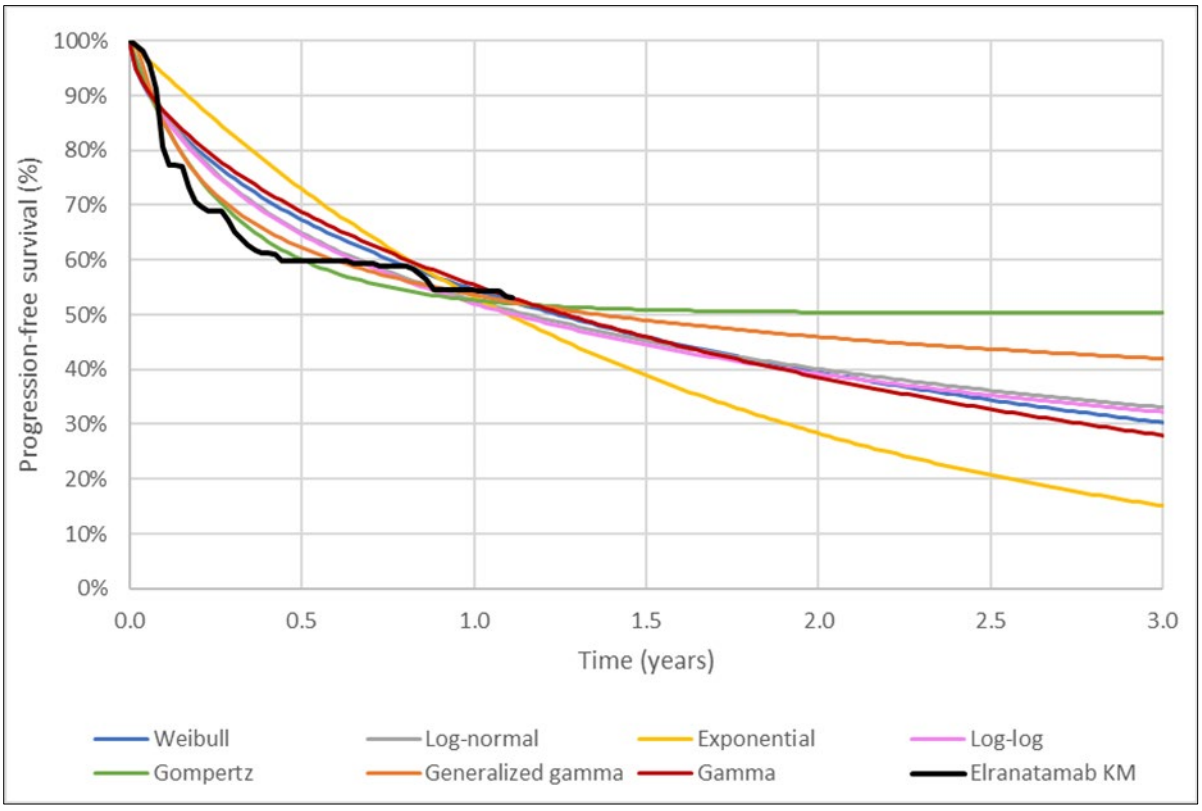
Key: PFS, progression-free survival.

Standard parametric fits were applied on the Kaplan–Meier curves based on the MagnetisMM-3 15-month data. We evaluated the standard parametric survival models suggested by NICE DSU TSD 14[105] (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma) using the following criteria:

- Statistical fit using the Akaike information criterion (AIC) and Bayesian information criterion (BIC)
- Visual fit and clinical plausibility of the fitted values to the observed Kaplan–Meier data
- Clinical plausibility of the long-term extrapolation beyond the extent of the Kaplan–Meier data before and after the application of the SMR

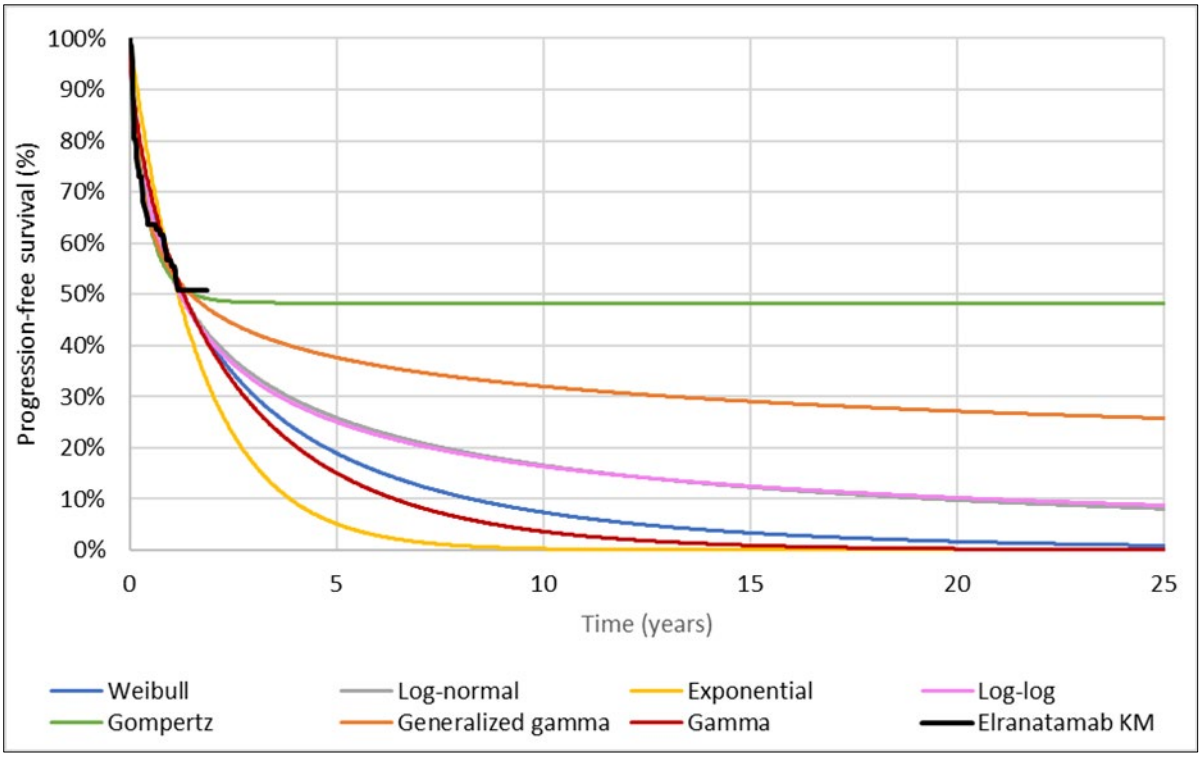
The range of parametric model fits to PFS Kaplan–Meier data is shown in Figure 29 (3-year time horizon) and Figure 30 (lifetime time horizon) for elranatamab. These standard parametric distributions were compared to the PFS Kaplan–Meier data, with statistical fit AIC and BIC values provided in Table 24.

Figure 29: Standard parametric fits of PFS, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (3-year time horizon)



Key: KM, Kaplan–Meier; PFS, progression-free survival.

Figure 30: Standard parametric fits of PFS, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (lifetime time horizon)



Key: KM, Kaplan–Meier; PFS, progression-free survival.

Table 24: AIC and BIC statistics of the standard parametric fits of PFS, elranatamab (MagnetisMM-3 15-month data-cut)

Parametric model	AIC	BIC	Average	Rank
Weibull	413.29	418.92	416.11	5
Log-normal	403.92	409.54	406.73	2
Exponential	426.76	429.58	428.17	7
Log-logistic	408.94	414.56	411.75	4
Gompertz	403.92	409.54	406.73	3
Generalised gamma	396.88	405.32	401.10	1
Gamma	415.67	421.30	418.49	6

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

AIC/BIC indicate that the generalised gamma and Gompertz are the only models which provide a reasonable fit to the observed data, which is also confirmed when considering the visual fit, with all other parametric models which substantially

overestimate survival up to approximately 10 months. The Gompertz slightly underestimates the observed data from around 6 to 10 months. The generalised gamma is the only model that provides a suitable fit to the observed data.

This noticeable difference in fit to the observed data is evident in the disparity in the extrapolations . The largest difference observed when comparing the Gompertz curve, which plateaus compared to the exponential curve, which when extrapolated results in survival that appears implausibly low.

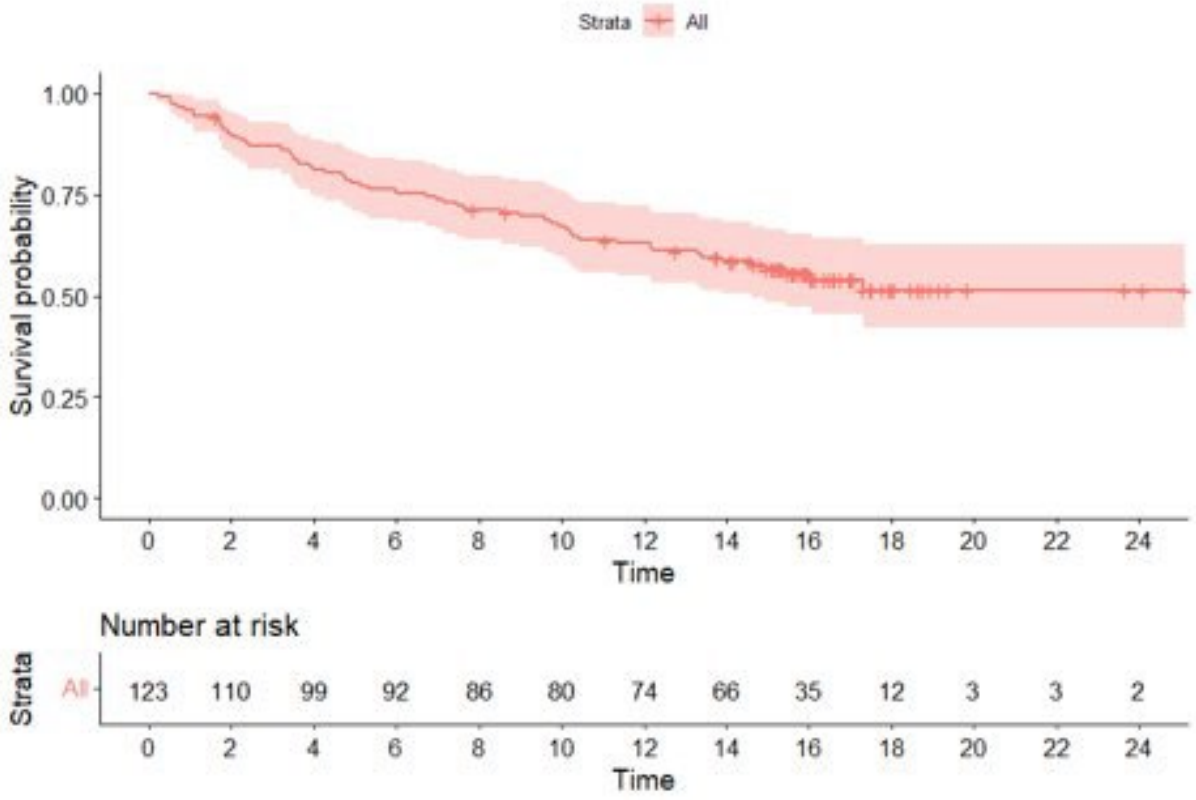
However, as detailed in NICE's DSU TSD 14[105], AIC/BIC tests are based only upon the relative fit of parametric models to the observed data and do not provide an accurate description of data fitted beyond the observed trial follow-up; they are therefore of limited value to immature data.

Given the maturity of the elranatamab efficacy data, the extrapolation of PFS has resulted in unrealistically optimistic extrapolations for many curves over the long-term. Clinicians estimate a 5-year survival estimate of between 10% to 20% and less than 15% at 10 years. However, given the evidence of a deep and durable response from the observed hazard profile, some flattening of the curve would be expected. Therefore, adjustments were required, which are discussed further in the base case survival selections in B.3.3.2.3

B.3.3.2.2. Elranatamab overall survival

The following section describes OS (defined in MagnetisMM-3 as the time from the date of first dose until death due to any cause). The OS Kaplan–Meier data at the data cut-off date of 14 March 2023 are presented in Figure 31 for Cohort A patients in MagnetisMM-3 and the corresponding underlying number of patients at risk over time. The Kaplan–Meier curve shows that median OS was not met, with a total of 55 OS events (44.7% of patients) observed. The number of OS events is low, which is expected given the deep and durable response observed (see Figure 31).

Figure 31: Kaplan–Meier curve for OS in Cohort A of MagnetisMM-3 15-month data-cut



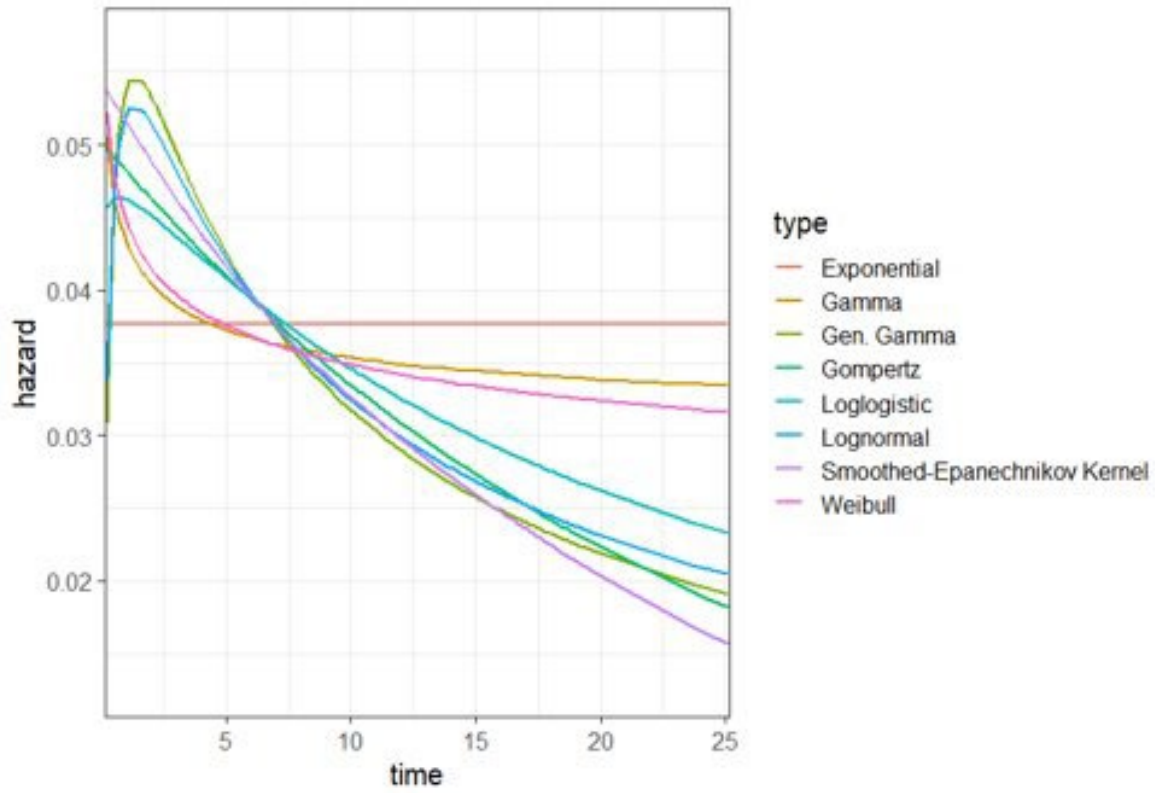
Key: OS, overall survival.

Extrapolation of OS

For elranatamab, NICE DSU TSD 21 guidance[106] states that more complex survival curves should be considered when hazard functions are observed or expected to have complex shapes in the longer-term. Flexible parametric models such as spline models represent one tool that can potentially be used to characterise more complex hazard functions. Smoothed hazard plots enable the comparison of the hazard rate of the parametric distributions against the smoothed hazards of the Kaplan–Meier data to be visualised, therefore determining whether the parametric distributions are clinically plausible compared to the Kaplan–Meier data. If the hazard function does not show a non-monotonic trend, then a spline can be fitted. Figure 32 shows how the smoothed-Epanechnikov Kernel hazards plot method was explored. This clearly demonstrates an unchanging, decreasing hazard over time. Therefore, the use of splines cannot be justified, and was not explored any further. Generalised gamma or

Gompertz extrapolations fit the elranatamab OS data best over the trial period, observed by the similar hazard profiles.

Figure 32: Hazard function for OS fitted parametric models, elranatamab



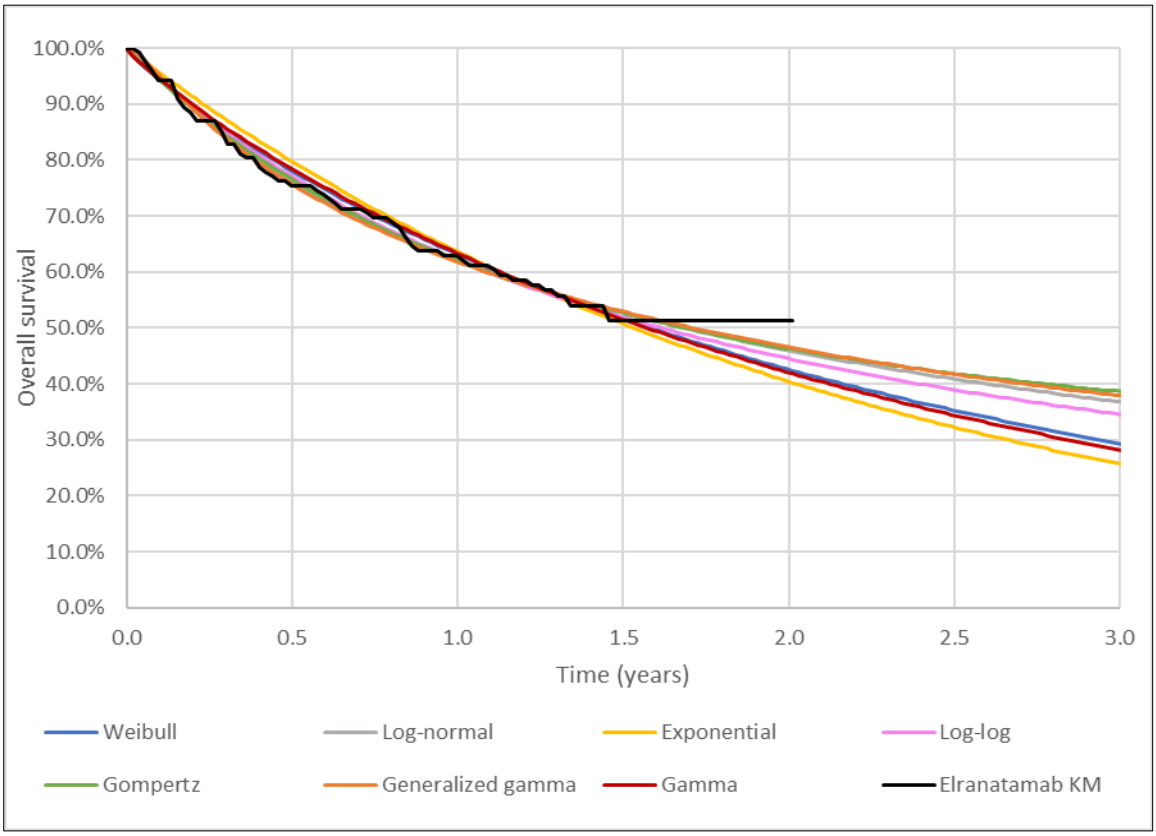
Key: OS, overall survival.

Standard parametric survival models were fitted according to NICE DSU TSD 14[105] as detailed in Section B.3.3.2.

The range of parametric model fits to OS Kaplan–Meier data is shown in Figure 33 (3-year time horizon) and Figure 34 for elranatamab, adjusting for general population mortality.

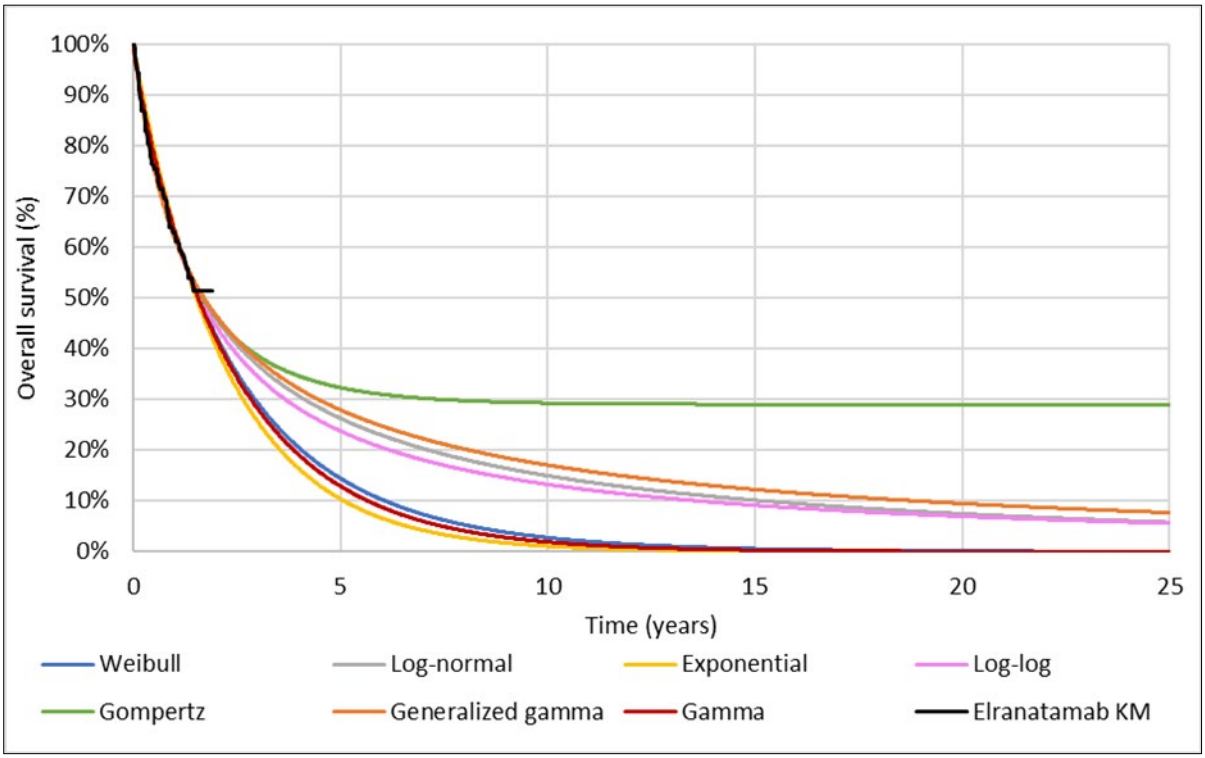
AIC and BIC values are provided for the standard parametric extrapolations in Table 25.

Figure 33: Standard parametric fits of OS, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (3-year time horizon)



Key: KM, Kaplan–Meier; OS, overall survival.

Figure 34: Standard parametric fits of OS, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (lifetime time horizon)



Key: KM, Kaplan–Meier; OS, overall survival.

Table 25: AIC and BIC statistics of the standard parametric fits of OS, elranatamab (MagnetisMM-3 15-month data-cut)

Parametric model	AIC	BIC	Average	Rank
Weibull	473.70	479.32	476.51	5
Log-normal	470.89	476.52	473.71	1
Exponential	472.57	475.39	473.98	2
Log-logistic	472.38	478.01	475.20	3
Gompertz	472.43	478.05	475.24	4
Generalised gamma	472.83	481.27	477.05	7
Gamma	473.95	479.58	476.77	6
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.				

In contrast to PFS, all parametric models had similar statistical (AIC/BIC) and visual fits (Figure 33) to the observed data. Nonetheless, the generalised gamma does appear to have marginally better fit to the observed data (Figure 31), being the lowest curve between approximately 2 and 12 months and adjusting to the plateau beyond 12 months.

However, there were disparities between extrapolations, though to a lesser extent than the PFS data. Similar to the PFS, the largest difference is observed when comparing the Gompertz curve, which plateaus (at a later stage when compared to the PFS) when extrapolated, compared to the exponential curve which results in an extrapolation of survival that appears implausibly low, when considering landmark survival rates from clinical opinion[3]. Both the Weibull and Gamma similarly resulted in implausibly low extrapolations.

However, as with PFS, given the maturity of the elranatamab efficacy data, other extrapolations resulted in unrealistically optimistic OS over the long-term. Clinicians supported the same reasoning for OS as with PFS and noted that survival estimates at 10 years of 3% were harsh on not plausible, but that estimates of 17% were not implausible. Again, given the evidence of a deep and durable response from the observed hazard profile, some flattening of the curve would be expected. Therefore, adjustments were required, which are discussed further in the base case survival selections in B.3.3.2.3

B.3.3.2.3. Base case elranatamab PFS and OS selection

The change in hazards over time is indicative of a deep and durable response as observed in the PFS outcome (Figure 28). However, sufficient time has not elapsed for this to be observed in the OS outcome (Figure 9). As described in Section B.2.6.1.2.4, elranatamab has a novel mechanism of action, which redirects cytotoxic T lymphocytes against the myeloma cells. A regular dosing schedule may explain the observed deep and durable responses.

As discussed in Section B.3.2.2, if using independent extrapolations of PFS and OS as recommended in conventional partitioned survival analysis, the model predicts negative numbers occupying the PF off treatment health state. As shown in Figure 35, the elranatamab and OS and PFS Kaplan–Meier curves are very close at the end of trial follow-up. The PFS curve had had a greater number of events, compared to the OS curve, allowing us to observe a plateau during trial follow-up. Whereas the plateau in the OS Kaplan–Meier curve is only beginning to emerge. The result of the converging OS and PFS Kaplan–Meier curves is that if we use the traditional logic (of the OS extrapolation dominating the PFS extrapolation) the base case selected

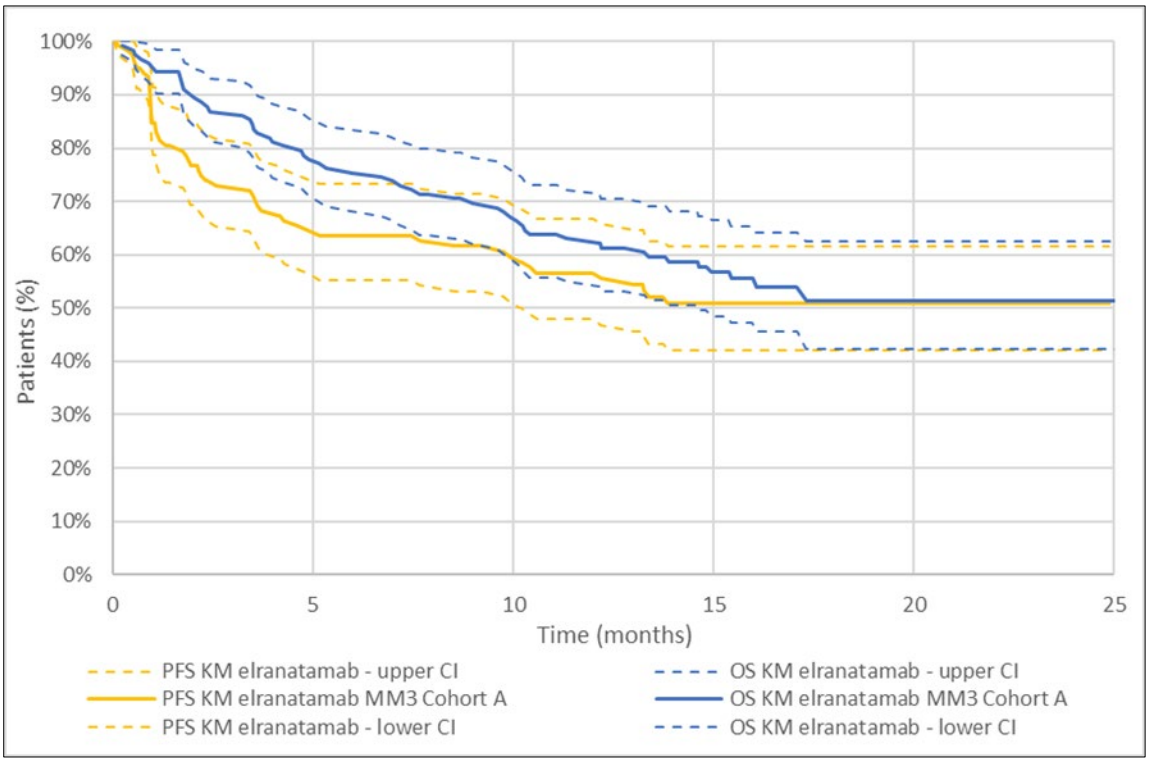
curves for PFS and OS, the PFS extrapolated curve crosses the OS curve after a brief period, at approximately 2 years (within 6 months of the observed Kaplan–Meier data) as shown inside the red circle in Figure 36 (short time horizon) and in Figure 37 (lifetime time horizon).

A constraint was therefore necessary, either applied with PFS dominating OS or OS dominating PFS. The latter choice is more prevalent when survival curves intersect well after an extended duration, typically when fewer than 10% of patients remain alive. However, we believe that there is greater justification for the constraint in favour of PFS. Given the relative immaturity in the OS data, the PFS provides more mature data and therefore less uncertainty when extrapolated. The mechanism of action (discussed in Section B.2.6.1.2.4) and clinical results support a sustained deep response and is more representative of it efficacy (See Section B.2.6.1.2.4). In addition, the constraint prevents the model predicting negative patient numbers, maintaining the internal logic of the model.

Therefore, a constraint has been added to the model to prevent OS dropping below the PFS curve (see Figure 25). The method of assuming precedence of the PFS outcome over OS outcome is consistent with the agreed methodology in other HTA appraisals where similar benefits were observed .[102, 107]

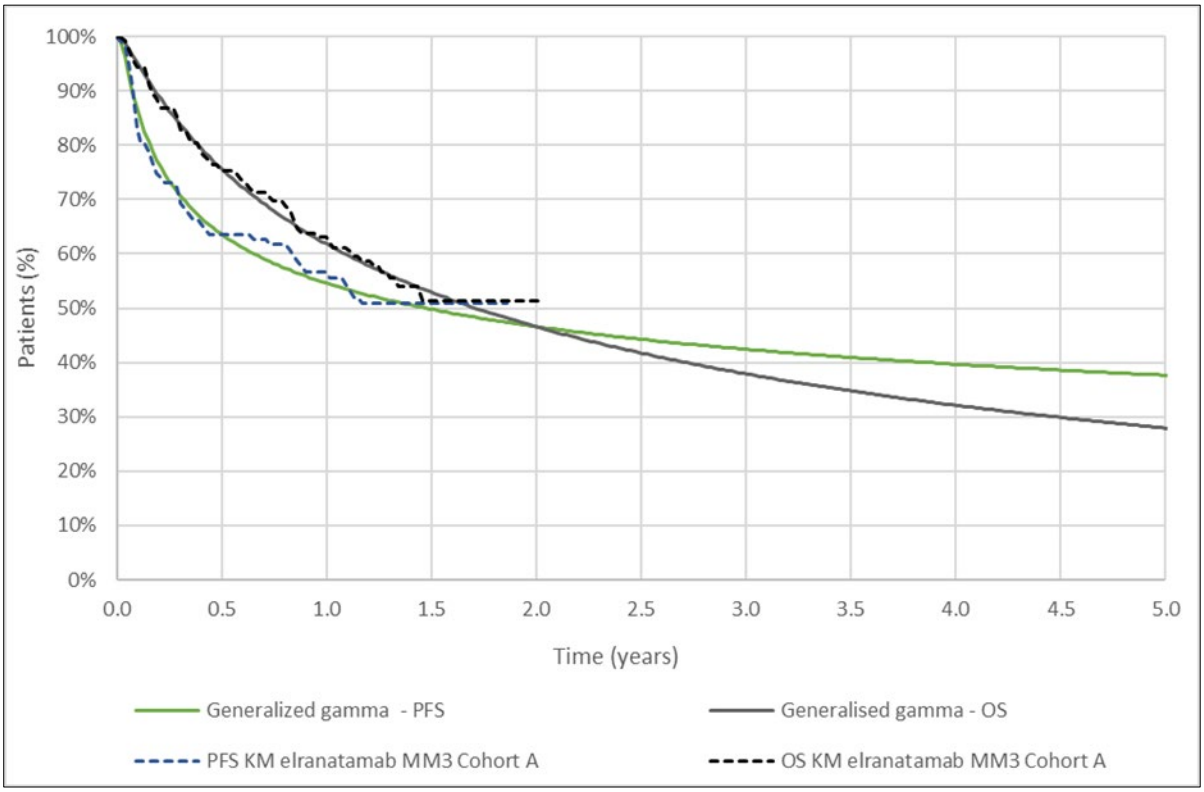
Note that we do not apply this assumption to the POM+DEX arm, given the ample long-term evidence available for the POM+DEX arm, lack of biological rationale and lack of evidenced curve crossing discussed in section B.3.3.3. Furthermore, this aligns with maintaining consistency in line with its NICE appraisal.[72]

Figure 35: Elranatamab PFS and OS Kaplan–Meier curve and 95% CI



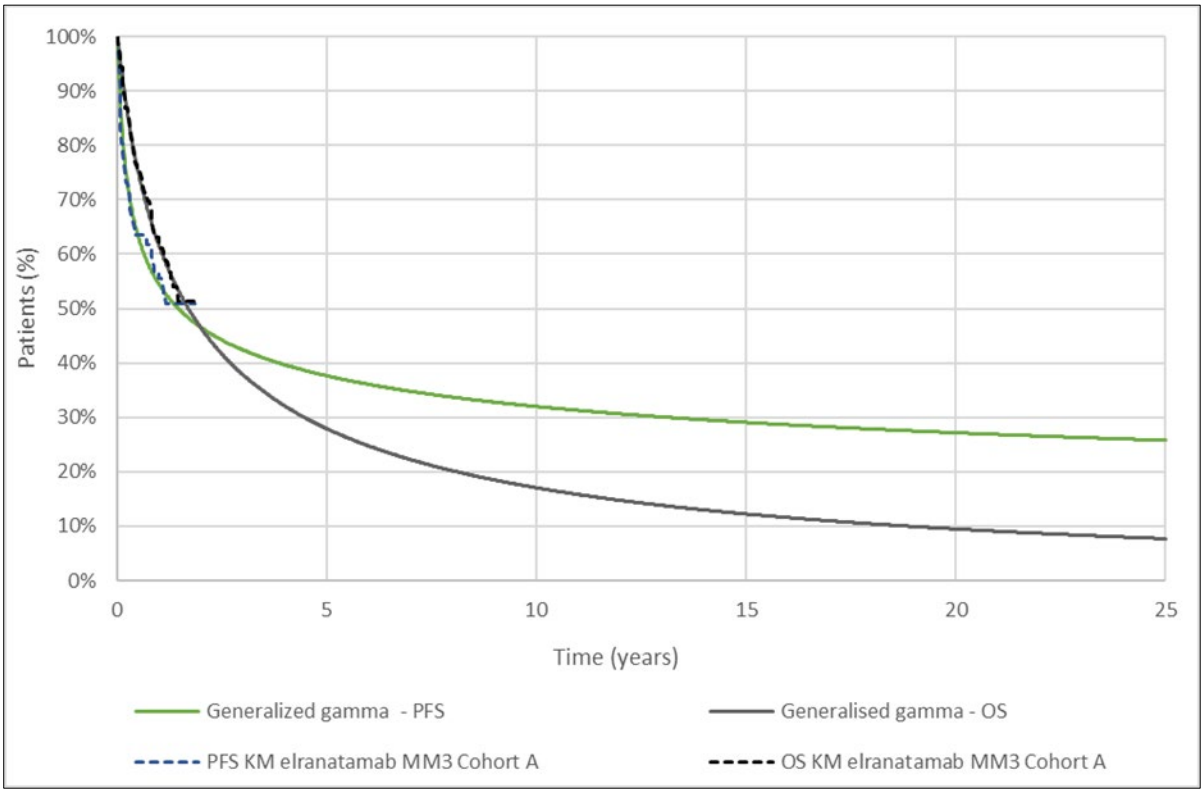
Key: CI, confidence interval; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

Figure 36: Elranatamab PFS and OS curves selected: PFS crossing OS – unadjusted for excess mortality



Key: KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

Figure 37: Elranatamab PFS and OS curves selected: PFS crossing OS (lifetime time horizon) – unadjusted for excess mortality



Key: KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

Standardised mortality ratio – a targeted literature review

As discussed in Section B.3.3.2.1 and Section B.3.3.2.2, given the maturity of the elranatamab efficacy data, the extrapolation of both PFS and OS endpoints has resulted in unrealistically optimistic extrapolations for many curves over the long-term. However, patients with RRMM have heightened mortality risk, as compared with patients in earlier phases of MM and the general public.

As described in Appendix P, a targeted literature review (TLR) with systematic searches was conducted to assess the heightened SMR of patients with RRMM. A TLR with systematic searches was conducted using Pubmed.com. Following a search of the databases, 11 full text articles were assessed for eligibility and seven were included in the TLR. Full details of the TLR search are presented in Appendix Q. Seven potentially relevant studies were identified by the TLR reporting on long-

term survival and standardised mortality in patients with advanced stages of MM such as RRMM.

An overall constant SMR of 5.27 as reported by Giri et al. was explored, however, when applied to parametric curves, it either resulted in poor visual fit in the early part of the curves or implausible extrapolation at the tail. [108] As described in Appendix P, the studies show a wide range of SMRs for patients with MM with significant differences, especially by age and comorbidity. In our analysis, we have applied a time-varying SMR as reported by Giri et al., where the SMR peaks at 15.31 within the first 5 years of follow-up, then declines to 3.50 in Years 6–10 and equals the general population after 10 years (SMR = 1.0; 95% CI: 0.85,1.16). This is representative of later-line MM patients as they are post-transplantation patients and representative of the MagnetisMM-3 trial population where approximately [redacted] of patients had a prior stem cell transplant. An overall constant SMR of 5.27 as reported by Giri et al. is applied in a scenario analysis.[108]

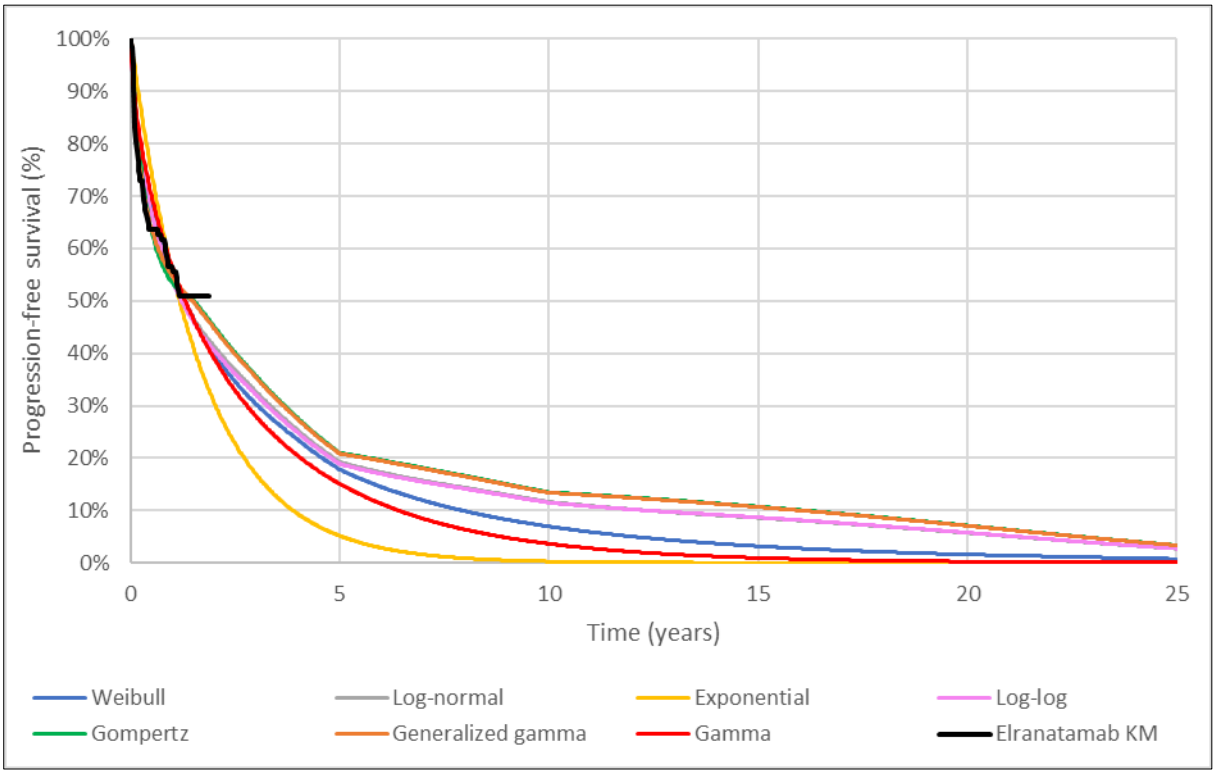
The SMR is applied to the background mortality, once the proportion of patients drops below 10% at risk (based on elranatamab) and applied to the post-trial period thereafter. In Table 26, elranatamab survival landmarks for PFS are provided inclusive of the survival of patients over the long-term, which was reflected through age- and gender-matched background mortality calculated using the England life tables (2018–2020).[101]

With the application of general population mortality and SMR to account for a heightened mortality risk for patients, the PFS 5- and 10- year extrapolations provide a range of predictions within the estimates as stated by clinicians during validation interviews.[3]

Elranatamab progression-free survival (adjusted for excess mortality)

The range of parametric model fits to PFS Kaplan–Meier data adjusted for excess mortality are shown in Figure 38Figure 31 for elranatamab. In Table 26Table 26, elranatamab survival landmarks for PFS are provided inclusive of the survival of patients over the long-term, which was reflected through age- and gender-matched background mortality calculated using the England life tables (2018–2020).[101]

Figure 38: Standard parametric fits of PFS, elranatamab (MagnetisMM-3 15-month data-cut) – adjusted for excess mortality



Key: KM, Kaplan–Meier; PFS, progression-free survival.

Table 26: Survival landmarks for PFS, elranatamab – adjusted for excess mortality

Distribution	Proportion of patients alive at:					
	6 months	1-year	2-years	5-years	10-years	25-years
Weibull	68.82%	55.69%	39.98%	17.88%	6.98%	0.75%
Log-normal	66.63%	54.22%	41.34%	19.28%	11.67%	2.75%
Exponential	74.41%	55.37%	30.66%	5.20%	0.27%	0.00%
Log-logistic	66.66%	53.88%	40.57%	18.92%	11.51%	2.77%
Gompertz	63.35%	53.44%	45.13%	21.04%	13.51%	3.43%
Generalised gamma	63.72%	54.66%	44.78%	20.88%	13.40%	3.41%
Gamma	70.03%	56.39%	39.03%	15.16%	3.67%	0.07%
Key: PFS, progression-free survival.						

The landmark survival rates estimate a 2-year survival probability of 44.78% (generalised gamma) and 39.98% (Weibull). The landmark survival rate estimate of a 5-year survival probability of 5.20% (exponential) is inconsistent with the other

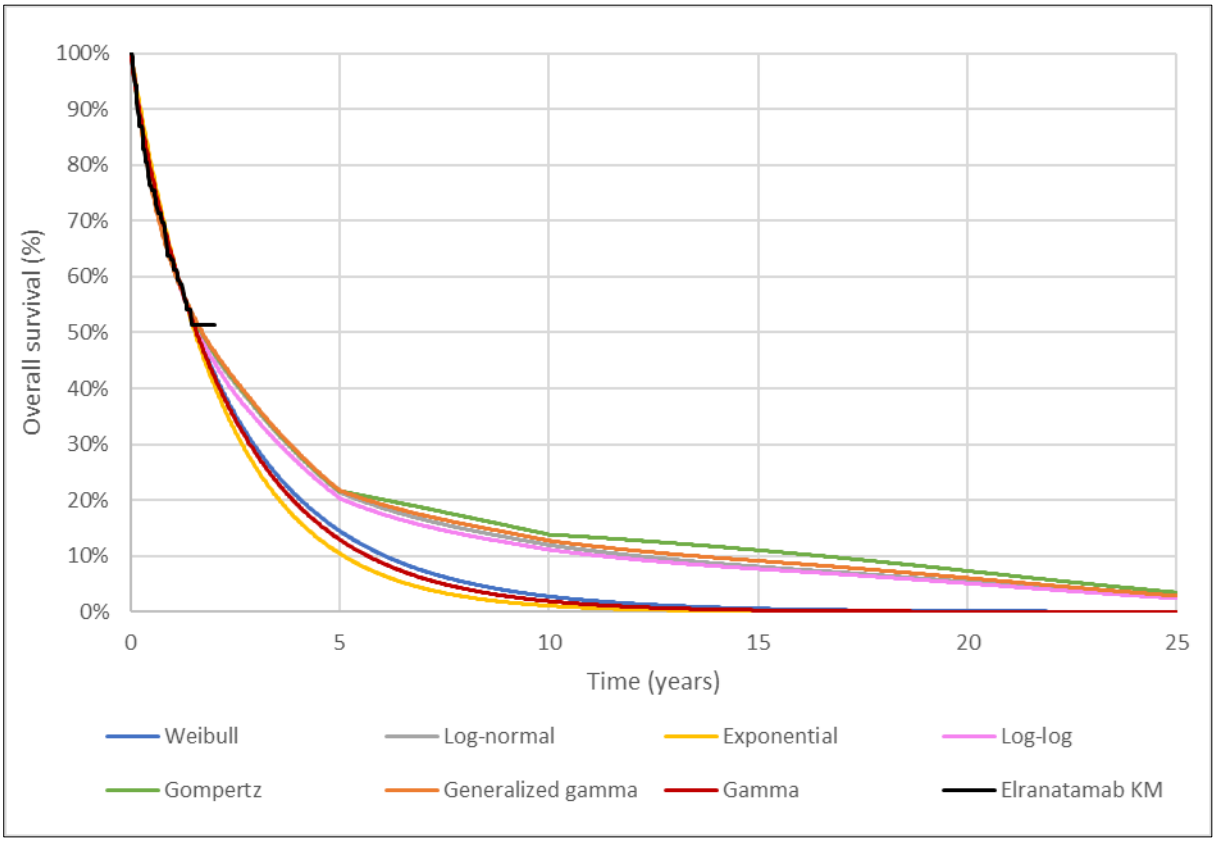
curve predictions ranging between 15.16% and 21.04%. Moreover, this estimate appears notably lower than expected based on clinical estimates for 5-year survival, presenting an implausible scenario. The generalised gamma curve, which provides a 5- and 10-year survival probability of 20.88% and 13.40% is consistent with the landmark survival estimates stated by the clinician experts.[3]

Based on the smaller AIC/BIC, the visual fit to the hazard functions and Kaplan–Meier data, the generalised gamma standard parametric model fit the data best. Furthermore, with adjustment by general population mortality and SMR, the extrapolation of the curve is consistent with clinical opinion[3]; therefore, generalised gamma was adopted in the base case. Note, Gompertz was explored under a scenario analysis (B.3.11.3) as the only other model with plausible fit to the observed data.

Elranatamab overall survival (adjusted for excess mortality)

The range of parametric model fits to OS Kaplan–Meier data adjusted for excess mortality is shown in Figure 39 for elranatamab. In Table 27Table 27, elranatamab survival landmarks for OS are provided inclusive of the survival of patients over the long-term, which was reflected through age- and gender-matched background mortality calculated using the England life tables (2018–2020).[101]

Figure 39: Standard parametric fits of OS, elranatamab (MagnetisMM-3 15-month data-cut) – adjusted for excess mortality



Key: KM, Kaplan–Meier; OS, overall survival.

Table 27: Survival landmarks for OS, elranatamab – adjusted for excess mortality

Distribution	Proportion of patients alive at:					
	6 months	1-year	2-years	5-years	10-years	25-years
Weibull	78.12%	63.23%	42.70%	14.54%	2.79%	0.03%
Log-normal	76.10%	62.00%	46.08%	21.42%	12.00%	2.58%
Exponential	79.81%	63.70%	40.58%	10.49%	1.10%	0.00%
Log-logistic	77.11%	62.24%	44.63%	20.37%	11.16%	2.45%
Gompertz	76.61%	62.15%	46.37%	21.62%	13.88%	3.53%
Generalised gamma	75.74%	61.90%	46.66%	21.76%	12.77%	2.92%
Gamma	78.51%	63.42%	42.17%	13.02%	1.93%	0.01%
Key: PFS, progression-free survival.						

The landmark survival rates estimate a 2-year survival probability of 46.66% (generalised gamma) and 42.70% (Weibull). The generalised gamma curve, which provides a 5- and 10-year survival probability of 21.76% and 12.77%, is consistent with the landmark survival estimates stated by the clinician experts.[3]

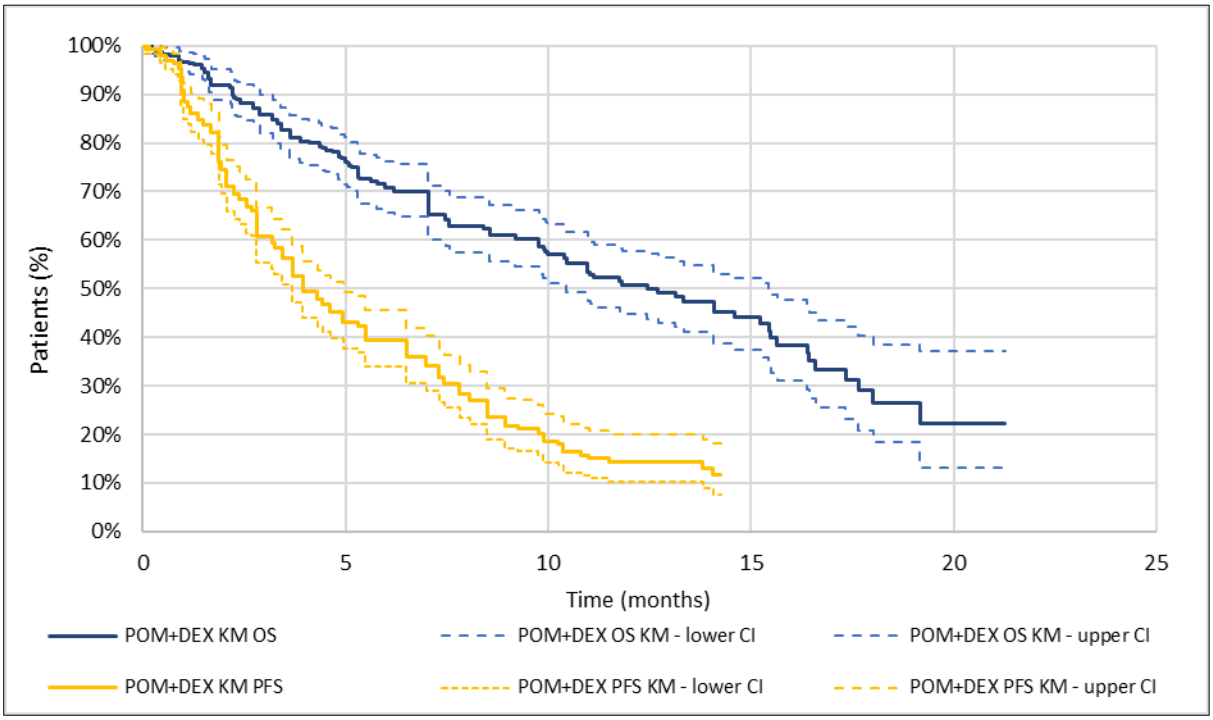
Based on the better visual fit to the hazard functions and Kaplan–Meier data, the generalised gamma standard parametric model seems to fit the data best. With the application of adjustment by general population mortality and an SMR, the long-term extrapolation matches clinical estimates.[3] Therefore, the generalised gamma curve was adopted in the base case. Alternative curves, Gompertz and Log Normal are explored under scenario analysis (B.3.11.3).

Note, with the application of general population mortality and the SMR, the PFS extrapolated curve crosses the OS curve at approximately 5 years, thus meaning the independent OS 10-year estimates are provided here for illustration only.

B.3.3.3. POM+DEX comparative efficacy

As described in B.3.3.3, in the absence of head-to-head evidence from which to derive a comparison of elranatamab versus POM+DEX, an MAIC using the POM+DEX arm from the MM-003 trial was conducted. Further details on the comparison can be found in Section B.2.9.1. Figure 40 shows the Kaplan Meier curve and 95% CI for OS and PFS, based on the MM-003 trial, this demonstrated that OS and PFS extrapolations are unlikely to cross.

Figure 40: POM+DEX PFS and OS Kaplan–Meier curve and 95% CI – MM-003 trial



Key: CI, confidence interval; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

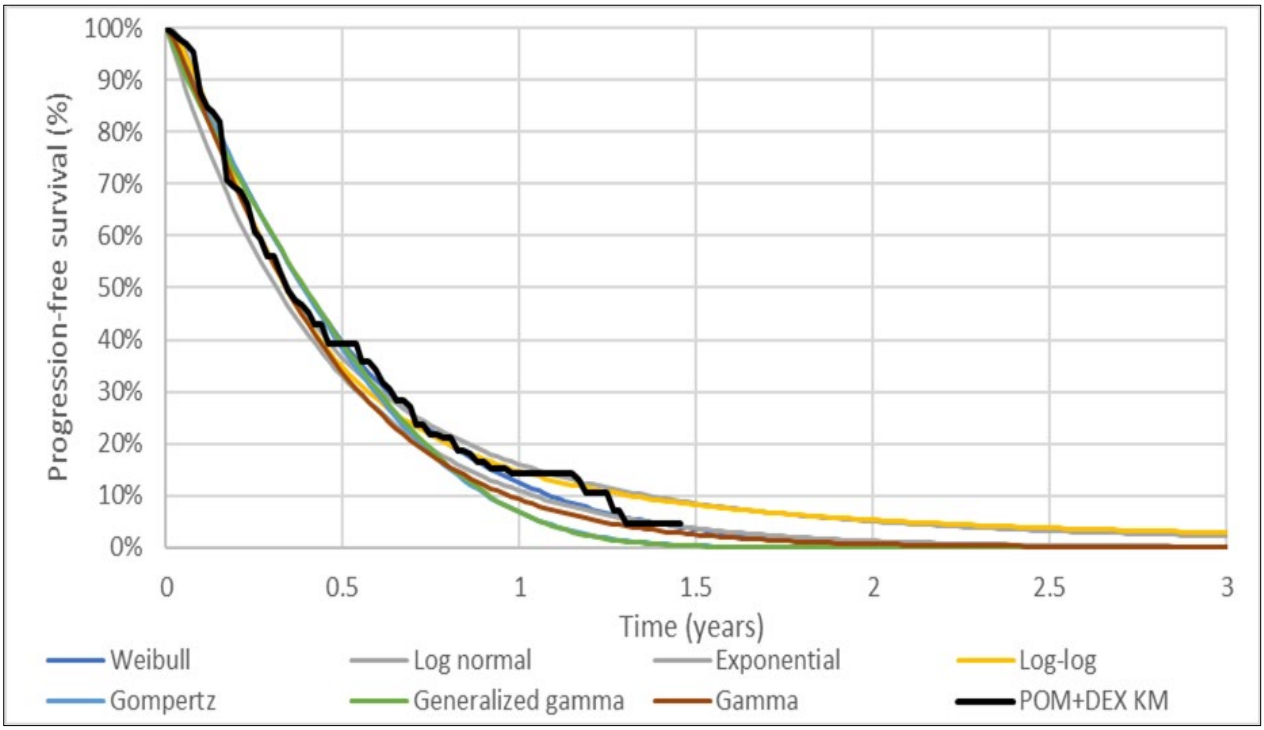
B.3.3.3.1. POM+DEX progression-free survival

Results from the comparison to the MAIC showed that the unadjusted (naïve) comparison for elranatamab has a substantially better PFS than POM+DEX (Table 15). Following MAIC adjustment, PFS for elranatamab decreases but remains higher than the PFS of POM+DEX. The more favourable PFS suggests a longer time in progression-free for patients treated with elranatamab versus POM+DEX. Further details of the MAIC are detailed in Appendix O.

As discussed in B.2.9.1.2, PH assumptions were tested to ensure the validity of applying hazard ratios (HRs). Schoenfeld tests were conducted and supplemented by the log-cumulative hazard plots. The PHs assumption did not hold when clinical trial differences were adjusted for. Additionally, as detailed in NICE DSU TSD 21[106], assuming proportional treatment effects is restrictive and may result in poorly fitting (and implausible) survival models and extrapolations. Therefore, independent parametric models were fitted to the MAIC MM-003 data. Following the MAIC, standard parametric fits were calculated for MAIC MM-003 curves. The range of

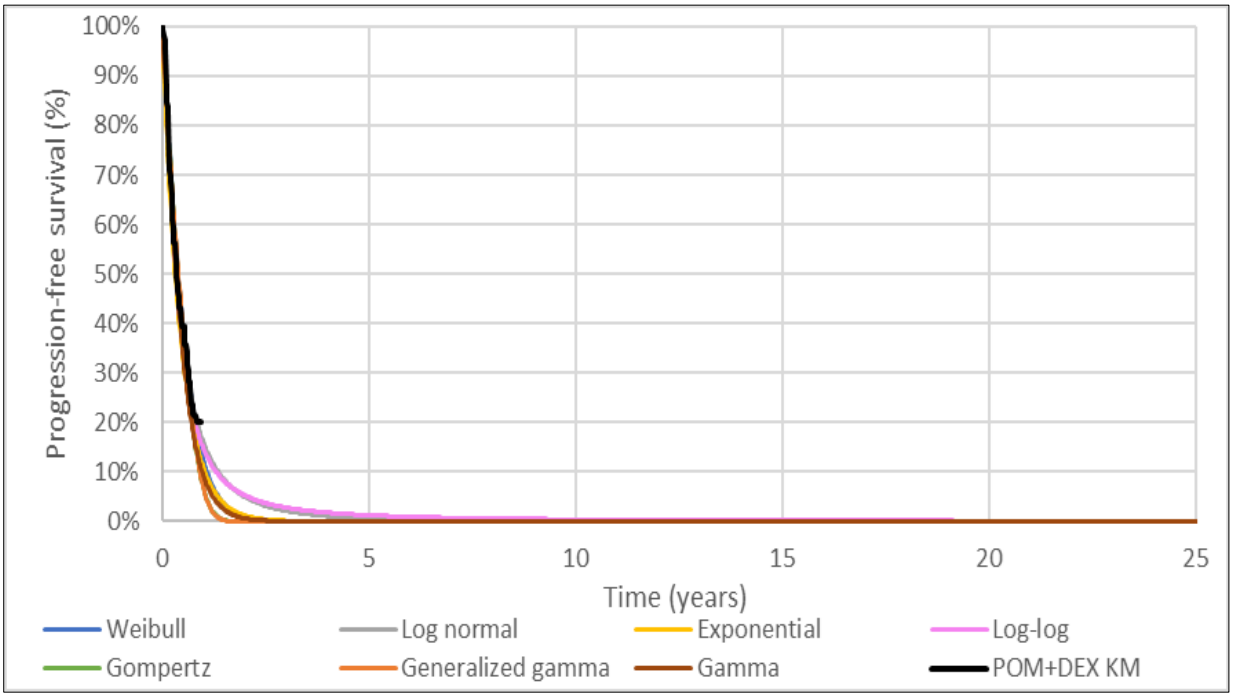
parametric model fits to PFS Kaplan–Meier data is shown in Figure 41 and Figure 42 for POM+DEX. AIC and BIC values are provided for the standard parametric extrapolations in Table 28. Landmark survival probabilities for POM+DEX are detailed in Table 29.

Figure 41: Standard parametric fits of PFS, POM+DEX (MM-003 parametric fits) – adjusted for excess mortality (3 -year time horizon)



Key: KM, Kaplan–Meier; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone.

Figure 42: Standard parametric fits of PFS, POM+DEX (MM-003 parametric fits) – adjusted for excess mortality (lifetime time horizon)



Key: KM, Kaplan–Meier; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone.

Table 28: AIC and BIC statistics of the standard parametric fits of PFS, POM+DEX (MM-003)

Parametric model	AIC	BIC	Average	Rank
Weibull	1,327.43	1,334.85	1,331.14	5
Log-normal	1,320.96	1,328.38	1,324.67	3
Exponential	1,334.13	1,337.84	1,335.99	6
Log-logistic	1,319.10	1,326.52	1,322.81	1
Gompertz	1,334.57	1,341.99	1,338.28	7
Generalised gamma	1,318.82	1,329.95	1,324.39	2
Gamma	1,323.95	1,331.37	1,327.66	4
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.				

Table 29: Survival landmarks for PFS, POM+DEX (MM-003) – adjusted for excess mortality

Distribution	Proportion of patients alive at:					
	6 months	1-year	2-years	5-years	10-years	25-years
Weibull	39.74%	12.45%	0.91%	0.00%	0.00%	0.00%
Log-normal	36.68%	16.06%	5.01%	0.61%	0.08%	0.00%
Exponential	38.92%	15.15%	2.30%	0.01%	0.00%	0.00%
Log-logistic	36.00%	15.33%	5.51%	1.29%	0.42%	0.06%
Gompertz	39.84%	13.72%	0.95%	0.00%	0.00%	0.00%
Generalised gamma	37.26%	14.25%	3.00%	0.11%	0.00%	0.00%
Gamma	39.19%	12.30%	1.06%	0.00%	0.00%	0.00%

Key: MAIC, matching-adjusted indirect comparisons; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone.

The log-logistic, generalised gamma, log-normal and gamma had similar statistical fit (AIC/BIC), with all other models providing relatively worse fits to the observed data (greater than 5 point difference in AIC/BIC). Given the maturity of the data, the statistical fit/ visual fit is of greater importance. Therefore, only these four models were considered in the extrapolation phase.

The landmark survival rates estimate at 2-year survival probability ranged from of 5.51% (log-logistic) to 1.06% (gamma). The generalised gamma curve, which provides a 5-year probability of 0.11% was selected, as this was consistent with the curve selected for elranatamab and the results were considered clinically plausible according to clinical experts.[3] The 2-year rate of the gamma was considered too low. Therefore, log-logistic and log-normal were considered as scenarios (B.3.11.3).

A scenario is also provided based on independent parametric curves fit to the ECA study data (see Appendix O for further details). As in Section B.2.9.2, the unadjusted direct comparison versus the ECA study provides a practical example of the observed effectiveness of POM+DEX in a TCR population. As would be expected the outcomes for these POM+DEX patients are less favourable than for those modelled using the less exposed MM-003 cohort. Hence, this offers decision makers

a spectrum of projected results for patients undergoing POM+DEX treatment for consideration.

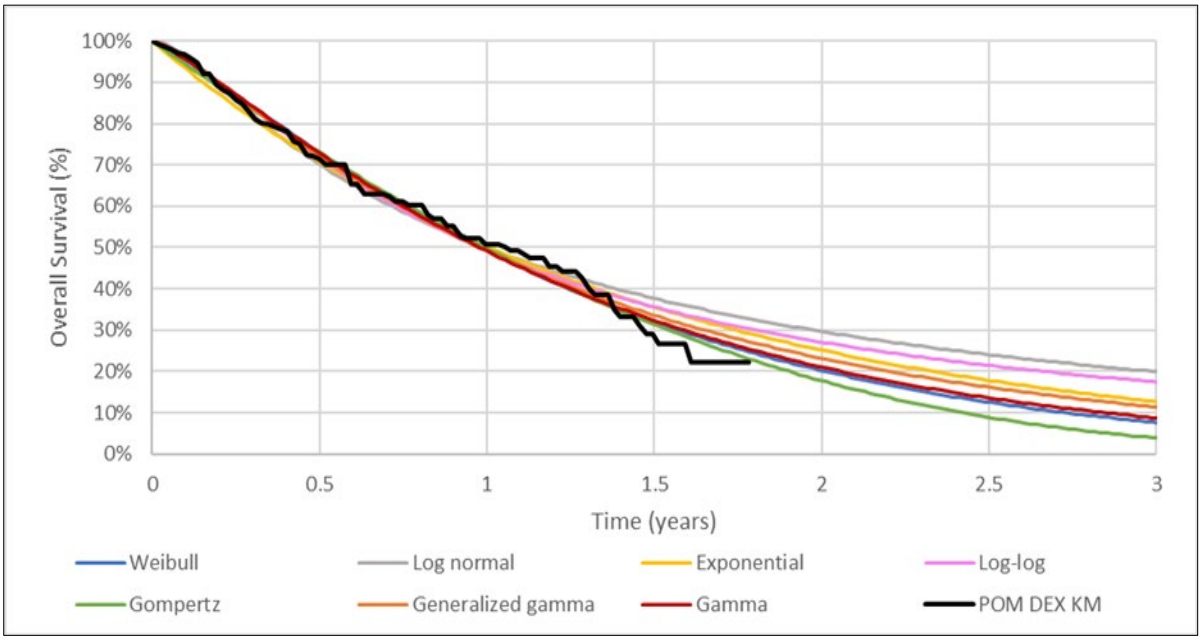
B.3.3.3.2. ***POM+DEX overall survival***

Results showed that in the unadjusted (naïve) comparison, elranatamab has a substantially better OS than POM+DEX from MM-003 (Table 15). Following MAIC adjustment, OS is still favourable with elranatamab. The more favourable OS suggests a longer survival time for patients treated with elranatamab versus POM+DEX.

As discussed in B.2.9.1.2, PH assumptions were tested to ensure the appropriateness of applying HRs. Schoenfeld tests were conducted and supplemented by log-cumulative hazard plots. Further details of the MAIC, Schoenfeld tests and log-cumulative hazard plots are detailed in Appendix O. Additionally, as detailed in NICE DSU TSD 21[106], assuming proportional treatment effects is restrictive and may result in poorly fitting (and implausible) survival models and extrapolations.

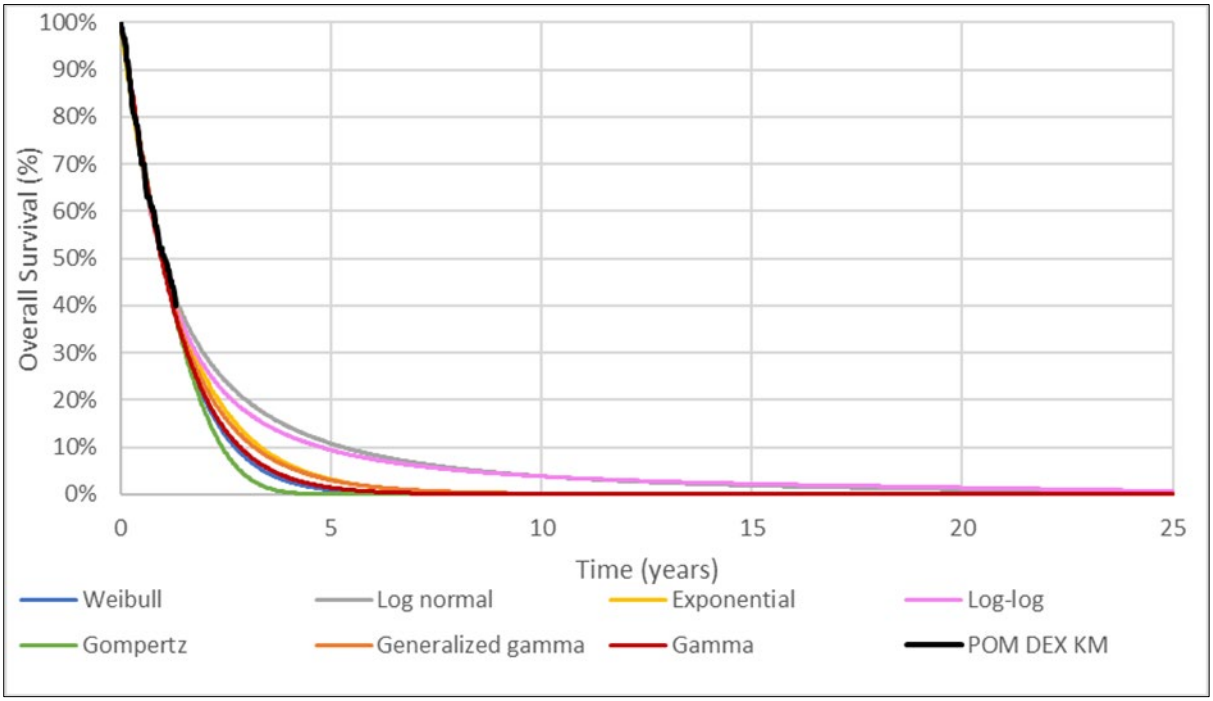
Therefore, independent parametric models were fitted to the MAIC MM-003 trial data. The range of parametric model fits to OS Kaplan–Meier data is shown in Figure 43 (3-year time horizon) and Figure 44 (lifetime horizon) for POM+DEX. AIC and BIC values are provided for the standard parametric extrapolations in Table 30. Landmark survival probabilities for POM+DEX are detailed in Table 31.

Figure 43: Standard parametric fits of OS, POM+DEX (MAIC MM-003 parametric fits) – adjusted for excess mortality (3-year time horizon)



Key: KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparisons; OS, overall survival; POM+DEX, pomalidomide and dexamethasone.

Figure 44: Standard parametric fits of OS, POM+DEX (MAIC MM-003 parametric fits) – adjusted for excess mortality (life-time horizon)



Key: KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparisons; OS, overall survival; POM+DEX, pomalidomide and dexamethasone.

Table 30: AIC and BIC statistics of the standard parametric fits of OS, POM+DEX (MM-003)

Parametric model	AIC	BIC	Average	Rank
Weibull	1,117.41	1,124.83	1,121.12	2
Log-normal	1,121.20	1,128.62	1,124.91	7
Exponential	1,120.07	1,123.78	1,121.92	3
Log-logistic	1,118.77	1,126.19	1,122.48	4
Gompertz	1,119.05	1,126.47	1,122.76	5
Generalised gamma	1,118.74	1,129.87	1,124.30	6
Gamma	1,117.07	1,124.49	1,120.78	1
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.				

Table 31: Survival landmarks for OS, POM+DEX (MM-003) – adjusted for excess mortality

Distribution	Proportion of patients alive at:					
	6 months	1-year	2-years	5-years	10-years	25-years
Weibull	73.14%	49.37%	20.33%	0.94%	0.00%	0.00%
Log-normal	70.22%	49.98%	29.74%	10.81%	3.86%	0.51%
Exponential	70.89%	50.26%	25.26%	3.21%	0.10%	0.00%
Log-logistic	71.80%	49.35%	27.16%	9.40%	3.82%	0.68%
Gompertz	73.13%	49.97%	17.88%	0.01%	0.00%	0.00%
Generalised gamma	72.24%	49.24%	23.28%	3.05%	0.16%	0.00%
Gamma	72.92%	49.26%	21.16%	1.44%	0.01%	0.00%
Key: MAIC, matching-adjusted indirect comparisons; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone.						

Similar to that of Elranatamab OS, all parametric models had similar statistical (AIC/BIC) and visual fits to the observed data. There were disparities between extrapolations, though to a lesser extent than the PFS data.

The landmark survival rates estimate a 5-year survival probability ranged from of 10.81% (log-normal) to 0.01% (Gompertz). the generalised gamma curve, which provides a 5-year probability of 3.05% was selected, as this was consistent with the

curve selected for elranatamab and the results were considered clinically plausible according to clinical experts.[3] Additionally, exponential was explored in a scenario given it has similar landmark survival rates (B.3.11.3).

A scenario is also provided based on independent parametric curves fit to the ECA study data (see Appendix O for further details). As detailed in Section B.2.9.2, the unadjusted direct comparison versus the ECA study offers a tangible demonstration of the effectiveness observed with POM+DEX, showcasing outcomes that are less optimistic for patients compared with our base case analysis projections. Similarly to the POM+DEX PFS analysis, it presents decision makers with a range of anticipated results for patients receiving POM+DEX treatment for their consideration.

B.3.3.4. Base case OS and PFS comparison: elranatamab versus POM+DEX Progression-free survival

Following the extrapolated curve selection process of establishing the most appropriate OS extrapolation curves, the generalised gamma curve was selected for the comparison of elranatamab versus POM+DEX. As discussed in Section B.2.9.1.1, MAIC weighting was applied to elranatamab; therefore, elranatamab weighted data are used in the economic analysis as shown in Figure 45. Further details of elranatamab reweighted data are provided in Appendix O.

Figure 45: Base case: elranatamab reweighted MAIC curve compared with POM+DEX MM-003 PFS curve – adjusted for excess mortality

Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone.

Overall survival

Following the extrapolated curve selection process of establishing the most appropriate OS extrapolation curves, the generalised gamma curve was selected for the comparison of elranatamab versus POM+DEX. As discussed in Section B.2.9.1.1, MAIC weighting was applied to elranatamab. Therefore, elranatamab weighted data are used in the base case economic analysis as shown in Figure 46. Further details of elranatamab ECA weighted data are provided in Appendix O.

Figure 46: Base case: elranatamab reweighted MAIC curve compared with POM+DEX MM-003 OS curve – adjusted for excess mortality

Key: MAIC, matching-adjusted indirect comparison; OS, overall survival; POM+DEX, pomalidomide and dexamethasone.

B.3.3.5. Time to discontinuation

B.3.3.5.1. Elranatamab time to discontinuation

The following section describes the TTD outcome (defined in MagnetisMM-3 as the time from the date of first dose until last exposure date due to any cause). The TTD Kaplan–Meier data at the data cut-off date of 14 March 2023 are presented in Figure 47.

Patients with MM discontinue treatment due to different causes such as AEs, disease progression, investigator-determined or patient preference. Thus, TTD curves were fitted to account for the time spent on the treatment within the PFS state, and patients were partitioned into on and off treatment while remaining progression-free.

Figure 47: Kaplan–Meier curve for TTD in Cohort A of MagnetisMM-3 15-month data-cut

Key: TTD, time to treatment discontinuation.

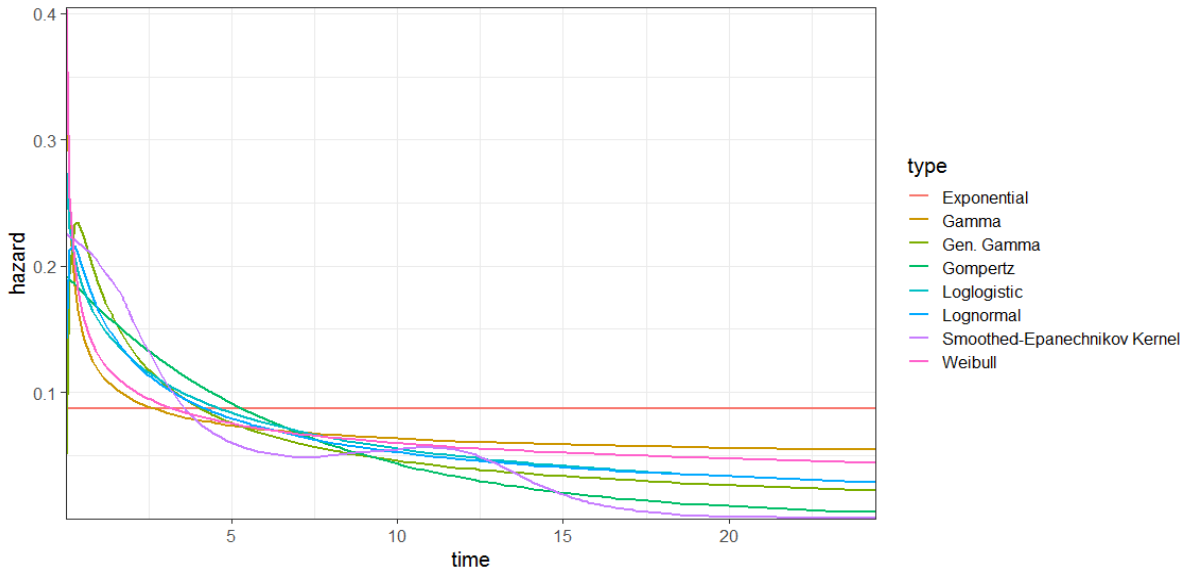
As discussed in Section B.2, as of the 15-month data-cut for MagnetisMM-3, [redacted] patients had discontinued elranatamab therapy. [redacted] of these were due to death or progressive disease, leaving [redacted] patients with non-progressive disease. These patients experienced an enduring treatment effect whereby they had an ongoing PFS despite cessation of elranatamab therapy. Therefore, a gap between TTD and PFS which is greater than would have been expected in the context of previous trials in MM.

As detailed in Section B.2, there are clinical and biological explanations for the discrepancy between TTD and PFS including the prolonged half-life of elranatamab, the avoidance of an exhausted T-cell phenotype through treatment cessation, deep disease suppression, and an additional immunomodulatory effect related to its primary mechanism of action which could result in an enduring response off treatment. Taken together, these effects provide an explanation for the cohort of patients who experienced an enduring treatment effect whilst off treatment and progression-free (see Appendix N.1 for further details).

Extrapolation of TTD

In line with the approach for OS and PFS, the standard parametric curves were fitted to the TTD on the Kaplan–Meier curves based on the MagnetisMM-3 (Cohort A) 15-month data-cut. Standard parametric survival models were fit according to criteria as detailed in Section B.3.3.2. Smoothed-Epanechnikov Kernel plots were fitted to determine the hazard plots over the trial period (see Figure 48). The shape of the TTD hazards varies over time suggesting differing time-dependent rates of discontinuation.

Figure 48: Hazard function for OS fitted parametric models, elranatamab



Key: OS, overall survival.

The range of parametric model fits to TTD Kaplan–Meier data are shown in Figure 49 and Figure 50 for elranatamab. AIC and BIC values are provided in Table 32 and landmark survival extrapolations are detailed in Table 33.

Figure 49: Standard parametric fits of TTD, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (3-year time horizon)

Key: KM, Kaplan–Meier; TTD, time to treatment discontinuation.

Figure 50: Standard parametric fits of TTD, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (life-lifetime time horizon)

Key: KM, Kaplan–Meier; TTD, time to treatment discontinuation.

Table 32: AIC and BIC statistics of the standard parametric fits of TTD, elranatamab (MagnetisMM-3 15-month data-cut)

Parametric model	AIC	BIC	Average	Rank
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation.

The range of parametric model fits to TTD Kaplan–Meier data adjusted for excess mortality is shown in Figure 51 for elranatamab. In Table 33, elranatamab survival landmarks for PFS are provided inclusive of the survival of patients over the long-term, which was reflected through age- and gender-matched background mortality calculated using the England life tables (2018–2020).[101]

Figure 51: Standard parametric fits of TTD, elranatamab (MagnetisMM-3 15-month data-cut) – adjusted for excess mortality

Key: KM, Kaplan–Meier; TTD, time to treatment discontinuation.

Table 33: Survival landmarks for TTD, elranatamab

Distribution	Proportion of patients alive at:					
	6 months	1-year	2-years	5-years	10-years	25-years
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: TTD, time to treatment discontinuation.						

The log-normal distribution yielded the best statistical fit (i.e., the lowest AIC/BIC) and visual fit, followed by the Gompertz and log-logistic with all other models substantially diverging from the observed data from statistical and/or visual fit. The landmark survival rates estimate a 2-year survival probability of [redacted]%, [redacted]% and [redacted]%, respectively. Given the similar landmark rates, the log-normal curve was selected as the base case extrapolation of the TTD curve of elranatamab, with the log-logistic and Gompertz explored in scenario analysis .

B.3.3.5.2. POM+DEX time to discontinuation

In the absence of head-to-head evidence from which to derive a comparison of elranatamab versus POM+DEX, a MAIC using the POM+DEX arm from the MM-003 trial was conducted to compare the efficacy of elranatamab to the efficacy of POM+DEX for both PFS and OS outcomes. However, suitable data for a TTD comparison were lacking from the MM-003 trial with only median treatment duration reported (4.7 months)[109]; therefore, three TTD options for POM+DEX were explored using MM-003:

- An exponential distribution based on the median treatment duration (4.7 months). However, given the implausibility of this assumption and inconsistency with the elranatamab assumptions, these data are only used in a scenario analysis

- PFS:TTD ratio (1.18) based on the observed median reported outcomes from Miguel 2015[109], for POM+DEX. The reported median PFS MM-003 is 4.0 months and median TTD is 4.7 months, therefore with TTD greater than PFS.
- Assuming TTD is equal to PFS[109], this assumption is explored in a scenario; however, these data are limited as the underlying data are unavailable and it is unknown if TTD is greater than PFS over a longer follow-up

Given the indication that treatment continues beyond the point of progression (in both MagnetisMM-3 and the ECA study), the assumption of PFS:TTD ratio was applied in the base case analysis.

B.3.3.5.3. Base case TTD comparison: elranatamab versus POM+DEX

Following the process of establishing the most appropriate TTD extrapolation curve, the log-logistic curve was selected for elranatamab. The assumption of PFS:TTD ratio was applied to POM+DEX. The base case economic analysis TTD curves are shown in Figure 52.

Figure 52: Elranatamab TTD curve compared with POM+DEX TTD curve – adjusted for excess mortality

Key: POM+DEX, pomalidomide and dexamethasone; TTD, time to treatment discontinuation.

B.3.3.6. Adverse reactions

The rates of AEs for patients treated with elranatamab and POM+DEX in the model are detailed below. The model considers the effects of AEs on costs and HRQL. Only Grade 3 or higher AEs with an incidence of 5% or more were considered since AEs not meeting this criterion are unlikely to have any material impact on cost-effectiveness. Probabilities of AEs for patients receiving elranatamab or POM+DEX were based on patients receiving treatment in the MagnetisMM-3 (Cohort A) 15-month data-cut and MM-003 (Table 34).

The AEs were accounted for using established methodology and the same methodology accepted in previous NICE RRMM submissions.[10, 72] This means that the numbers of AEs were converted into rates and probabilities per model cycle (1 week) and calculated using the patient population size and the duration of treatment exposure. AEs were incorporated as a one-off cost and disutility in the first model cycle.

Pomalidomide had a particularly toxic profile causing serious AEs, with 61% of patients reported to have had a Grade 5 event (defined as requiring hospitalisation or which resulted in disability or incapacity) and 4% reported to have had treatment-related death (eight cases of infections and infestations, two cases of multi-organ failure or sudden death and one case of nervous system disorder).

Table 34: Probabilities of Grade ≥ 3 AEs, frequency in ≥ 5% of patients

AE rates	Elranatamab	POM+DEX
Neurotoxicity (Grade 1–2)*	[redacted]	NR
Neurotoxicity (Grade 3–4)*	2%	NR
CRS (Grade 1–2)†	58%	NR
CRS (Grade 3–4)†	0%	NR
Alanine aminotransferase increased	[redacted]	NR
Aspartate aminotransferase increased	[redacted]	NR
Anaemia	37%	33%
Fatigue	3%	5%
Febrile neutropenia	[redacted]	9%
Hypertension	[redacted]	NR
Infection	[redacted]	NR
Leukopenia	[redacted]	9%

AE rates	Elranatamab	POM+DEX
Lymphopenia	25%	NR
Nausea	0.0%	15%
Neutropenia	49%	48%
Pneumonia	[redacted]	14%
Renal and urinary disorders	[redacted]	NR
Sepsis	[redacted]	NR
Thrombocytopaenia	24%	22%

Key: AE, adverse event; CRS, cytokine release syndrome; POM+DEX, pomalidomide and dexamethasone; NR, not reported.
Notes:* AEs of clinical interest. † AEs of special interest.

Infections (specifically linked to IVIG) are also explored as the MagnetisMM-3 trial ran during the COVID-19 pandemic. This likely led to a higher infection rate and values may present a conservative estimate that may not be clinically representative of general practice today. Therefore, we sought to identify those patients who would likely receive IVIG in clinical practice. Overall, 43.1% of patients in Cohort A received IVIG. However, [redacted] of the [redacted] patients received IVIG as prophylaxis for hypogammaglobulinemia, or as treatment for a non-bacterial infection, whereas [redacted] patients initiated IVIG due to bacterial infection or developed a bacterial infection whilst on IVIG treatment. The company is aware that the Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) in England defines the criteria which must be met in order for IVIG to be used in the context of an anti-myeloma bispecific antibody.[97] Furthermore, advice was received from an expert with previous experience in developing UK IVIG guidance and the commissioning of high-cost medicines. Based on the commissioning policy and expert advice, the company concluded that those receiving IVIG as; prophylaxis for hypogammaglobulinemia, or treatment for a non-bacterial infection, would be unlikely to receive it based on current UK practice.[1, 3] Therefore, of those treated with IVIG in the MagnetisMM-3 trial, [redacted] patients ([redacted]%) have been included in our analysis with a treatment duration of [redacted] months based on mean duration reported from cohort A, and dosage of 0.5 g/kg[97] per month as detailed in Table 35. See Appendix M for further explanation on IVIG usage.

Table 35: IVIG adverse event

	Elranatamab (Cohort A)
Dosage (g/kg/month)	0.5
Treatment duration (months)	[redacted]
Proportion receiving IVIG	[redacted]
Key: IVIG; Intravenous immunoglobulin.	

B.3.4. Measurement and valuation of health effects

For patients with RRMM, quality of life is known to be substantially affected by disease symptoms and recurring relapses. This causes an emotional and physical well-being burden and negative impact on social interactions, which also affects family or caregivers. Treatment-related toxicity, a treatment burden which intrudes on daily life and progresses with time, poses an additional burden on patients (including travel time to appointments), leading to the inevitable mortality, as described in Section B.1.3.

Additionally, decrements to HRQL due to AEs were considered as well as natural decline of age-related HRQL using UK weights for the evaluable population. Age-based utility multipliers in line with NICE guidance were considered.[103]

B.3.4.1. Health-related quality of life data from clinical trials

In line with the NICE reference case[103] and to incorporate the important impact on HRQL described above, EQ-5D-5L questionnaire data were used. Patient-reported outcomes were collected from the MagnetisMM-3 trial 15 month data-cut and used in the economic model base case for PFS and post-progression survival (PPS) health states and AE disutilities.

The EQ-5D-5L questionnaire assessment are being collected in MagnetisMM-3 at the following time points:

- Screening
- Day 1 of each cycle (only every third cycle after the first year)
- Day 15 of each cycle (Cycles 1–3 only)
- End-of-treatment visit

- Follow-up visit

Both univariate regression and multivariate repeated-measures mixed-effect regressions were conducted to estimate the utility values. The covariates that were potential prognostic variables or effect modifiers were identified and univariate analyses were performed to analyse the impact of including these covariates. In line with the protocol, elranatamab was given until confirmed disease progression, unacceptable toxicity, withdrawal of consent or study termination. Therefore, on/off treatment status was not selected as a variable in the analyses as it overlapped with progression status. The AE variables were defined as follows:

- If a utility observation was recorded between the start and end date of an AE, that observation was included and assumed to impact the utility (via having AEs) during that period
- AE in pre-progression state indicated that the reading was in the pre-progression state
- CRS was a defined AE with code ‘cytokine release syndrome’
- Neurotoxicity: the AE terms indicated in the Pfizer protocol were used (including the cluster names)

All statistically significant covariates ($p \leq 0.05$) from the univariate analysis were considered in multivariate analyses along with the corresponding interaction terms. A backwards stepwise approach was used to remove non-significant predictors at each step until a final model containing only the significant terms was left. To determine the best-fitting model, the appropriateness was also assessed by evaluating the AIC and BIC scores. For details of AEs see Appendix N.

The results from univariate analyses showed that the covariates ‘Common AE, Grade 3–4, treatment emergent’ and ‘pre-progression or post-progression status’ were significant (Appendix M). These variables were then carried into the multivariate analyses. Multivariate analyses were conducted by including the significant covariates from univariate analyses (Table 36). However, despite reaching significant, given a lack of EQ-5D assessments beyond the point of progression, the PPS value is unlikely to reflect the full decline in HRQL experience by RRMM patients.

Table 36: Results of multivariate analyses for utility analysis

Coefficient	Estimate	SE	p value	Significance	AIC	BIC
(Intercept)	[redacted]	[redacted]	[redacted]	***	[redacted]	[redacted]
Pre-progression or post-progression status indicator (1 or 0)	[redacted]	[redacted]	[redacted]	**		
Common AE, Grade 3–4, treatment emergent	[redacted]	[redacted]	[redacted]	*		

Key: AE, adverse events; AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival; SE, standard error.
Notes: * Statistically significant (≤ 0.05), statistically significant (≤ 0.1). ** Statistically significant (≤ 0.01). *** Statistically significant (≤ 0.001).

The utility values in the economic model are driven by the underlying impact of the disease over time, based on patients' progression status applied to both the elranatamab and POM+DEX arms. See Table 40 for a summary of utility values used in the cost-effectiveness analysis. This approach has been previously accepted in other oncology appraisals by NICE including, but not limited to, TA783 and TA247.[5, 72] Additionally, in the absence of comparative data, these estimates are reasonably comparable to both arms. Though, as detailed in Table 37, the utilities from NICE TA427 (the HTA of POM+DEX) are slightly lower, suggesting some difference is potentially due to variations in depth of response. It is therefore expected that these values potentially underestimate the incremental benefits compared to patients receiving POM+DEX.

B.3.4.2. Mapping

In the MagnetisMM-3 trial, data on the EQ-5D-5L questionnaire were collected. In line with the NICE reference case, utility estimates derived from mapping the EQ-5D-5L to -3L version were used in the cost-effectiveness analysis, based on the mapping method published by Hernández et al. (2023)[110] and NICE DSU TSD 22.[111]

B.3.4.3. Health-related quality of life studies

An SLR was conducted on utility and HRQL in RRMM. HRQL SLR results were crosschecked against utility/disutility-containing publications identified from the economic SLR to ensure the consistency of the model estimates with other appraisals. Only studies reporting utilities in the EQ-5D questionnaire or data that could be mapped to the EQ-5D questionnaire were included. The SLR identified 91 unique studies summarised in 123 reports including HRQL when applying eligibility criteria and 9 unique studies summarised in 16 reports when applying the additional criteria to match the NICE decision problem. A further six economic evaluation studies that contained HRQL evidence were identified in the economic evaluation search, and five HTA assessments. Full details of the review are provided in Appendix H. HRQL data from previous NICE appraisals for the treatment of RRMM are summarised in Table 37.

Given the potential underestimation of the impact of progression, PFS (average on treatment 0.724) and PPS (0.553) values from TA658[4] and PFS (0.76) and PPS (0.0.62) values TA427[72] were applied in scenario analyses. A further analysis including treatment specific values from TA658[4] to demonstrate the potential impact of higher rates of response in the elranatamab arm was also explored.

Table 37: Summary of utility values from previous NICE TAs

NICE TA	Intervention	PFS utility	PPS utility	Notes
TA427[72]	POM+DEX	On treatment: 0.76 Off treatment: 0.66	0.62	Utilities above are without AEs and hospitalisations, for which disutilities were calculated separately
TA658[4]	ISA+POM+DEX and POM+DEX	On ISA+POM+DEX treatment: 0.731 (CI 0.695, 0.768) On POM+DEX treatment: 0.717 (CI 0.677, 0.758) Off ISA+POM+DEX treatment: 0.473 (CI 0.288, 0.658) Off POM+DEX treatment: 0.621 (CI 0.527, 0.714)	On treatment: 0.649 (CI 0.591, 0.707) Off treatment: 0.553 (CI 0.478, 0.629)	Utility decrease off-treatment was significant and utilities varied per treatment arm. The model also used a terminal decrement of 0.204, lasting over a period of 12 weeks.
TA510/TA783[112]	Dara	0.61 (95% CI 0.59, 0.63) [113]	0.57 (CI 0.55, 0.59)	The utility values used may be considered conservative as they do not account for differences in response across treatments. Alternative values from TA338 and TA380 are explored under scenario analysis.

Key: AE, adverse events; CI, confidence intervals; Dara, daratumumab; ISA+POM+DEX, isatuximab with pomalidomide and dexamethasone; POM+DEX, pomalidomide and dexamethasone; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal.

The EQ-5D questionnaire analysis from the MagnetisMM-3 trial remains the most relevant and robust source of data for this appraisal, and follows methods outlined in the NICE reference case.[103]

B.3.4.3.1. Disutilities for adverse events

In the base case, the regression equation (described in Appendix M) was used to model the HRQL impact associated with AEs. For patients receiving elranatamab, the disutilities and the durations of the common AEs were estimated based on MagnetisMM-3 trial data. A similar approach was implemented for POM+DEX utilising MM-003 data.[104] Only Grade 3 or higher AEs with an incidence of 5% or more were considered see section B.3.3.6.

Due to the limited observations of the reported AEs, the estimates for individual AE disutility were highly uncertain. As a result, the same disutility was estimated for all common Grade 3 and 4 AEs (except for CRS and neurotoxicity; Table 38). For the common AEs not observed within the MagnetisMM-3 trial (i.e. nausea, which is a relevant AE for POM+DEX reported in MM-003 and ICARIA), disutility measures from NICE TA510 were implemented.[112]

For the disutilities of CRS and neurotoxicity, the number of the observations was limited in the MagnetisMM-3 trial, making the estimation of the disutility unreliable or implausible. Therefore, inputs from the literature were used for the disutilities of CRS and neurotoxicity.[114] The durations of Grade 1 and 2 CRS and neurotoxicity events for elranatamab were derived from the MagnetisMM-3 trial. For the durations of Grade 3 and 4 CRS and neurotoxicity of elranatamab, data were unavailable to derive the estimates from MagnetisMM-3; therefore, it was sourced from the literature based on median durations reported for teclistamab (Tecvayli®).[80] Table 39 provides the disutilities and durations of CRS and neurotoxicity; Table 40 summarises the utilities and disutilities used in the model.

Table 38: AE disutilities and durations

AE*	Disutility	Duration (days)
Alanine aminotransferase increased	-0.0255	
Anaemia	-0.0255	
Fatigue	-0.0255	
Febrile neutropenia	-0.0255	
Hypertension	-0.0255	
Increased aspartate aminotransferase	-0.0255	
Infection	-0.0255	
Leukopenia	-0.0255	
Lymphopenia	-0.0255	
Nausea	-0.1000	
Neutropenia	-0.0255	
Pneumonia	-0.0255	
Renal and urinary disorders	-0.0255	
Sepsis	-0.0255	
Thrombocytopenia	-0.0255	

Key: AE; adverse event.
Notes: Disutilities were sourced from utility analysis on MagnetisMM-3 data. Duration of AEs was sourced the MagnetisMM-3 data.[99]
*Only Grade 3 or higher AEs with an incidence of 5% or more were considered see section B.3.3.6.

Table 39: AE disutilities and durations of clinical and special interest

AE	Disutility*[115]	Duration (days)
CRS Grade 1–2	-0.05	
CRS Grade 3–4	-0.23	2.0**
Neurotoxicity Grade 1–2	-0.04	
Neurotoxicity Grade 3–4	-0.18	7.0**

Key: AE, adverse event; CRS, cytokine release syndrome.
Notes: * Disutilities were derived from Howell et al. (2022), assumptions have been clinically validated and deemed appropriate for elranatamab. ** For the median duration for CRS Grade 3–4 and neurotoxicity Grade 3–4, no median durations were derived from MagnetisMM-3. It is assumed to have the same duration as teclistamab (MajesTEC-1)

B.3.4.4. Health-related quality of life data used in the cost-effectiveness analysis

As described in Section B.3.4.1, disease-progression-specific utility estimates from MagnetisMM-3 are used in the model base case. The approach to capture AE disutility was set out in Section B.3.4.3.1. These utility assumptions are summarised in Table 40. The utility values used may be considered conservative as they do not

account for differences in response across treatments. As described in Section B.3.4.2, EQ-5D-5L questionnaire data were collected in MagnetisMM-3 and mapped to EQ-5D-3L questionnaire values using public preference tariffs as per the UK time-trade-off valuation set. Multivariate analysis was then conducted to determine the most significant predictors of HRQL. The impact of AEs on HRQL was also included, with a weighted average utility applied per cycle, detailed in Table 38. Additionally, at each model cycle, utility values are adjusted to account for the natural decline in quality of life associated with age, based on the Ara and Brazier standard published regression algorithm commonly used in NICE TAs.[116]

Table 40: Summary of utility values for cost-effectiveness analysis

State		Utility value: mean	95% CI	Justification
PFS (on and off treatment)		0.71	[0.64,0.79]	Estimated directly from systematic analysis, mapping EQ-5D-5L to EQ-5D-3L data from patients informing effectiveness estimates, in line with the NICE reference case[103]
PPS		0.63	[0.59,0.67]	
AE disutility	Elranatamab	-0.0051*		
	POM+DEX	-0.0034*		
Key: AE, adverse events; CI, confidence interval; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; PPS, post-progression survival. **Note**: *Calculated in the cost effectiveness model				

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify cost-effectiveness studies, healthcare costs and healthcare resource utilisation associated with the treatment of RRMM relevant to the UK. For full details of the methods used for the SLR and the identified studies, see Appendix I. The SLR identified 12 studies ranging from early RRMM and double class exposed MM, four of which were exclusively UK studies. The remaining were multi-country, including the UK. Full details of the SLR strategy, study selection process and results are presented in Appendix I. Where appropriate, cost and resource use estimates in the model were used from previous NICE Technology Appraisal (TA) submissions[112, 117], UK studies (identified from the SLR) with more recent costs sourced from the UK cost databases where relevant. The remaining

studies were excluded from the analysis and not used to inform inputs in the cost-effectiveness model as they were based on countries other than the UK.

The following cost categories are incorporated into the economic model:

- Drug acquisition costs
- Drug administration costs
- Subsequent treatment costs
- Health state resource use costs (e.g., ongoing monitoring and follow-up)
- AE costs
- End of life care costs

B.3.5.1. Intervention and comparators' costs and resource use

Drug acquisition costs

Treatment costs are calculated based on the recommended dosing regimen for each drug for the modelled treatment duration, as detailed in Sections B.3.2.3 and B.3.2.4. The recommended dose per administration, cost per administered dose and list prices for relevant treatments are presented in Table 41.

As previously described, elranatamab is implemented in the economic model according to the SmPC dosing.[16] Drug acquisition costs were based on the full recommended dose including wastage and relative dose intensity (RDI) of [redacted] (based on RDI of MagnetisMM-3, 15-month data-cut). This accounts for the higher threshold for the Q2W de-escalation in the MagnetisMM-3 trial protocol versus the expected SmPC criteria (i.e. after 24 weeks, patients were required to maintain a response for 2-months to step-down in the trial, versus having to achieve a response in the SmPC). Additionally, vials are a fixed dose (i.e., not weight-based), thus wastage will not occur, unless a patient is on a reduced dosing level. A patient access scheme (PAS) discount of [redacted] has been submitted to reduce the net price [redacted]

In the base case analysis, a stopping rule for elranatamab is applied after 36 months. This is deemed a pragmatic approach to the maturity of the current data and

risk–benefit balance with long-term elranatamab use. See Appendix N for a detailed explanation on rationale.

An additional scenario is modelled,

[redacted]

This change is tested in scenario analysis below.

For POM+DEX, pomalidomide is available as 4 mg tablets with a list price per 21-day supply of £8,884.00[118] (note there is a PAS discount available, which is confidential and thus the list price is considered in the analyses). The recommended dose of pomalidomide is 4 mg, orally administered once daily for 3 weeks followed by a 1-week break every 4-week cycle. Dexamethasone is available as 2 mg tablets inclusive of a pack size of 50 at a list price of £3.27. The recommended dose of dexamethasone is 40 mg once a week, orally administered. This dosing regime is consistent with the observed dose of POM+DEX in the MM-003 study.[104] Medication costs were adjusted for differences between planned and actual doses received based on drug-specific estimates of relative dose intensity obtained from MagnetisMM-3 for elranatamab and MM-003 for POM+DEX. Premedication patients are assumed to receive all of their planned doses, i.e., no relative dose intensity is applied.

Table 41: Unit costs of drug acquisition costs for intervention and comparators including premedication

Regimen component	Unit size	Pack size	Unit cost per pack (£)	Dose required	Relative dose intensity	Source
Elranatamab	44 mg	1	List Price [redacted] PAS Price [redacted]	12 mg 32 mg	[redacted]	Pfizer Inc.[99]
Elranatamab	76 mg	1	List Price [redacted] PAS Price [redacted]	76 mg	[redacted]	
Pomalidomide	4 mg	21	8,884.00	4 mg	90%	MIMS UK 2023[118]
Dexamethasone	2 mg	50	2.46	40 mg	90%	eMIT[119], TA510[112]
Paracetamol	500 mg	100	0.88	500 mg	No RDI applied	
Dexamethasone (orally or intravenously)	20 mg/ 5 mL	50 mL	30.63	20 mg		
Chlorphenamine	4 mg	28	0.56	25 mg		

Key: eMIT electronic market information tool; MIMS, Monthly Index of Medical Specialties; RDI relative dose intensity.

Drug administration costs

In the economic model, drug administration costs are accrued for the duration of treatment in the elranatamab and POM+DEX arms (Section B.3.2.3 and B.3.2.4, respectively). The unit costs of the intravenous administration of dexamethasone were sourced from NHS reference costs (Table 42). Premedication (Table 41) is administered orally, with the exception of dexamethasone which is administered intravenously.

SB12Z (£207.59) is used for the first elranatamab dose in Cycle 1; all subsequent doses of elranatamab used SB12Z, which also assumed £207.59 per administration. For POM+DEX, SB11Z (£197.25) is used for the first dose only. Subsequent doses have zero cost associated as this is an oral treatment. For premedication of dexamethasone, which requires IV administration, SB13Z (£256.95) is used for the first dose in Cycle 1; all IV subsequent doses use SB15Z (£326.46) per

administration using latest NHS reference costs 2021–2022[120] and codes, which are in line with codes used in previous submissions.[72, 112]

As per the trial protocol, elranatamab-treated patients require hospitalisation during the step-up dosing protocol to mitigate the risks of CRS and neurotoxicity for the first dose (48 hours) and the second dose (24 hours). Patients should also be within proximity of a healthcare facility for 48 hours, therefore assuming a total of 5 days, in line with premedication specifications detailed in Section B.3.2.3.1. A total of 5 days was validated through clinical and NHS commissioner expert advice[2]. A conservative scenario is modelled where patients were hospitalised for a total of 7 days. However, if a bed can be released this could be as little as 3 days. Furthermore, clinicians have confirmed that as they become more familiar with the management of dosing and adverse events resource use impact may change over time.[3] Hospitalisation unit costs per day are presented in Table 43.

Table 42: Administration costs

Type of administration	NHS reference code	Cost (£)	Source
Oral, first dose	SB11Z	197.25	NHS reference costs (cost year 2021–2022)[120]
Oral, subsequent dose(s)	Assumed same as TA658	0.00	
Injection, first dose	SB12Z	207.59	
Injection, subsequent dose(s)	SB12Z	207.59	
IV, first dose	SB13Z	256.95	
IV, subsequent dose(s)	SB15Z	326.46	
Key: IV, Intravenous; NHS, National Health Service.			

Table 43: Resource use cost

Resource use	Unit cost (£)	Source
Hospitalisation (days)*	517.19	MagnetisMM-3, NICE TA567[117], NHS Reference Costs – 2021/22.[120] Day case – weighted average of malignant lymphoma, SA31A – SA31F
Note: *Elranatamab required hospitalisation during the step-up dosing protocol to mitigate the risks of CRS and neurotoxicity. **Key:** CRS, cytokine release syndrome; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.		

B.3.5.1.1. Subsequent treatment costs

After progressing on elranatamab, some patients will receive subsequent treatment (see Section B.2.6 and Table 10.) As shown in Section B.2.6, several treatments have been recommended by NICE for patients with RRMM that would be suitable for use after a patient experiences PD on elranatamab. To reflect that patients are expected to receive treatment following progression, the model includes the cost of subsequent therapies. In accordance with the NICE position statement on the inclusion of therapies recommended via the CDF, only those treatments that have been recommended for routine funding by NICE, and not via the CDF, have been considered as subsequent therapies in the base case analysis.[121]

In the model, which consists of only four alive health states (PF [on/off treatment] and PD), the cost of subsequent therapies has been included as a single, one-off cost applied to patients who progress from PF (on/off treatment) to the PD health states.

As the majority of subsequent therapies are 'treat to progression', the total cost of treatment was based on the median subsequent treatment duration reported by MagnetisMM-3.[99]

The proportion of patients receiving treatment with each subsequent therapy is detailed in Table 44 and based on treatment options conveyed by expert UK clinicians' experience of treatment use following elranatamab and POM+DEX in 3L, 4L and 5L (see Section B.3.11.3). Additionally, feedback from clinician interviews and a clinical advisory board meeting confirmed that, if elranatamab were to be given at 3L or 4L, subsequent therapy would be POM+DEX[1-3]. If elranatamab was given later at 5L, POM+DEX would likely have been used at 4L. Thus, subsequent therapy is difficult to determine but would include PANO+BORT+DEX (if not already given at 3L), or any alkylation treatment options left, such as cyclophosphamide or melphalan, or a recycling of previous therapy.[3]

The dosing regimens of subsequent therapies included in the model are presented in Appendix M. These were based on dosing schedules outlined in their respective

SmPC submissions or pivotal trials for each regimen. The unit costs and total costs per administration associated with the individual therapies included within the subsequent treatment regimens are presented in Appendix M. In calculating the cost of subsequent therapies in the model, it should be noted that:

- In the model, the subsequent treatment durations were capped by the estimated PPS durations of each treatment, so that the subsequent treatment durations were not longer than the PPS durations
- NICE recommendations are subject to manufacturers providing the relevant treatments in accordance with the terms of a confidential commercial arrangement. In the cost-effectiveness analyses provided in this submission, these treatments have all been included at list price
- For patients receiving the POM+DEX comparator in the model, POM+DEX was set to 0% as it was assumed that patients treated with POM+DEX would not be retreated with a subsequent treatment

Table 44: Subsequent therapy proportions – clinical expert advice

Subsequent treatment	Distribution elranatamab	Distribution POM+DEX
Pomalidomide, dexamethasone	90.0%	0.0%
Panobinostat, bortezomib, dexamethasone,	8.0%	70.0%
Cyclophosphamide, dexamethasone	2.0%	30.0%
Key: POM+DEX, pomalidomide and dexamethasone.		

Table 45: Summary of drug acquisition costs for subsequent treatments – drug costs per cycle

Treatment	Total subsequent treatment one-off cost (weighted)	Total subsequent administration one-off cost (weighted)
Elranatamab	[redacted]	209.46
POM+DEX	47,271.33	4,335.90
Key: POM+DEX, pomalidomide and dexamethasone **Note:** Subsequent treatment cost differ due to lower calculated post-progression time for elranatamab patients.		

B.3.5.2. Health state unit costs and resource use

Costs associated with ongoing disease management, monitoring and patient follow-up are included in the economic model. Healthcare resources were included which

were specific to each health state (i.e., PF or PD). Costs were applied to each resource and accrued according to the time spent in each health state. In line with the NICE reference case[103], relevant unit costs were sourced from either the Personal Social Services Research Unit[122] or the NHS reference cost documentation and reflect 2021–2022 prices.[120] The approach to health state costs was based on NICE TA510.[112] It was assumed that patients receiving RRMM treatment require frequent monitoring, including physician visits, complete blood counts and biochemistry.

Table 46 describes each of the monitoring test costs associated with each health state for elranatamab and POM+DEX. It is assumed the health state costs are the same for all treatments. In each health state the model calculates frequencies of the monitoring tests which were obtained from the NICE TA658 submission.[4] Costs are weighted differently according to the proportion of patients in pre- or post-progression state. In the post-progression phase, the same monitoring test frequencies were applied to all treatments. Unit costs were multiplied by the frequency of each resource to generate the total disease monitoring cost per cycle for each health state.

Table 46: Health-state-specific resource use frequencies and costs

Resource use	Progression free	Post progression	Unit cost (£)	Source
Monitoring test				
Complete blood count test	0.23	0.23	2.96	NICE TA658[4], 2021/22 NHS reference costs[120] (DAPS05: haematology)
Biochemistry test	0.23	0.23	1.55	NICE TA658[4], 2021/22 NHS reference costs*** (DAPS04: clinical biochemistry)
Medical resource use				
Physicians' office visit	0.23	0.23	193.99	NICE TA658[4], 2021/22 NHS reference costs[120] (Services code 303: clinical haematology)

Key: CRS, cytokine release syndrome; NHS; National Health Service; TA, technical appraisal.
Notes: * Unit cost was sourced from NHS Reference Costs (2021–2022). directly accessed pathology services – DAPS05: haematology. ** Unit cost was sourced from NHS reference costs – 2021–2022. directly accessed pathology services – DAPS04, clinical biochemistry. *** Unit cost was sourced from NHS reference costs – (2021–2022). Directly accessed pathology services – DAPS04, clinical biochemistry.

B.3.5.3. Adverse reaction unit costs and resource use

In the model, the cost of AEs was incorporated as a one-off cost in the first model cycle. Costs were sourced from relevant NICE TAs[4, 112, 117] and supplemented by the NHS reference costs where applicable.[120] Table 47 details AE costs per episode included in the model. Total average AE management costs are calculated based on the incidence, recurrence and duration of Grade 3+ AEs observed in ≥ 5% of patients in MagnetisMM-3 or MM-003 for POM+DEX and included in the model, as presented in Section B.3.4.4. Adverse events specific to elranatamab include

neurotoxicity, CRS and IVIG usage. Note the monitoring costs for CRS are likely a conservative estimate and likely double counting would occur after already including costs for patient monitoring under healthcare resource use costs.

Table 47: AE costs

AE	Cost per episode (£)	Source
AE applicable to elranatamab only		
Neurotoxicity (Grade 1–2)	2,982	NHS reference cost 2021/22[120] weighted average AA22F – AA22G; elective inpatient
Neurotoxicity (Grade 3–4)	10,675	NHS reference cost 2021/22[120] weighted average AA22C – AA22D; elective inpatient
CRS (Grade 1–2)	2,755*	NICE TA559[123]
CRS (Grade 3–4)	9,957*	NICE TA567[117] NHS reference cost 2021/22[120] (XC01Z-XC07Z)
IVIG	1,573.58**	MagnetisMM-3
AE applicable to elranatamab and POM+DEX		
Anaemia	866	NICE TA658,[4] NHS reference cost 2021/22[120] (SA04G, SA04L)
Alanine aminotransferase increased	385	Assume to be the same as aspartate aminotransferase increase
Aspartate aminotransferase increased	385	Assumed to be the same as hypokalaemia
Fatigue	535	NICE TA658,[4] NHS reference cost 2021/22[120] (SA01G-SA01K)[4]
Febrile neutropenia	5,430	NICE TA658[4] (PM45B-PM45D)
Hypertension	640	NICE TA658[4]
Infection	431	NICE TA567[117]
Leukopenia	1,365	NICE TA510, NHS reference cost 2021/22[120] (SA08G-SA08H, SA08J)
Lymphopenia	1,365	Assumed to be the same as leukopenia
Nausea	750	NICE TA658[4] (clinic visit)
Neutropenia	1,365	NICE TA567, NHS reference cost 2021/22[120] (SA08G, SA08H, SA08J)
Pneumonia	2,512	NICE TA658,[4] NHS reference cost 2021/22[120] (DZ11K, DZ11V)
Renal and urinary disorders	4,130	NHS reference costs 2021/22[120]
Sepsis	4,974	NICE TA658[4]
Thrombocytopenia	993	NICE TA658, NHS reference cost 2021/22[120] (SA12G-SA12K)

Key: IVIG; Intravenous immunoglobulin; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.
Note: *CRS costs inclusive of tocilizumab based on TA567 and ICU costs taken from NHS reference cost 2021/22112 based on weighted average of codes XC01Z-XC07Z, critical care. These costs therefore represent a conservative estimate and double counting could be involved for monitoring costs as monitoring costs assigned for the observation of patients would be inclusive of monitoring for those that experienced CRS.
**Based on a unit cost of £42.50 per g, following NHS commissioning guidance.[124] See section B.3.3.6 for further detail of IVIG calculation.

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. End of life costs

The approach to end of life costs was aligned to approaches in previous RRMM submissions.[71, 112] A one-off cost was used to account for the costs of patients in their last week of life. The utilisation of terminal care was informed by TA427[72], during which an advisory board was conducted for a prior submission. According to this data, 20% of patients opt for hospital services, 40% choose hospice services, and another 40% opt for home services when approaching the end of life. Costs per day by setting were obtained and multiplied by seven to obtain weekly costs.[125] The uplifted cost, using the inflation indices from the Personal Social Services Research Unit for 2022[122], gives a one-off end of life care cost of £961.67. This cost is applied in the model when a patient enters the death health state.

B.3.6. Severity

Based on the quality-adjusted life year (QALY) shortfall calculator published by Schneider et al.[126], elranatamab meets the criteria for the application of a QALY modifier reflecting the severity of RRMM in patients who have received at least three prior treatments (including a PI, an IMiD and an anti-CD38 mAb) and have demonstrated disease progression on the last therapy. It was concluded that the most appropriate severity modifier is 1.2x (i.e., an >85% proportional shortfall) indicating that the application of a QALY modifier should be considered for this appraisal. The main features of the QALY shortfall analysis are summarised in Table 48.

Based on the median age of 67.10 years for the three or more prior therapies in the MM-3 clinical trial, the expected QALYs for a healthy individual are 10.22. The discounted QALYs (without the severity modifier weighting) in the POM+DEX arm in

the base case are 0.89 (Table 49). Therefore, the absolute QALY shortfall is 9.33 (i.e., 10.22–0.89). The proportional QALY shortfall is 91.27% (i.e., 9.33/10.22).

Table 48: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution	55%	B.3.2.1
Starting age	67	MagnetisMM-3, 15-month data. CSR Table 14.1.2.1.
Discount rate	3.5%	NICE reference case[103]
Key: CSR, clinical study report; QALY, quality-adjusted life year.		

Table 49: Summary of QALY shortfall analysis

Treatment	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall (absolute/proportional)
POM+DEX	10.22	0.89	9.33/ 90.27%
Key: POM+DEX, pomalidomide and dexamethasone; QALY, quality-adjusted life year.			

B.3.7. Uncertainty

We aim to present an analysis that is as robust as technically feasible with the data available. Nevertheless, some uncertainties remain and are due to changing treatment landscape and limitations in the available data. These uncertainties are discussed below. In addition, the impact of these uncertainties is further explored through sensitivity analyses where possible, as discussed in Section B.3.11.

One source of uncertainty relates to the fact that MagnetisMM-3 is a single-arm trial. Therefore, an MAIC was considered necessary to calculate the relative benefit of elranatamab compared with real-world practice. As discussed in Section B.1.1, POM+DEX is the relevant comparator in this submission, with comparative evidence from the MM-003 trial analysed via an MAIC. However, there were some uncertainties around this MAIC, including differences in patient population. For POM+DEX, previous treatment with pomalidomide is an exclusion criterion. In the

elranatamab trial, 81% of patients in Cohort A are previously treated with pomalidomide.[84, 85]

Additionally, patients who are refractory to anti-CD38 are not included in POM+DEX. In the MagnetisMM-3 study, 99% of patients in Cohort A were refractory to anti-CD38.[84] Another limitation is that extramedullary disease and cytogenetic risk are excluded from the POM+DEX MAICs as they are not reported in the MM-003 trials, and the definitions do not match to MagnetisMM-3. This causes bias in the relative estimation of elranatamab's efficacy, as patients in MM-003 were not TCR, meaning efficacy outcomes from this trial will provide upper bound estimates, given that true TCR patients will have worse outcomes. As discussed in Section B.2.9, several of these uncertainties were explored in a series of scenarios, which resulted in similar HRs to the base case MAIC. To mitigate some of these challenges, an alternative source of efficacy was investigated in an alternative scenario. The ECA study provides data on [redacted] patients treated with POM+DEX, providing a practical example of the observed effectiveness of POM+DEX and demonstrating potentially more realistic outcomes for patients than expected based on our base case analysis for POM+DEX. These outcomes offer decision makers a spectrum of projected results for patients undergoing POM+DEX treatment. This scenarios impact on model results, is discussed in Section B.3.11.

Another uncertainty is the need for more mature data. At the time of submission, only 15-month data were available for elranatamab with median PFS and OS having not yet been reached. Extrapolating these data beyond the observed creates uncertainty around the OS, PFS and TTD extrapolations. Further data-cuts are expected for elranatamab in [redacted] and [redacted] to supplement the existing evidence. Nevertheless, these uncertainties are explored in scenarios assessing different extrapolations. In addition, any parameter uncertainty around the extrapolations is explored in the probabilistic sensitivity analysis (PSA); data from an ECA are explored in scenario analysis.

Another source of uncertainty is that most of the subsequent treatments from MagnetisMM-3 are unavailable to patients as the treatments are not reimbursed, licensed or available at this treatment line. Therefore, treatment regimens for

subsequent treatment were sourced from clinicians, and some variation was noted between experts for patients post-treatment with elranatamab or POM+DEX.[3] Acknowledging this source of uncertainty, a scenario is included utilising the subsequent treatment MagnetisMM-3 reweighted to those used in UK clinical practice.

IVIG usage provides another aspect of uncertainty. MagnetisMM-3 was predominantly a US population, where there is more liberal use of prophylactic IVIG, whereas the UK has a more limited supply and has restricted use to specific indications. In order to prescribe IVIG clinicians must show that specific criteria have been met, prophylactic IVIG use with bispecific antibodies in MM, outside of clinical trials, is not permitted.[97] Furthermore, MagnetisMM-3 was conducted during the COVID-19 pandemic which may have increased IVIG usage. The differing IVIG use practices, stringent UK policies and the COVID-19 pandemic mean that UK post-pandemic usage would be expected to be lower than in the MagnetisMM-3 trial.

B.3.8. Managed access proposal

As detailed in Section B.2.12.2, in recognition of the uncertainty within the current evidence base and the immaturity of data from the MagnetisMM-3 study, elranatamab may be considered as a candidate for managed access with the CDF. The company are developing a UK real world evidence strategy for elranatamab which could inform any data collection and are considering the development of a managed access proposal. Therefore, should any identified uncertainty be resolvable through data collection, the company would consider this option at that time to allow earlier access to patients.

B.3.9. Summary of base case analysis inputs and assumptions

B.3.9.1. Summary of base case analysis inputs

Appendix M summarises the variables applied in the economic model and refers to the section in the submission where it is explained in more detail.

B.3.9.2. Assumptions

A summary of modelling assumptions is provided, divided by aspect of the cost-effectiveness model, in Table 50.

Table 50: Summary of assumptions applied in the cost-effectiveness analysis

Category	Base case analysis assumptions	Justification/impact	Reference to section
Time horizon	Lifetime (25 years)	The time horizon was considered long enough to capture the long-term clinical and economic impacts of RRMM, an incurable disease requiring treatment until end of life. Given the median age of 67.10years for the MagnetisMM-3 trial population, 25 years is a fair approximation of a lifetime time horizon. Alternative time horizons (10 and 15 years) are considered in scenario analyses	B.3.2.2
Model cycle length	1 week	A cycle length of 1 week was considered sufficient to capture the rapid progression of RRMM	B.3.2.2.1
Discount	3.5%	Per the guidelines for the economic evaluation of HTAs in the UK	B.3.2.2.1
Modelling approach	PSM	A PSM closely models PFS and OS trial data and is commonly used in oncology models, as reported in the NICE DSU TSD 21 and 14 and in prior evaluations of treatments for RRMM[105, 106]	B.3.2.2
Population	Patients with no prior BCMA-directed treatment, RRMM	The model uses efficacy data from the Cohort A of the MagnetisMM-3 ITT population which included patients who were TCR	B.3.2.1
Survival projections	Elranatamab: It was assumed that: • PFS cannot be longer than OS (until curves cross at 2 years) from which • PFS dominates OS POM+DEX: It was assumed that:	The elranatamab PFS and OS curves are very close nearer the end of the available trial follow period (18 months). This may be explained by the greater number of events and more mature PFS curve which, unlike the OS Kaplan-Meier, has had time to plateau during trial follow-up. The converging OS and PFS Kaplan-Meier curves mean that, the traditional logic (of the OS extrapolation dominating the PFS extrapolation), extrapolated curves rapidly cross, violating the key assumptions underpinning partitioned survival modelling mentioned in NICE TSD 19.[100] Therefore, drawing on the approach adopted by the York ERG in TA559,	B.3.2.2

Category	Base case analysis assumptions	Justification/impact	Reference to section
	• PFS cannot be greater than OS TTD, PFS and OS cannot be greater than SMR adjusted survival in general population	we assume that the typical PSM assumptions would not apply and instead assume that PFS dominates OS after 2 years. As no OS and PFS curve crossing or plateauing of data is observed in the POM+DEX KM data, typical assumptions of partitioned survival modelling, along with trends in hazards over trial period that are generalizable over the extrapolation period.[100]	
Extrapolation	TTD, PFS on-treatment, PFS, and OS curves were extrapolated by fitting parametric distributions to the Kaplan–Meier curves. Curve selections were based on best statistical fit and clinical face validity of predictions	Per NICE guidance. Because the trial duration was insufficiently long to capture the full long-term benefits of intervention and comparators, survival had to be extrapolated beyond the end of trial follow-up. General population mortality includes beyond the end of trial follow-up, with the application on a SMR to maintain the plausibility of parametric extrapolations	B.3.3
Treatment duration	Follows TTD distribution in MagnetisMM-3	TTD distributions were estimated based on the MagnetisMM-3 trial data	
Subsequent treatments	Based on clinical expert advice. Scenario analysis explores re-weighted MagnetisMM-3 options based on options that would be available to patients in the UK after 3rd line.	Treatment options in MagnetisMM-3 trial were validated by clinical experts. The proportion of patients receiving subsequent treatment is based on Cohort A MagnetisMM-3, 15-month data, CSR Table 14.4.2.6.2.	B.3.5.1.1
AEs	MagnetisMM-3 trial for elranatamab and MM-003 for POM+DEX	The model includes AEs for which Grade 3+ events were reported in ≥ 5% of the patients in any of the treatment arms of MagnetisMM-3 or for the relevant pivotal trial of the key comparator MM-003[99]	B.3.3.6
Follow up	Follow-up costs were assumed	The frequencies and types of follow-up and monitoring costs used in the	B.3.5

Category	Base case analysis assumptions	Justification/impact	Reference to section
costs	to be the same for all treatments	model were based on clinical expertise in the UK, with clinicians believing that resource use would not vary by treatment	
Utilities	EQ-5D-3L utility data obtained via a mapping EQ-5D-5L from MagnetisMM-3 trial	In line with the NICE reference case[103]	B.3.4
General population utilities	General population utilities applied as a floor	It was assumed that utilities among all treatments would not exceed that of the general population	B.3.2.2
Key: AEs, adverse events; BCMA, B-cell maturation antigen; DSU, Decision Support Unit; HTA, health technology assessment; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; PPS, post-progression survival; PSM, partitioned survival model; TBC, to be confirmed; TSD, technical support document; TTD, time to discontinuation; RRMM, relapsed/refractory multiple myeloma.			

B.3.10. Base case results

B.3.10.1. Base case incremental cost-effectiveness analysis results

Table 51 displays base case cost-effectiveness results for the RRMM population, in the comparisons of elranatamab versus POM+DEX. Results are inclusive of a confidential [redacted] PAS discount to the elranatamab list price. Table 52 display the net health benefit results, at willingness-to-pay (WTP) thresholds of £20,000 and £30,000.

Elranatamab is estimated to result in a high per-patient incremental health benefit, offering a substantial life year (LY) and time-preference discounted QALY benefit versus POM+DEX (3.47 LYs and [redacted] QALYs for elranatamab versus 1.36 LYs and [redacted] QALYs for POM+DEX). Using the elranatamab PAS price, the estimated incremental cost-effectiveness ratio (ICER) for elranatamab versus POM+DEX is £[redacted] per QALY gained.

Estimates of clinical outcomes compared with trial results and disaggregated results are presented in Appendix J.

Table 51: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Elranatamab	[redacted]	3.47	[redacted]				
POM+DEX	[redacted]	1.36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; POM+DEX, pomalidomide and dexamethasone; QALYs, quality-adjusted life years.

Table 52: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Elranatamab	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; POM+DEX, pomalidomide and dexamethasone.

B.3.11. Exploring uncertainty

B.3.11.1. Probabilistic sensitivity analysis

The PSA results presented herein are based on 5,000 random draws from uncertain input parameter distributions. The mean outcomes (see Table 53) appear robust to additional PSA draws, as illustrated within the cost-effectiveness model. Figure 54 shows the 5,000 iterations of the probabilistic analysis alongside the deterministic and probabilistic ICER for elranatamab versus POM+DEX. Figure 53 displays probabilistic cost-effectiveness results for the base case population between elranatamab and its comparator POM+DEX. Mean probabilistic results are close to deterministic results, with a probabilistic ICER of £[redacted], compared with a deterministic ICER of £[redacted] indicating outcomes are robust to uncertainty from parameter distributions. Figure 54 shows the cost-effectiveness acceptability curve; elranatamab is predicted to be the most cost-effective treatment option at WTP thresholds over £30,000.

Figure 53: PSA scatterplot, elranatamab versus POM+DEX

Key: POM+DEX, pomalidomide and dexamethasone; QALYs, quality-adjusted life years.

Figure 54: Cost-effectiveness acceptability curve

Key: POM+DEX, pomalidomide and dexamethasone.

Table 53: Mean probabilistic base case results

	Total costs	Total LYs	Total QALYs	Incremental Elranatamab versus POM+DEX			ICER
				Costs	LYs	QALYs	
Elranatamab	[redacted]	3.56	[redacted]				
POM+DEX	[redacted]	1.44	[redacted]	[redacted]	2.13	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; POM+DEX, pomalidomide and dexamethasone; QALYs, quality-adjusted life years.

B.3.11.2. Deterministic sensitivity analysis

Figure 55 is a tornado diagram depicting the 10 parameters that have the greatest influence on the elranatamab ICER versus the base case comparator. For one-way sensitivity analysis (OWSA), values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the CIs reported in Appendix M. Multivariate parameters are treated as having univariate uncertainty distributions for this analysis, given its purpose of illustrating model drivers.

Figure 55: Tornado diagram showing OWSA results, elranatamab versus POM+DEX

Key: MRU, medical resource use; OWSA, one-way sensitivity analysis; POM+DEX, pomalidomide and dexamethasone; PPS, post-progression survival; QALY, quality-adjusted life year; RDI, relative dose intensity.

B.3.11.3. Scenario analysis

The scenario analyses reported here test the sensitivity of cost-effectiveness results to methodological, parameter and structural assumptions in the cost-effectiveness analysis, and form an important element of this submission.

A key scenario was the analysis of the ECA study. This analysis provides a real-world practical example of the effectiveness of POM+DEX in patients. We report the detailed results of this analysis first and provide a summary of all other scenarios tested in Section B.3.11.3.

ECA study scenario

The results of the ECA study scenario are presented in Table 54. Using the elranatamab PAS price elranatamab is associated with incremental QALYs of [redacted] and an estimated ICER for elranatamab versus POM+DEX of £[redacted] per QALY gained. Table 55 display the net health benefit results, at willingness-to-pay (WTP) thresholds of £20,000 and £30,000.

The higher ICER estimated in this scenario compared with the base case analysis are largely due to the poorer outcomes as predicted based on the ECA data. This results in a much lower time on treatment and in the progression free health state, and worse health outcomes. As noted previously the MAIC informed analysis is likely to lead to the effectiveness of POM+DEX being overestimated because the MM-003 population is less treatment exposed, and therefore easier to treat than the MagnetisMM-3 Cohort A population.

Table 54: ECA study scenario

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Elranatamab	[redacted]	3.59	[redacted]				
POM+DEX	[redacted]	1.27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; POM+DEX, pomalidomide and dexamethasone.

Table 55: ECA study scenario: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Elranatamab	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; POM+DEX, pomalidomide and dexamethasone.

OWSA was conducted to explore the sensitivity in the ECA study scenario results when one parameter is varied at a time. Each parameter was set to its lower and upper bound, and the deterministic model results were recorded. A summary of the parameters varied in the analysis is presented in Appendix Q alongside further probabilistic and scenario analysis.

Figure 56 is a tornado diagram depicting the 10 parameters that have the greatest influence on the elranatamab ICER versus POM+DEX. For OWSA, values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the CIs reported in Appendix Q.

Figure 56: Tornado diagram showing OWSA results, elranatamab versus POM+DEX - ECA study scenario

Key: MRU, medical resource use; OWSA, one-way sensitivity analysis; POM+DEX, pomalidomide and dexamethasone; QALY, quality-adjusted life year; RDI, relative dose intensity.

All other scenarios

Table 56 describes different scenarios tested and the rationale behind each and documents the ICERs associated with each scenario in turn. Summary results are generally robust to changes tested across the broad range of scenarios. The most impactful scenario was using an alternative stopping rule applied when less than 10% of patients are on treatment, (increases ICER by 156%), however, this is still

below the £30,000 WTP threshold. Many of the other scenarios did not significantly change the ICER, with the difference to the ICER being less than 20%, including changing the selected curve choice, utility source and time horizon. Scenarios which reduce the ICER include changing the source of POM+DEX PFS extrapolation to lognormal and log-logistic, which resulted in elranatamab dominating which was within the range of survival estimates stated by clinical experts. This shows the ICER is robust despite varying key assumptions surrounding SMR, utility sources and elranatamab hospitalisation.

Table 56: Scenario analysis

Element	Base case	Scenario analysis	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
Base case			[redacted]	[redacted]	£[redacted]	
Time horizon	25 years	15 years	[redacted]	[redacted]	£[redacted]	[redacted]
Time horizon		20 years	[redacted]	[redacted]	£[redacted]	[redacted]
Discount rates	3.5%	1.5%	[redacted]	[redacted]	£[redacted]	[redacted]
PFS Parametric curve, elranatamab	Generalised gamma	Gompertz	[redacted]	[redacted]	£[redacted]	[redacted]
PFS Parametric curve, POM+DEX	Generalised gamma	Log-logistic	[redacted]	[redacted]	£[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]	£[redacted]	[redacted]
OS Parametric curve, elranatamab	Generalised gamma	Gompertz	[redacted]	[redacted]	£[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]	£[redacted]	[redacted]
OS Parametric curve, POM+DEX	Generalised gamma	Exponential	[redacted]	[redacted]	£[redacted]	[redacted]
Elranatamab hospitalisation	5	7	[redacted]	[redacted]	£[redacted]	[redacted]

Element	Base case	Scenario analysis	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
Elranatamab stopping rule	36 months	Less than 10% of patients on treatment	[redacted]	[redacted]	£[redacted]	[redacted]
Alternative health state utilities, based on TA427[72]	PFS: 0.71 PPS: 0.63	PFS: 0.76 PPS: 0.62	[redacted]	[redacted]	£[redacted]	[redacted]
Alternative health state utilities, based on TA658[4] (assume same for both treatment arms)		PFS: 0.72 PPS: 0.55	[redacted]	[redacted]	£[redacted]	[redacted]
Alternative health state utilities, based on TA658[4] (treatment specific utilities)		PFS (elranatamab): 0.73 PFS (POMDEX): 0.72 PPS: 0.55	[redacted]	[redacted]	£[redacted]	[redacted]
SMR	Time varied	Constant	[redacted]	[redacted]	£[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; Q2W, once every two weeks; Q4W, once every four weeks; RDI; relative dose intensity; SMR, standardised mortality ratio; TTD, time to discontinuation; WTP, willingness-to-pay.

B.3.12. Subgroup analysis

No subgroup analysis is provided in this submission (Section B.1.1).

B.3.13. Benefits not captured in the QALY calculation

Elranatamab is a BCMA–CD3 bispecific antibody and is the only fixed-dose monotherapy treatment given by SC injection, which is a mode of administration preferred by patients compared with intravenous infusion.[42, 60] As an alternative to IV administration, SC dosing also has the potential to impact healthcare resourcing and reduce time of administration. As described in Section B.1.3.4, there are currently no BCMA-targeted therapies reimbursed in the UK. As such, if elranatamab is approved, this would allow TCR MM patients to have access to a BCMA-targeted therapy, which UK clinicians argue represents the fourth pillar alongside PI, IMiDs and anti-CD38 mAbs for the treatment of RRMM.[2]

In addition, as described in Section B.1.3.2.4, caregivers of MM patients can experience a substantial impact on their HRQL, can be affected by patients' treatment regimens and can experience financial difficulties.[61-65] Carer disutilities are not captured within the QALY calculation.

B.3.14. Validation

B.3.14.1. Validation of cost-effectiveness analysis

Substantial efforts have been undertaken to validate the modelling approach and results. This section describes, in turn:

- Expert opinion used to validate the modelling approach
- Quality checks performed on the model (internally and by external experts)

B.3.14.1.1. Expert opinion

Expert clinical and health economic input was sought during the development of the cost-effectiveness model for NICE submission. This helped to ensure that the inputs and assumptions used in the base case analysis were relevant to UK clinical practice in order to validate the clinical plausibility of the outcomes predicted by the model. Clinical expert interviews were conducted whereby model inputs and assumptions

were discussed and validated.[1] Five clinicians with experience treating patients with RRMM attended the meetings. Topics covered in the meetings included:

- Unmet medical need in patients with TCR MM
- Current treatment landscape and comparator landscape in UK practice
- Generalisability of trial data to UK practice
- Modelling approach and data inputs
- Estimating relative efficacy of elranatamab and survival curve extrapolations
- Subsequent treatment in UK practice
- IVIG usage in practice

An additional, a strategic review of both the clinical and economic analyses, was provided by Professor Stephen Palmer (acting in a personal capacity)

B.3.14.1.2. Model functionality checks

The model was subjected to rigorous internal verification as a quality assurance measure. Two separate researchers checked the model programming and mathematical calculations. Equations and parameters were assessed to ensure they were correctly cross-referenced against their sources and all modules of code were error-free and replicable. A cell-by-cell check of all Microsoft Excel® sheets in the model was conducted to identify calculation errors. In addition to the calculation and code, the auditing team validated inputs in the model against the original source. Scenario analyses were performed to check if the model behaved as expected when stress-tested using extreme input values.

Additionally, a thorough quality assessment of the early cost-effectiveness model was undertaken by an external reviewer, Praveen Thakola (PT health economics, Sheffield). The external review included error-checking of the model structure, calculations and code implementation, along with an assessment of the plausibility of assumptions and inputs used in the model. Suggestions provided by the expert were carefully addressed and incorporated into the model as deemed appropriate. In summary, the cost-effectiveness model was found to be well designed, appropriately implemented and fit for the purpose of supporting the economic assessment of elranatamab versus POM+DEX.

B.3.15. Interpretation and conclusions of economic evidence

B.3.15.1. Summary of the evidence of the cost-effectiveness analysis

The cost-effectiveness of elranatamab versus POM+DEX was based on an economic model with robust design and thorough validation. The model shows that elranatamab offers marked survival benefits for patients with RRMM after at least three prior therapies, to at least one PI, one IMiD and one anti-CD38 mAb in terms of LYs and QALYs, in comparison with chemotherapy. The results demonstrate that elranatamab is a highly effective treatment associated with PFS and OS benefits for patients who have a high unmet need.

In the deterministic base case cost-effectiveness analysis, elranatamab is cost-effective when compared with POM+DEX over a lifetime time horizon, with [redacted] additional QALYs and £[redacted] costs, including the confidential discount and application of disease severity modifier. The probability of being cost-effective compared with usual care is [redacted]% at a WTP threshold of £30,000 per QALY gained.

The application of a disease severity QALY modifier (of 1.2, applicable for the absolute loss of between 12 to 18 QALYs) reduced the ICER by -20.00%, with no disease severity modifier applied.

The ICER was mostly insensitive to parameters and assumptions tested in one-way sensitivity and scenario analyses. The scenario analyses highlight that the model is robust to changes in key modelling assumptions with all ICERs tested in scenario under the £30,000 threshold. While the ECA efficacy source scenario increases the ICER, it significantly reduces patient survival and patients discontinue POM+DEX treatment earlier, thus the incremental decrease in QALYs is offset by the incremental decrease in costs.

Of the other scenarios, those which showed the biggest change in the ICER is associated with including an alternative stopping rule applied when less than 10% of patients are on treatment, however, this is still below the £30,000 WTP threshold.

B.3.15.2. Generalisability to the UK

The base case analysis was designed to provide a cost-effectiveness estimate that is as generalisable to UK practice as is feasible. The efficacy input for elranatamab in the model was based on the MagnetisMM-3 trial, which contained 123 ([redacted]) patients (Cohort A), and was confirmed by UK clinical experts to be generalisable to the label and anticipated indication for UK clinical practice (see Section B.1.3.1).[3] In addition, all model inputs and assumptions were validated by UK clinical experts who confirmed that the MagnetisMM-3 population reflected the current patient population in the UK. Finally, despite potential limitation of the MAIC-derived POM+DEX efficacy, the ECA provided as an alternative data source is derived from the exact target population of the decision in UK clinical practice, thus is directly generalisable.

B.3.15.3. Strengths and weaknesses

No previous economic analyses submitted to NICE were identified for this patient population, thus it was not possible to compare the model results with previous submissions.

The model has been built under the best available evidence and most recent published literature. In the absence of comparative economic analyses, data from a real-world source – the ECA – as described in Section B.3.3.2, were compared to POM+DEX data calculated via an MAIC to validate the data in the context of real-world patients.

One notable advantage of this examination is the utilisation of data on patients' HRQL from the MagnetisMM-3 trial. This gives the analysis a first-hand perspective on the experiences of patients and their encounters with elranatamab.

Whilst the economic analysis has many strengths, some limitations remain. Firstly, the main challenge of the cost-effectiveness analysis relates to the selection of the source to inform the relative efficacy of elranatamab versus POM+DEX. The pivotal MagnetisMM-3 trial informing elranatamab efficacy is a single-arm trial so there is no common comparator when comparing to POM+DEX. This is an important limitation as only unanchored MAICs can be run. Unanchored MAICs come with significant

uncertainty, especially as there are key differences between the trials used in this economic evaluation. The standard limitations of unanchored MAICs are exacerbated in this specific assessment by the limited overlap between the MM-003 population and the decision problem – with the MM-003 population exposed to fewer treatments and therefore easier to treat. Acknowledging the uncertainty of the MAIC, we have provided a scenario based on the ECA study; although this is limited by patient numbers, it provides another source of POM+DEX efficacy for consideration.

However, as discussed in Section B.3.7 and Section B.3.11.3, all these uncertainties were explored in a series of scenario analyses; elranatamab remained cost-effective in all scenarios. This shows that although there is some uncertainty in the model, it is likely that elranatamab is a cost-effective treatment option in RRMM patients who have received at least three prior treatments, including a PI, an IMiD and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy.

B.4. References

1. Pfizer. HTA Advisory Board for Elranatamab for Treating Relapsed or Refractory Multiple Myeloma after Three Therapies 2023.
2. Pfizer. ILAP HTA Access Forum engagement meeting with Pfizer (OMA-1125 – ILAP-111).
3. Pfizer. Clinical Validation Interview Report for the NICE Submission of Elranatamab for Treating Relapsed or Refractory Multiple Myeloma after Three Therapies. 2023.
4. National Institute for Health and Care Excellence (NICE). Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [TA658] 2020 [Available from: https://www.nice.org.uk/guidance/ta658/evidence.
5. National Institute for Health and Care Excellence (NICE). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [TA783] 2022 [Available from: https://www.nice.org.uk/guidance/ta783.
6. Pfizer. Burden of disease in patients diagnosed with multiple myeloma in England: A descriptive, retrospective population-based cohort study using national cancer registry data. 2023.
7. National Institute for Health and Care Excellence (NICE). Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies 2019 [updated 26.06.2019. Available from: https://www.nice.org.uk/guidance/ta171.
8. National Institute for Health and Care Excellence (NICE). Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014] 2023 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10914.
9. National Institute for Health and Care Excellence (NICE). Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma 2021 [updated 03.03.2021. Available from: https://www.nice.org.uk/guidance/ta680.
10. National Institute for Health and Care Excellence (NICE). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma 2023 [updated 06.06.2023. Available from: https://www.nice.org.uk/guidance/TA897.
11. National Institute for Health and Care Excellence (NICE). Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma 2021 [updated 28.04.2021. Available from: https://www.nice.org.uk/guidance/ta695.
12. National Institute for Health and Care Excellence (NICE). Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib Technology appraisal guidance [TA586] 2019 [updated 26 June 2019. Available from: https://www.nice.org.uk/guidance/ta586.
13. National Institute for Health and Care Excellence (NICE). Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 2 therapies [ID5108] 2023 [updated 15.03.2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11018.
14. National Institute for Health and Care Excellence (NICE). Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701] 2023 [updated 14.06.2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10568.

15. National Institute for Health and Care Excellence (NICE). Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026] 2023 [updated 16.05.2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10918.
16. Pfizer. Elranatamab. Draft Summary of Product Characteristics 2023.
17. Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clinic Proceedings. 2016;91(1):101-19.
18. Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos MV, et al. Multiple myeloma. Nat Rev Dis Primers. 2017;3:17046.
19. Callander NS, Baljevic M, Adekola K, Anderson LD, Campagnaro E, Castillo JJ, et al. NCCN Guidelines® Insights: Multiple Myeloma, Version 3.2022. J Natl Compr Canc Netw. 2022;20(1):8-19.
20. UK CR. Myeloma incidence statistics 2021 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-One.
21. Howell D, Smith A, Appleton S, Bagguley T, Macleod U, Cook G, et al. Multiple myeloma: routes to diagnosis, clinical characteristics and survival–findings from a UK population-based study. Br J Haematol. 2017;177(1):67-71.
22. National Health Service (NHS). Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021 2023 [updated 16 February 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021/survival-by-cancer-group.
23. National Institute for Health and Care Excellence (NICE). Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable [TA763] 2022 [Available from: https://www.nice.org.uk/guidance/ta763.
24. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e46.
25. Morè S, Corvatta L, Manieri MV, Olivieri A, Offidani M. Real-world assessment of treatment patterns and outcomes in patients with relapsed-refractory multiple myeloma in an Italian haematological tertiary care centre. British journal of haematology. 2023;201(3):432-42.
26. Moreau P, Kumar SK, San Miguel J, Davies F, Zamagni E, Bahlis N, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol. 2021;22(3):e105-e18.
27. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. Haematologica. 2016;101(4):396-406.
28. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016;175(2):252-64.
29. Costa LJ, Giri S, Bal S, Ravi G, Godby KN. Drug class refractoriness, not number of prior lines of therapy, properly classify patients with relapsed and refractory multiple myeloma. Br J Haematol. 2023;200(6):824-7.
30. BGM D. Multiple Myeloma, Cancer of the Bone Marrow: Concise Review of the Disease and Treatment Options. International Myeloma Foundation North Hollywood, CA; 2011.

31. Goel U, Charalampous C, Kapoor P, Binder M, Buadi FK, Dingli D, et al. Defining drug/drug class refractoriness vs lines of therapy in relapsed/refractory multiple myeloma. Blood Cancer J. 2023;13(1):11.
32. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022;97(8):1086-107.
33. Varughese P, Smith R, Xue M, Dorrow N, Hogea C, Maiese EM, et al. Real-world treatment patterns and outcomes of triple-class treated patients with multiple myeloma in the United States. Expert Rev Hematol. 2023;16(1):65-74.
34. Mateos M-V, Weisel K, De Stefano V, Goldschmidt H, Delforge M, Mohty M, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia. 2022;36(5):1371-6.
35. Elsada A, Zalin-Miller A, Knott C, Caravotas L. A registry study of relapsed or refractory multiple myeloma pre-exposed to three or more prior therapies including a proteasome inhibitor, an immunomodulatory agent and CD38-targeted monoclonal antibody therapy in England. EJHaem. 2021;2(3):493-7.
36. Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-75.
37. Jordan K, Proskorovsky I, Lewis P, Ishak J, Payne K, Lordan N, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. Support Care Cancer. 2014;22(2):417-26.
38. Shapiro YN, Peppercorn JM, Yee AJ, Branagan AR, Raje NS, Donnell EKO. Lifestyle considerations in multiple myeloma. Blood Cancer J. 2021;11(10):172.
39. Ramsenthaler C, Osborne TR, Gao W, Siegert RJ, Edmonds PM, Schey SA, et al. The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. BMC cancer. 2016;16(1):1-16.
40. Molassiotis A, Wilson B, Blair S, Howe T, Cavet J. Unmet supportive care needs, psychological well-being and quality of life in patients living with multiple myeloma and their partners. Psychooncology. 2011;20(1):88-97.
41. Richardson EM, Schüz N, Sanderson K, Scott JL, Schüz B. Illness representations, coping, and illness outcomes in people with cancer: a systematic review and meta-analysis. Psychooncology. 2017;26(6):724-37.
42. Pfizer. Multiple Myeloma Lifelines - TCR Cohort.
43. Song X, Cong Z, Wilson K. Real-world treatment patterns, comorbidities, and disease-related complications in patients with multiple myeloma in the United States. Curr Med Res Opin. 2016;32(1):95-103.
44. Dimopoulos MA, Terpos E, Niesvizky R, Palumbo A. Clinical characteristics of patients with relapsed multiple myeloma. Cancer Treat Rev. 2015;41(10):827-35.
45. Chari A, Romanus D, DasMahapatra P, Hoole M, Lowe M, Curran C, et al. Patient-Reported Factors in Treatment Satisfaction in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). Oncologist. 2019;24(11):1479-87.
46. Despiégel N, Touboul C, Flinois A, Saba G, Suzan F, Gonzalez-McQuire S, et al. Health-Related Quality of Life of Patients With Multiple Myeloma Treated in Routine Clinical Practice in France. Clinical lymphoma, myeloma & leukemia. 2019;19(1):e13-e28.

47. Kamal M, Wang XS, Shi Q, Zyczynski TM, Davis C, Williams LA, et al. Symptom burden and its functional impact in patients with “symptomatic” relapsed or refractory multiple myeloma. Support Care Cancer. 2021;29(1):467-75.
48. Kumar SK, Dimopoulos MA, Kastritis E, Terpos E, Nahi H, Goldschmidt H, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia. 2017;31(11):2443-8.
49. Lee HC, Ramasamy K, Weisel K, Abonour R, Hardin JW, Rifkin RM, et al. Treatment Patterns, Survival, Quality of Life, and Healthcare Resource Use Among Patients With Triple-Class Refractory Multiple Myeloma in US Clinical Practice: Findings From the Connect MM Disease Registry. Clinical lymphoma, myeloma & leukemia. 2023;23(2):112-22.
50. Tang D, Hari P, Ramasamy K, Weisel K, Joshi P, Liu L, et al. Real-world treatment patterns and clinical, economic, and humanistic burden in triple-class refractory multiple myeloma: analysis of the connect® Multiple Myeloma (MM) disease registry. Blood. 2021;138:117.
51. Hu XH, Bozena K, Lowe M, Purnomo L, Gibson C, Rodriguez AM. Health related quality of life in patients with multiple myeloma in relation to line of treatment and response. European Hematology Association 2016.
52. Dimopoulos MA, Moreau P, Terpos E, Mateos M-V, Zweegman S, Cook G, et al. Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Hemasphere. 2021;5(2):e528.
53. National Institute for Health and Care Excellence (NICE). Lenalidomide plus dexamethasone for previously untreated multiple myeloma 2019 [updated 26.06.2019. Available from: https://www.nice.org.uk/guidance/ta587.
54. National Institute for Health and Care Excellence (NICE). Myeloma: diagnosis and management [NG35] 2018 [updated 25.10.2018. Available from: https://www.nice.org.uk/guidance/ng35/chapter/Recommendations#managing-newly-diagnosed-myeloma.
55. Colson K. Treatment-related symptom management in patients with multiple myeloma: a review. Support Care Cancer. 2015;23(5):1431-45.
56. Burwick N, Sharma S. Glucocorticoids in multiple myeloma: past, present, and future. Ann Hematol. 2019;98(1):19-28.
57. National Health Service (NHS). Multiple myeloma treatment 2021 [updated 02.06.2021. Available from: https://www.nhs.uk/conditions/multiple-myeloma/treatment/.
58. Argyriou AA, Cavaletti G, Bruna J, Kyritsis AP, Kalofonos HP. Bortezomib-induced peripheral neurotoxicity: an update. Arch Toxicol. 2014;88(9):1669-79.
59. Bird SA, Boyd K. Multiple myeloma: an overview of management. Palliat Care Soc Pract. 2019;13:1178224219868235.
60. Barbee MS, Harvey RD, Lonial S, Kaufman JL, Wilson NM, McKibbin T, et al. Subcutaneous Versus Intravenous Bortezomib:Efficiency Practice Variables and Patient Preferences. Ann Pharmacother. 2013;47(9):1136-42.
61. Lyall M, Crawford R, Bell T, Mamolo C, Neuhof A, Levy C, et al. Characterizing the Patient Journey in Multiple Myeloma: Qualitative Review. JMIR cancer. 2022;8(3):e39068.
62. Molassiotis A, Wilson B, Blair S, Howe T, Cavet J. Living with multiple myeloma: experiences of patients and their informal caregivers. Support Care Cancer. 2011;19(1):101-11.

63. Goodwin JA, Coleman EA, Sullivan E, Easley R, McNatt PK, Chowdhury N, et al. Personal financial effects of multiple myeloma and its treatment. Cancer Nurs. 2013;36(4):301-8.
64. Kurtin S, Lilleby K, Spong J. Caregivers of multiple myeloma survivors. Clin J Oncol Nurs. 2013;17 Suppl:25-32.
65. Tang W, Thomas R, Parikh K, Goldschmidt D, Pelletier C, Swallow E, et al. PCN218 Burden of Illness on Patients And Caregivers and Quality of Life Outcomes of Triple-Class Exposed (TCE) Patients With Multiple Myeloma (MM) In The United States. Value in Health. 2021;24:S60.
66. National Institute for Health and Care Excellence (NICE). Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation [TA311] 2014 [updated 23.04.2014. Available from: https://www.nice.org.uk/guidance/ta311.
67. National Institute for Health and Care Excellence (NICE). Bortezomib and thalidomide for the first-line treatment of multiple myeloma [TA228] 2011 [updated 27.07.2011. Available from: https://www.nice.org.uk/guidance/ta228.
68. National Institute for Health and Care Excellence (NICE). Bortezomib monotherapy for relapsed multiple myeloma [ta129] 2007 [updated 23.10.2007. Available from: https://www.nice.org.uk/guidance/ta129.
69. National Institute for Health and Care Excellence (NICE). Carfilzomib for previously treated multiple myeloma [TA657] 2020 [updated 18.11.2020. Available from: https://www.nice.org.uk/guidance/ta657.
70. National Institute for Health and Care Excellence (NICE). Panobinostat for treating multiple myeloma after at least 2 previous treatments [TA380] 2016 [Available from: https://www.nice.org.uk/guidance/ta380/evidence.
71. National Institute for Health and Care Excellence (NICE). Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [TA870] 2023 [Available from: https://www.nice.org.uk/guidance/ta870/evidence.
72. National Institute for Health and Care Excellence (NICE). Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib [TA427] 2017 [Available from: https://www.nice.org.uk/guidance/ta427/evidence.
73. Pfizer. ECA in MM using RWE. 2023.
74. Rajkumar SV, Harousseau J-L, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-5.
75. Pfizer. Routes to TCR in the NICE pathway. 2023.
76. Goyal RK, Frugier G, Rombi J, Esterberg L, Davis K, Hlavacek P, et al. Treatment patterns of triple-class refractory (TCR) multiple myeloma (MM) across the united states US), Canada, and western Europe: a real-world observational chart review study. 2023.
77. Guillaume X, Horchi D, Gomez J, Hlavacek P, Ren J, Schepart A, et al. Real-world treatment patterns of triple-class refractory (TCR) multiple myeloma (MM) across the united states (US), Canada, and western europe: a retrospective chart study. 2023.
78. Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. Journal of hematology & oncology. 2020;13(1):125.

79. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. The Lancet. 2021;398(10297):314-24.
80. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. New England Journal of Medicine. 2022;387(6):495-505.
81. Munshi NC, Anderson LD, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. New England Journal of Medicine. 2021;384(8):705-16.
82. Bahlis NJ, Tomasson MH, Mohty M, Niesvizky R, Nooka AK, Manier S, et al. Efficacy and Safety of Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma Naïve to B-Cell Maturation Antigen (BCMA)-Directed Therapies: Results from Cohort a of the Magnetismm-3 Study. Blood. 2022;140(Supplement 1):391-3.
83. Mohamad Mohty M, Michael H. Tomasson, MD, Bertrand Arnulf, MD et al. Elranatamab, a B-cell maturation antigen(BCMA)-CD3 bispecific antibody, for patients with relapsed/refractory multiple myeloma: Extended follow up and biweekly administration from MagnetisMM-3. ASCO. Yokohama: Japan; 2023.
84. Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nature Medicine. 2023.
85. Miguel JS, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2013;14(11):1055-66.
86. Pfizer. 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. 2023.
87. Bahlis NJ, Costello CL, Raje NS, Levy MY, Dholaria B, Solh M, et al. Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial. Nature Medicine. 2023.
88. ClinicalTrials.gov. MagnetisMM-3: Study Of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb 2023 [updated 06042023. Available from: https://clinicaltrials.gov/ct2/show/NCT04649359.
89. Pfizer. MagnetisMM-3 15 Month Study Report Output. 2023.
90. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of epidemiology and community health. 1998;52(6):377-84.
91. Slaney CY, Wang P, Darcy PK, Kershaw MH. CARs versus BiTEs: A Comparison between T Cell-Redirection Strategies for Cancer Treatment. Cancer Discov. 2018;8(8):924-34.
92. Hipp S, Tai YT, Blanset D, Deegen P, Wahl J, Thomas O, et al. A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo. Leukemia. 2017;31(8):1743-51.

93. Dahlén E, Veitonmäki N, Norlén P. Bispecific antibodies in cancer immunotherapy. Ther Adv Vaccines Immunother. 2018;6(1):3-17.
94. Caraccio C, Krishna S, Phillips DJ, Schürch CM. Bispecific Antibodies for Multiple Myeloma: A Review of Targets, Drugs, Clinical Trials, and Future Directions. Front Immunol. 2020;11:501.
95. Pagano L, Salmanton-García J, Marchesi F, Busca A, Corradini P, Hoenigl M, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA). J Hematol Oncol. 2021;14(1):168.
96. Terpos E, Musto, P., Engelhardt, M., Delforge, M., Cook, G., Gay, F., van de Donk, N.W.C.J., Ntanasis-Stathopoulos, I., Vangsted, A.J., Driessen, C., Schjesvold, F., Cerchione, C., Zweegman, S., Hajek, R., Moreau, P., Einsele, H., San-Miguel, J., Boccadoro, M., Dimopoulos, M.A., Sonneveld, P., Ludwig, H. Management of patients with multiple myeloma and COVID-19 in the post pandemic era: a consensus paper from the European Myeloma Network (EMN)(Review). Leukemia. 2023;37(6):Pages 1175-85.
97. NHS. Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021 2021 [Available from: https://www.england.nhs.uk/wp-content/uploads/2021/12/cpag-policy-for-therapeutic-immunoglobulin-2021-update.pdf.
98. Dhanasiri S, Hollier-Hann G, Stothard C, Dhanda DS, Davies FE, Rodriguez-Otero P. Treatment Patterns and Outcomes in Triple-Class Exposed Patients With Relapsed and Refractory Multiple Myeloma: Findings From the Multinational ITEMISE Study. Clin Ther. 2021;43(11):1983-96.e3.
99. Pfizer. MagnetisMM-3: Study Of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb. 2023.
100. Beth Woods, Eleftherios Sideris, Stephen Palmer, Nick Latimer, Soares M. Technical Support Document 19: Partitioned survival analysis for decision modelling in health care: a critical review 2017 [Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD19-Partitioned-Survival-Analysis-final-report.pdf.
101. Office for National Statistics (ONS). National life tables 2021 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020.
102. National Institute for Health and Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies 2023 [Available from: https://www.nice.org.uk/guidance/ta872/history.
103. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013: The reference case 2013 [Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.
104. Weisel K SMJ, Song KW, Delforge M, Karlin L, Goldschmidt H, et al. MM-003 Phase 3 Study Of Pomalidomide In Combination With Low-Dose Dexamethasone (POM + LoDEX) Vs High-Dose Dexamethasone (HiDEX) In Relapsed/Refractory Multiple Myeloma (RRMM): POM + Lodex Is Beneficial For Elderly Patients (>65 Years of Age). Blood

2013;122(21):3198.
105. Latimer N. Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient level data 2011 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK395885/pdf/Bookshelf_NBK395885.pdf.
106. Rutherford MJ, Lambert PC, Sweeting MJ, Pennington B, Crowther MJ, Abrams KR, et al. Technical Support Document 21: Flexible Methods for Survival Analysis 2020 [Available from: https://www.sheffield.ac.uk/media/34188/download?attachment.
107. National Institute for Health and Care Excellence (NICE). Olaparib in combination with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab [Review of TA693] [ID4066] 2023 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10978/documents.
108. Giri S, Chen Y, Wu J, Hageman L, Richman J, Francisco L, et al. Reduction in Late Mortality Among Patients With Multiple Myeloma Treated With Autologous Peripheral Blood Stem Cell Transplantation-A Blood or Marrow Transplant Survivor Study Report. Transplant Cell Ther. 2021;27(10):840 e1- e7.
109. San Miguel JF, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica. 2015;100(10):1334-9.
110. Hernández Alava M PS, Wailoo A,. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. PharmacoEconomics. 2023;41(2):199-207.
111. Wailoo A, Alava MH, Pudney S. Technical Support Document 22: Mapping to estimate health state utilities 2023 [Available from: https://www.sheffield.ac.uk/media/42422/download?attachment.
112. National Institute for Health and Care Excellence (NICE). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [TA510] 2018 [Available from: https://www.nice.org.uk/guidance/ta510.
113. Palumbo A, Davies F, Lee D, Dhanasiri S, Facon T, Zaki M, et al. Quality of Life Weights (Utilities) in Refractory or Relapsed and Refractory Multiple Myeloma (RRMM) Patients Using EORTC-8D and EQ-5D. Lymphoma and Myeloma 2013: An International Congress on Hematologic Malignancies. New York: USA; 2013.
114. Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health technology assessment (Winchester, England). 2017;21(7):1-204.
115. Howell TA ML, Jun MP, Garcia J, Powers A, Maloney DG. Health State Utilities for Adverse Events Associated with Chimeric Antigen Receptor T-Cell Therapy in Large B-Cell Lymphoma. Pharmacoecon Open. 2022;6(3):367-76.
116. Ara R aBJ. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
117. National Institute for Health and Care Excellence (NICE). Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567] 2019 [Available from: https://www.nice.org.uk/guidance/ta567.

118. Monthly Index of Medical Specialities (MIMS). Imnovid 2023 [Available from: https://www.mims.co.uk/drugs/cancer/antineoplastics/imnovid.
119. Electronic Market Information Tool (eMIT). Drugs and pharmaceutical electronic market information tool (eMIT) 2023 [Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.
120. UK Department of Health National Health Services (NHS). 2021/22 National Cost Collection data Version 2022 [Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/.
121. National Institute for Health and Care Excellence (NICE). Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product 2016 [Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparators-and-sequences-jun-16.docx.
122. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2022 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/.
123. National Institute for Health and Care Excellence (NICE). Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies [TA872] 2023 [updated 28.02.2023. Available from: https://www.nice.org.uk/guidance/ta872/chapter/1-Recommendation.
124. NHS. Intravenous immonuglobulin for acute disseminated encephalomyelitis and autoimmune encephalitis 2021 [Available from: https://www.engage.england.nhs.uk/consultation/clinical-commissioning-wave8/user_uploads/f06x050-impact-assessmnt.pdf.
125. Addicott R, Dewar S. Improving choice at end of life: a descriptive analysis of the impact and costs of the Marie Curie Delivering Choice Programme in Lincolnshire. (King's Fund) 2008 [Available from: https://www.kingsfund.org.uk/publications/improving-choice-end-life.
126. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. QALY Shortfall Calculator 2021 [Available from: https://shiny.york.ac.uk/shortfall/.

B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality -of -life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional evidence to support Section B.2

Appendix N: Additional cost-effectiveness information

Appendix O: Indirect treatment comparisons for comparator efficacy

Appendix P: Standardised mortality ratio

Appendix Q: Additional results ECA study scenario supplementary results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]

Clarification questions

October 2023

File name	Version	Contains confidential information	Date
ID4026_Elranatamab Clarification letter_EAG to NICE_Company response_16042024_[noCIC]POSTFAC_FINAL	1.1	Yes	16th April 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Appendix D, page 45, 46, 50. Please clarify how many reviewers conducted the quality assessment of the MM-003, ECA, and MagnetisMM-3 studies and whether reviewers worked independently?

MM-003

One reviewer conducted the quality assessment for MM-003 assessed in accordance with the NICE user guide.

ECA study

For the ECA analyses presented in the submission, 3 reviewers independently conducted quality assessment of the real-world data. An analyst undertook code walkthroughs to ensure the ECA population and variables were appropriately defined as outlined in the study protocol, whilst an independent medical statistician conducted code walkthrough of all analytical code to ensure the statistical analysis was conducted as outlined in the statistical analysis plan (SAP). A second analyst then conducted independent quality checks on all reported study outputs, including tables, figures and lists. This analyst was also responsible for generating a combined dataset (ECA real world data and MagnetisMM-3 trial data), aligning all key variables to ensure

synergy across variables, naming conventions and label values. Additionally, the lead medical statistician (who was not part of the quality assessment team) undertaking the comparative effectiveness analyses was blinded to patient assignment to either the real world ECA cohort and MagnestisMM-3 cohort, with the use of a separate study ID to enable blinded analyses. A quality control log documented all of these assessments. Furthermore, NICE's DataSAT has been completed alongside the Methods to Address Bias reporting document (provided as supporting materials), and the RECORD-PE checklist will be completed with the final version ECA study report.

In addition to the above, one reviewer conducted the quality assessment for the ECA study using the Downs and Black checklist, which is recommended for use with non-randomised controlled trials.[1]

MagnetisMM-3

Two reviewers conducted the quality assessment for the MagnetisMM-3 study using the Downs and Black checklist, which is recommended for use with non-randomised controlled trials.[1] One reviewer conducted the assessment, and the second reviewer reviewed the assessment.

Methodology of clinical effectiveness evidence

A2. Appendix D, section D.1.3, page 28. Can the company provide the baseline participant characteristics data, including the lines of previous treatment, for the five POM+DEX trials that were identified in the SLR but were not used in the indirect comparison?

A systematic literature review was conducted in 2021 in RRMM, to identify prognostic variables (PVs); and effect modifiers to consider as part of any comparative assessment. PVs are variables which are significantly associated with the outcome of interest; Effect modifiers (EMs) are variables which modify the relationship between treatment and outcomes of interest.[2] This SLR included a review of the recent clinical trials in TCE/R MM, and a review of recently published indirect treatment comparisons in TCE/R MM. They were subsequently confirmed through clinical expert opinion. The details of the SLR are provided in Appendix A. The final list of PVs and EMs are summarized in CS, Document B, Table 14

(reproduced in Table 1**).** This data informed the analysis of comparator trial choice for the MAIC in the company submission. A selected list of reported baseline characteristics across the 7 trials can be found in Table 2. Where possible, these baseline characteristics were reviewed for sources of heterogeneity or bias prior to study selection to support the choice of comparator study in the MAIC.[3]

Table 1: Prognostic variables and effect modifiers identified based on the SLR conducted in 2021 (CS, Appendix D), and clinical opinion.

	OS	**PFS**
1 Prognostic variables and effect modifiers	• Age • Sex • Time since initial diagnosis • Revised International Staging System (R-ISS) or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • Eastern Cooperative Oncology Group (ECOG) performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)	• Age • Time since initial diagnosis • R-ISS or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • ECOG performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)

Note: Revised ISS (R-ISS) was prioritized as a PV/EM if it was reported in the comparator's trial.
Abbreviations: OS = overall survival; PFS = progression-free survival

Table 2: Selected Baseline characteristics of trials identified for POM+DEX in the systematic literature review (Appendix D, section D.1.3, company submission).

		MagnetisMM-3[4, 5], elranatamab (Cohort A) (n = 123)	**MM-003[6], POM+DEX (n = 302)**	**MM-002[7], POM+DEX (n = 113)**	**ICARIA-MM[8], POM+DEX (n = 153)**	**ELOQUENT-3[9], POM+DEX (n = 117)**	**NCT03170882[10], POM+DEX (n = 49)**	**OCEAN[11], POM+DEX (n = 249)**
Eligibility criteria		TCR	RRMM, prior lenalidomide, bortezomib, alkylator agent	RRMM, ≥2 prior therapies, including lenalidomide and bortezomib	≥2 prior therapies, including lenalidomide and a PI. Excluded if prior anti-CD38 monoclonal antibody exposure	≥2 prior therapies, refractory to lenalidomide and a PI	≥2 prior therapies, refractory to lenalidomide	2-4 prior therapies, refractory to lenalidomide, exposed to a PI
Age, n (%)	Median	68	64	64	66	66	68	68
	>75 years	21 (17%)	24 (8%)	12 (11%)	≥75: 29 (19%)	≥75: 12 (21%)	≥75: 9 (18%)	≥75: 39 (16%)
Sex	Male	68 (55%)	181 (60%)	62 (55%)	70 (46%)	35 (61%)	26 (53%)	140 (56%)
Time from initial diagnosis (median, years)		6.1	5.3	NR	4.1	4.4	4.9	3.9
ISS disease stage	Stage I – Stage II	82 (67%)	197 (65%)	37 (33%)	107 (70%)	103 (88%)	38 (78%)	218 (88%)
	Stage III	24 (20%)	93 (31%)	76 (67.3%)	43 (28%)	14 (12%)	11 (22%)	31 (12%)
Number of prior lines	Median	5	5	5	3	3	NR	3
	More than 2 lines	[redacted]	285 (94%)	107 (95%)	NR Range: 2-4	NR 2 or 3: 36 (63%)	26 (53%)	138 (55%)
Lenalidomide refractory		98.4% prior lenalidomide	95%	78%	92%	82.5%	100% prior lenalidomide	99%
PI refractory		96.7% TCR	79%	71%	75%	NR	100% prior bortezomib	65%
Anti-CD38mAb refractory		96.7% TCR	NR	NR	NR	NR	NR	16%

		MagnetisMM-3[4, 5], elranatamab (Cohort A) (n = 123)	MM-003[6], POM+DEX (n = 302)	MM-002[7], POM+DEX (n = 113)	ICARIA-MM[8], POM+DEX (n = 153)	ELOQUENT-3[9], POM+DEX (n = 117)	NCT03170882[10], POM+DEX (n = 49)	OCEAN[11], POM+DEX (n = 249)
TCR		96.7% TCR	NR	NR	NR	NR	NR	12%
ECOG status	0	45 (37%)	110 (36%)	32 (28%)	NR	NR	21 (43%)	92 (37%)
	1	71 (58%)	138 (46%)	68 (60%)	NR	NR	23 (47%)	136 (55%)
	2	7 (6%)	52 (17%)	13 (12%)	NR	NR	5 (10%)	21 (8%)
Cytogenetic Risk	High %	25.2%	25.5	NR	23.5%	24.6%	NR	86 (35%)
EMD	%	32%	NR	NR	NR	NR	NR	12%
Creatinine clearance	<60mL/min	[redacted]	95 (31%)	NR	NR	NR	12 (24%)	68 (27%)

Notes: Patient characteristics that were identified PVs and EMs and were mutually reported are shown in the table above along with eligibility criteria and additional data on refractoriness to prior lines. Where data is not reported, and where possible, contextual data has been added.

The percentage was rounded to whole numbers, and as such, the sum of each subcategory may not exactly equal 100% as observed with ECOG from MM-003

The variables ISS disease stage has missing data in MagnetisMM-3 patient-level data. The variables of ISS disease stage and high-risk cytogenetics have missing data in MM-003 patient-level data.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EMD = extramedullary disease; ISS = International Staging System; PI = Proteasome inhibitor; POM+DEX = pomalidomide plus low-dose dexamethasone; NR = not reported; RRMM = relapsed refractory multiple myeloma; TCR = triple class refractory.

Table 2 presents the baseline characteristics of the various POM+DEX regimen containing trials for the purpose of comparison. When comparing across trials, certain baseline characteristics appear to be relatively consistent, such as age, proportion of male subjects and proportion of patients with CrCl<60ml/min.

Certain factors vary significantly across the above trials, the most notable being the number of prior lines and pattern of refractoriness, as these have a significant impact on outcomes.[12, 13] Extramedullary disease, cytogenetic risk and disease stage also vary significantly, these factors would be expected to affect outcomes.[14-17] Whilst a MAIC can mitigate against variation in demographic factors across trials, it is likely that, through the inclusion of a poorly matched trial for an indirect comparison with elranatamab, results which are not reflective of the utility of elranatamab would be produced.[18]

The clear difference between the above POM+DEX trials and MagnetisMM-3 is the level of anti-CD38 exposure/refractoriness and TCR. Only OCEAN reports (low levels of) anti-CD38 mAb exposure.[11] Of the remaining trials, MM-002, MM-003, and ELOQUENT-3 were run prior to the widespread adoption of anti-CD38 mAbs into clinical practice.[6, 7, 9] ICARIA-MM excluded patents with prior anti-CD38 mAb exposure, and NCT03170882 does not report the exposure.[8, 10]

MM-003:

Of the six POM+DEX containing trials Pfizer considered MM-003 to be the most relevant and submitted a MAIC with this trial in its NICE submission (see B.2.9). Like MagnetisMM-3, this trial had a median 5 prior lines, similar proportions of ISS 1-3, high cytogenetic risk, and lenalidomide refractoriness. Whilst PI refractoriness is lower than in MagnetisMM-3, it is the highest documented of the six POM+DEX trails.

MM-002:

Whilst also have a median of 5 prior lines of therapy, this trial has over three times the level of ISS-3 disease, whilst having significantly lower levels of lenalidomide and PI refractoriness.

ICARIA-MM:

Many of the demographic factors in ICARIA-MM and MagnetisMM-3 are aligned. However, the principal issue with this trial is that the median prior lines were 3 and patients with prior anti-CD38 mAb exposure were excluded.

ELOQUENT-3:

Similarly, the median prior lines in this trial were 3. Additionally, the level of lenalidomide refractoriness was lower, as were the proportion of patients with ISS-3 disease.

NCT03170882:

This study did not report median prior lines. However, only 53% of participants has received more than 2 lines of therapy, compared with 96% of the MagnetisMM-3 cohort, thus representing a significantly less heavily pre-treated cohort.

OCEAN:

This study had a median of 3 prior lines. In addition, the level of PI refractoriness was substantially lower than in MagnetisMM-3, which was 96.7% TCR. This trial also had a lower proportion of patients with ISS-3 disease whilst having significantly more patients with high cytogenetic risk. This trial did report anti-CD38 mAb exposure, however it was felt that this was not sufficient to balance the other demographic factors.

Decision problem

A3. Document B, Table 1, p12] The population addressed in the company submission is “Adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy.” Can the company clarify whether elranatamab would only be available to NHS patients who are triple class refractory or would elranatamab also be available to NHS patients who are triple class exposed? Can the company also comment on what percentage

of patients they would expect to be triple class refractory in the triple class exposed cohort seen in routine NHS clinical practice?

The population addressed in the company submission is the anticipated label; “Adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy.”

New treatment options have led to a dynamic treatment pathway and results in some heterogeneity as to how patients become eligible to elranatamab. Clinicians have confirmed that identifying TCR patients is challenging in a UK clinical setting.[19, 20] Figure 1 (adapted from B.1.3.3.6 Figure 3) demonstrates the current clinical pathway to TCE and TCR in the NHS. Figure 2 demonstrates the relative sizes of the TCE, label and TCR populations in the UK and its relative complexity. While exact proportions are hard to determine, UK clinicians state that they expect 100% of patients to be TCE by their 4th LOT in the current pathway, with up to 85% of these being TCR.[20] The company believes that the data presented is generalisable to the label given the heavily pre-treated (96.7% TCR) population in the MagnetisMM-3 trial compared with comparator populations in the MAIC (not TCE or TCR) and ECA (All TCE, [redacted]% TCR) is likely to be conservative. More detail is outlined below.

Target Population

- The company has submitted efficacy and safety data from cohort A - MagnetisMM-3 to support its HTA submission. Whilst this study was, per its eligibility criteria, a TCR study (96.7% were TCR), we consider the data to be generalisable to the label population in the UK in the 4th LOT, as per B.1.3.3.6. The company therefore considers that patients meeting the label criteria should be eligible for elranatamab.

- The company recognises that challenges across the recent treatment paradigm mean that the clinical trial cohort does not fully align with the label. The label (as outlined in question A3 (above) is not exactly TCE or TCR; it is a relapsed and refractory cohort who are TCE, have received three prior therapies and demonstrated disease progression on the last therapy. We

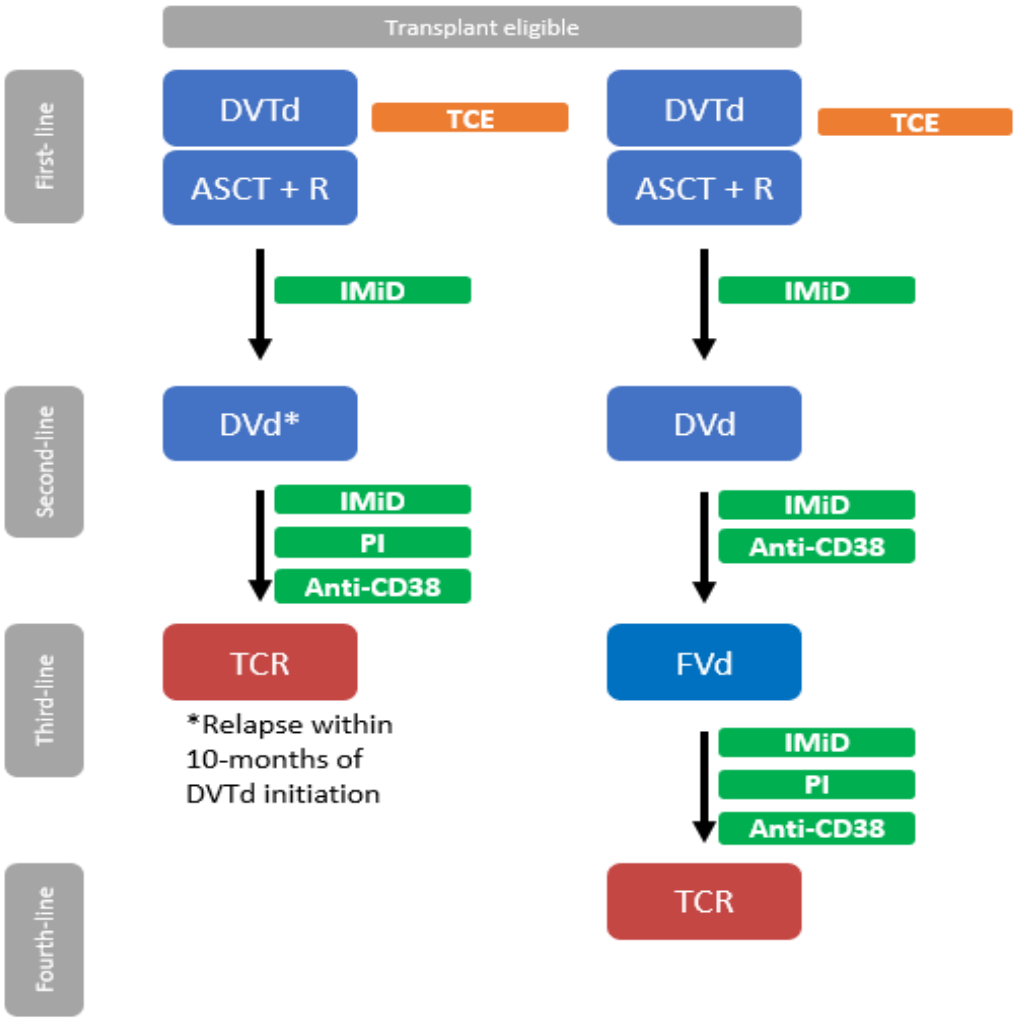
believe the label population to be substantially narrower than a purely TCE cohort, whilst being broader than a TCR cohort.

- To illustrate this point: since its approval in 2022, DARA+BORT+THAL+DEX, ASCT then LEN maintenance, has become the standard of care for newly diagnosed transplant eligible patients in the UK[21]. All patients thus treated will be TCE in the 1st LOT, this will represent a significant proportion of the ~6000 patients diagnosed with MM annually in the UK[22]. Consequently, the utility of the TCE cohort in clinical decision making has diminished, as most patients will now be TCE in their 1st or 2nd LOT.[19,20]

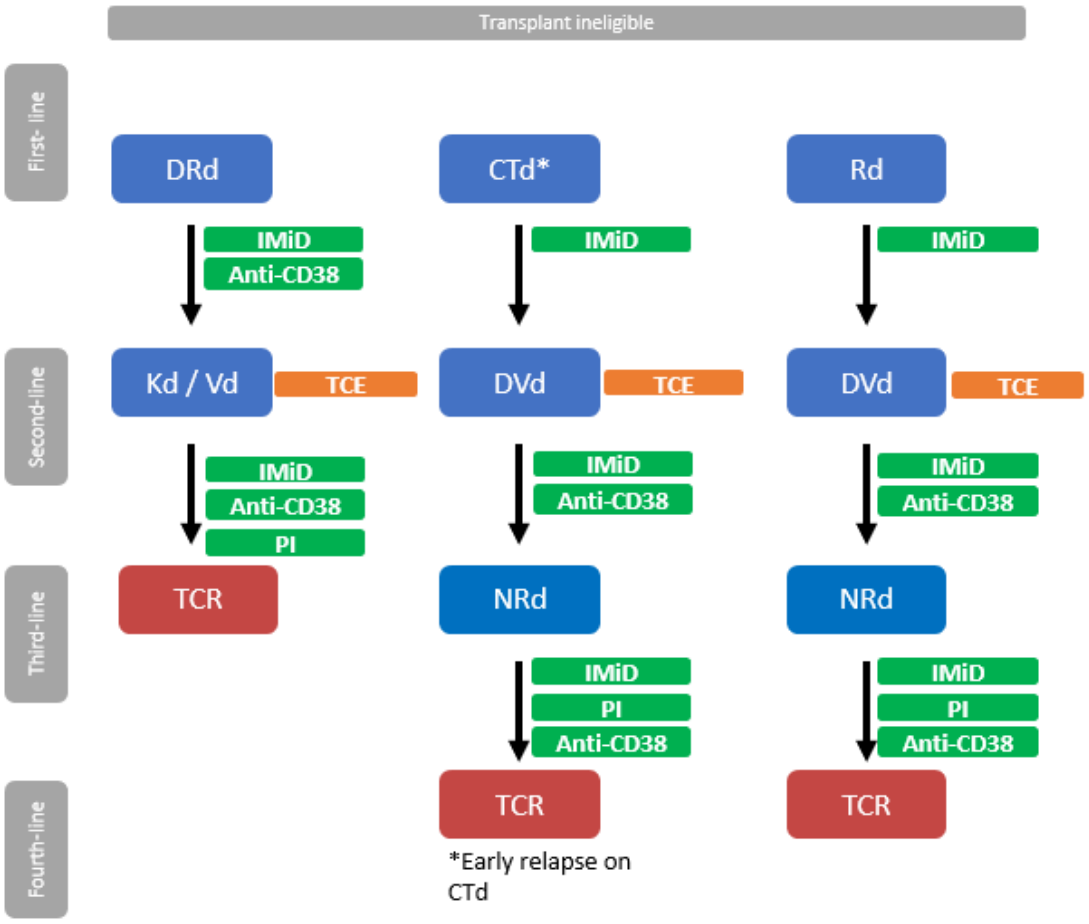
- As per B.1.3.3.6, by the 4th LOT all patients will be TCE with disease progression at last treatment (thus the label population) and most patients will also be TCR. A minority won't be TCR, most likely being PI sensitive, because of fixed-duration PI components in some regimens. Figure 1 (adapted from B.1.3.3.6 Figure 3) demonstrates the pathway to TCE and TCR in the NHS. Figure 1 demonstrates the relative sizes of the TCE, label and TCR populations in the UK.

Figure 1: Potential routes to TCE and TCR in the NICE pathway, (A) transplant eligible and (B) Transplant ineligible.

A


Transplant eligible
First- line
DVTd
TCE
ASCT + R
IMiD
DVTd
TCE
ASCT + R
IMiD
Second-line
DVd*
IMiD
PI
Anti-CD38
DVd
IMiD
Anti-CD38
Third-line
TCR
*Relapse within 10-months of DVTd initiation
FVd
IMiD
PI
Anti-CD38
Fourth-line
TCR

B



TCR **Indicates the point at which a patient is TCR**

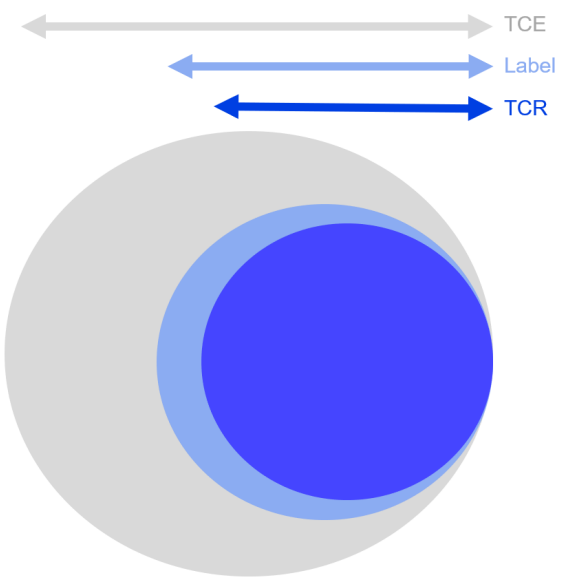
TCE **Indicates the point at which a patient is TCE**

Indicates the point at which a patient is class refractory

Key: Anti-CD38, anti-CD38 monoclonal antibody; ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, carfilzomib; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; LEN, lenalidomide; NICE, National Institute for Health and Care Excellence; PANO, Panobinostat; PI, proteasome inhibitor; TCR, triple class refractory; THAL, thalidomide.

Notes: TCE doesn't require refractoriness, patients become TCE in the LOT as opposed to after relapse.
*Relapse within 10-months of DARA+BORT+THAL+DEX initiation.
This diagram illustrates potential routes through the NICE pathway to becoming TCR, it is not exhaustive.
Owing to fixed-duration induction therapy, patients are typically only lenalidomide refractory after first line. Patients treated with daratumumab in combination with bortezomib and dexamethasone in second line are not typically bortezomib refractory, however they can be if they relapse early in treatment (within 10-months of starting).
Source: Pfizer data on file, 2023.[23]

Figure 2: Illustrative Diagram Demonstrating Relative Sizes of TCE, label and TCR Cohorts in the UK



TCE = received at least three prior therapies (drug classes) including an IMiD, a PI, and an anti-CD38

Label (RRMM) = TCE with three prior therapies and have demonstrated disease progression on the last therapy (i.e. they could be refractory to 1, 2 or all 3 classes)

TCR = TCE and refractory to all three classes

While it might seem that TCE and Label are equivalent to each other, a minority of patients who are TCE move onto a subsequent LOT for reasons other than disease progression, e.g. tolerability issues with current LOT. This is why the TCE and Label (RRMM) circles do not perfectly overlap.

For contextualisation, in phase 1 of the UK external control arm (ECA) study*, [redacted]% of patients who were TCE were also TCR (n=[redacted]) across all LOTs.

*ECA study phase 1 was intended to contextualise the characteristics of patients with TCE or TCR MM, their treatments and clinical outcomes using UK real world data collected from NHS centres. Results are not published.

Note: this diagram is for illustrative purposes only. Circle size is not intended to represent real life absolute patient population size. An estimate of proportion is based on Pfizer's external control arm study (phase 1), and clinical opinion.

What percentage of patients would be expected to be triple class refractory in the triple class exposed cohort seen in routine NHS clinical practice?

UK clinicians confirm that identifying TCR patients is challenging.[19, 20] This is due to the heterogenous routes that patients can take through the treatment pathway (which may also include novel therapies in clinical trials or expanded access schemes) and the real world challenges with NHS record keeping. We are not aware of available data from the NHS on the breakdown of TCE vs TCR across lines of therapy. Indeed, the SACT registry does not capture drug response or refractoriness data. Practicing UK clinicians state that the degree of class refractoriness will increase with each line of therapy. They expect by the 4th LOT 100% of patients to be TCE in the current pathway, with 80-85% of these being TCR[20].

In the Pfizer sponsored ECA study phase 1 (to characterise TCE and TCR patients, their treatments and clinical outcomes), [redacted] TCE patients were identified across 4 NHS centres in England and Scotland, of whom [redacted] were TCR. When considering the POM+DEX sub-cohort in the ECA study phase 2 (comparative effectiveness analyses), [redacted] of patients in this sub-cohort were TCR at index (n=[redacted]) whilst [redacted]

were double class refractory at index (n=[redacted]). It should be noted that these data are across all lines of therapy, the proportion of TCR would be expected to be greater in later lines of therapy, as patients will have been exposed to more treatments.

However, it is possible within the ECA study (in both phases 1 and 2) that the true number of patients who are TCR is under-reported. This would be due to inconsistent and limited availability of laboratory test results available across NHS centres to confirm whether a patient is refractory to a given regimen or not. Therefore, it is possible that some patients in the study who are assumed to be non-refractory (due to lack of test results in the dataset) may be refractory.

A4. Document B, Table 1, p12 (comparators). In section B.2.9, the external control arm (ECA) study is described. This uses data from the Arcturis UK dataset, and focusses on [redacted] patients identified to have received POM+DEX following at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, who have demonstrated disease progression on the last therapy (e.g. TCR MM). Can the same dataset, or the previously mentioned Systemic Anti-Cancer Therapy (SACT) database, be used to provide the relative frequency of different treatments that have been used in routine practice for the proposed population/positioning?

A total of [redacted] RRMM patients were identified from the ECA cohort (Arcturis dataset), of which [redacted] were treated with POM+DEX in the subsequent line following triple class exposure and demonstrated disease progression on the last treatment. Among the remaining [redacted] patients, a total of 12 index regimens were recorded, which are summarised in Table 3 below with regimens n≤5 listed alphabetically.

Table 3: Overview of the therapy used at index date in the relapsed and refractory multiple myeloma (RRMM) external control arm cohort

Line of Therapy	N (%)
Pomalidomide and dexamethasone (POM + DEX)	[redacted]
Ixazomib, lenalidomide and dexamethasone (IXA + LEN + DEX)	[redacted]
Carfilzomib and dexamethasone (CAR + DEX)	[redacted]
Therapy Lines with N≤5	[redacted]
Bendamustine	[redacted]
Bortezomib, Cyclophosphamide, Dexamethasone, Lenalidomide (CY + BOR + DEX + LEN)	
Bortezomib, Daratumumab, Dexamethasone (DARA + BORT + DEX)	
Bortezomib, Dexamethasone, Panobionostat (PANO + BORT + DEX)	
Cyclophosphamide, Daratumumab, Dexamethasone (DARA + CY + DEX)	

Cyclophosphamide, Dexamethasone, Thalidomide (CY + THAL + DEX)	
Daratumumab, Dexamethasone (DARA + DEX)	
Dexamethasone, Isatuximab, Pomalidomide (ISA + POM + DEX)	
Dexamethasone, Lenalidomide (LEN + DEX)	
Dexamethasone, Melphalan, Prednisolone (MP + DEX)	

Note: Results shown in the above table are reported as recorded in the dataset, without clinical validation or contextualisation of treatment or primary data collection decisions.

As can be seen in Table 3, POM + DEX was the most common regimen, with IXA + LEN + DEX [redacted] and CAR + DEX [redacted] the next most common. The remaining therapies were each received by [redacted] patients. These results demonstrate high variability in the types of therapy used in routine practice for the proposed population/positioning. Given the relatively low frequency of therapies other than POM + DEX recorded in this dataset, it was not possible to directly compare the elranatamab treated patients from MagentisMM-3 with these other treatment regimens from the broader ECA population. In addition, up until February 2023 IXA + LEN + DEX was accessed through the Cancer Drug Fund (CDF) and therefore given the relatively short availability of this regimen in routine practice, it was not appropriate to consider this regimen as a direct comparator for elranatamab in the UK. Although the findings are from four NHS centres, they reflect clinical expert opinion received at the Pfizer-organised clinical advisory board meeting, HTA Access Forum and clinician interviews that POM + DEX is the only suitable comparator for elranatamab. Given the relatively low frequency of therapies other than POM + DEX recorded in this dataset, it was not possible to directly compare the elranatamab treated patients from MagentisMM-3 with these other treatment regimens from the broader ECA population. In addition, up until February 2023 IXA + LEN + DEX was accessed through the Cancer Drug Fund (CDF) and therefore given the relatively short availability of this regimen in routine practice, it was not appropriate to consider this regimen as a direct comparator for elranatamab in the UK.

While SACT would provide a national perspective of treatments used in routine practice, the reporting of treatments within SACT is limited to only those that are not in the CDF and to patients who have not received a CDF treatment at any time in their treatment pathway. Therefore, we are unlikely to identify an accurate estimate of the relative frequency of different treatments used in routine practice for the

proposed population/positioning using SACT. This is why only estimates generated from the ECA (Arcturis) dataset are provided here.

A5. Document B, Table 1, p12. The company defines treatment refractory as "an inadequate response or disease progression whilst on treatment or within 60 days of the most recent treatment." Can the company clarify their definition of treatment relapsed?

- According to the criteria developed by the International Myeloma Working Group (IMWG), relapsed refractory MM (RRMM) is defined as a progressive disease, poor response despite treatment, progression within 60 days of the most recent treatment in a patient who had achieved remission, the absence of at least minimal response (MR), or primary refractory MM.[24]

- The MagnetisMM-3 Protocol considers the following as refractory: 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.[25]

- Inadequate response was not defined in the MagnetisMM-3 protocol. However, the protocol required a PR or better to be considered for Q2W step-down dosing.[25] Adequate response is defined as achieving an MR or better by the International Myeloma Workshop Consensus Panel.[26]

- Relapsed or progressive disease are defined by the International Myeloma Working Group and are outlined in Table 4.[27]

Table 4: IMWG Criteria for Progressive Disease or Relapse in Multiple Myeloma

Progressive disease	Increase of > 25% from lowest response value in any one or more of the following: • Serum M-component and/or (the absolute increase must be > 0.5 g/dL)* • Urine M-component and/or (the absolute increase must be > 200 mg/24 h) • Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Bone marrow plasma cell percentage; the absolute percentage must be > 10%** • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas

	• Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).* It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] • Decrease in haemoglobin of > 2 g/dL [1.25 mmol/L] • Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]

FLC, free light chain ration; CRAB, calcium, renal, anaemia, bone lesion

*For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL

**Relapse from CR has the 5% cut-off versus 10% for other categories of relapse

Efficacy results and data synthesis

A6. Document B, first sentence, p48]. This indicates Figure 6 – but should it be Figure 7?

This should read Figure 7 and not Figure 6 as highlighted.

A7. Document B, Table 9, p52. Please give a fuller explanation of the difference between sCR/CR Population and Evaluable population**.**

The definitions of stringent complete response (sCR)/complete response (CR) Population and Evaluable population are provided below:

- sCR/CR Population: includes patients who achieved sCR/CR.
- Evaluable population: includes patients who achieved sCR/CR and who had at least one MRD assessment.

In order to be assessed for minimal residual disease (MRD), patients must be in a CR/sCR per the IMWG criteria (above). The MagnetisMM-3 (Protocol C1071003 section 8.1.2) stated that bone marrow aspirates (BMA) “obtained while a participant is in suspected or actual CR will be evaluated by a central lab for MRD using NGS” (next generation sequencing)

BMA were assessed by a central lab. Screening samples needed to be available (per Protocol C1071003 section 8.8.1), the central lab also needed to be able to identify a dominant malignant clone at screening. There were also calibration failure rates. As such, not all CR/sCR patients were able to be assessed for MRD status.

A8. Document B, Figures 10-13 and possibly 14, p53-56. Could the sample size at each time point be reflected (similar to the K-M plots).

Please find below copies of Figures 10 through 14 referenced from document B, which include the sample size at each time point.

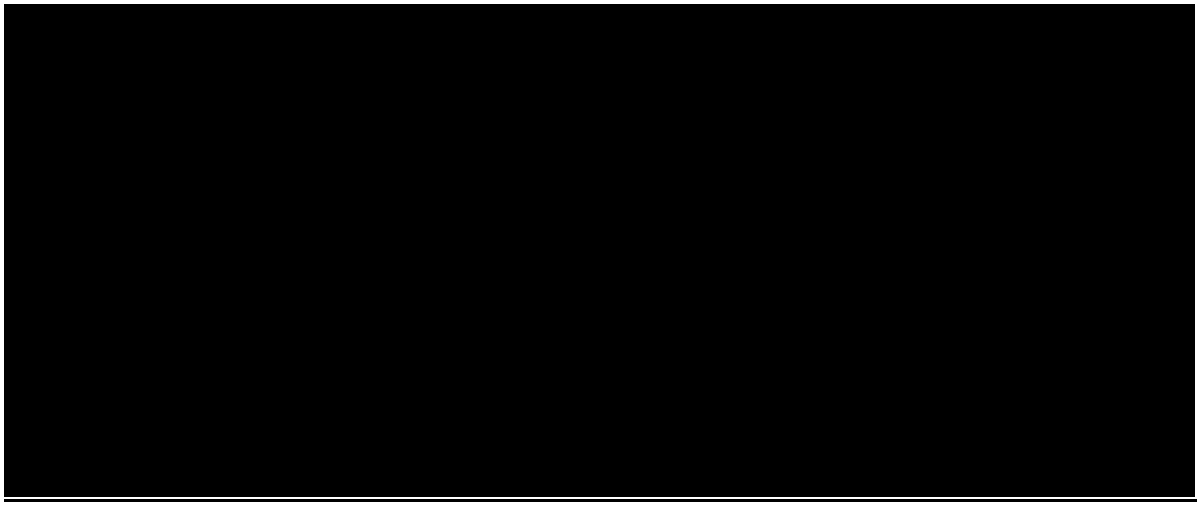
Figure 3: (Figure 10, Document B) LSM change from baseline in EORTC QLQ-C30 GHS score in Cohort A of MagnetisMM-3

Key: BL, baseline; C, Cycle; D, Day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer Core 30; GHS, global health status LSM, least square mean; QoL, quality of life.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Higher scores in the EORTC-QLQ-C30 GHS domain indicate better health. * $p < 0.05$.
Source: MagnetisMM-3 15-month data-cut, 2023.[28]

Figure 4: (Figure 11, Document B) LSM change in baseline in EORTC-QLQ-C30 pain scores in Cohort A of MagnetisMM-3

Key: BL, baseline; C, Cycle; D, Day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer Core 30; LSM, least square mean.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Lower scores in the EORTC QLQ-C30 pain domain indicate a decrease or improvement in pain * $p < 0.05$.
Source: MagnetisMM-3 15-month data-cut, 2023.[28]

Figure 5: (Figure 12, Document B) LSM change from baseline in EORTC QLQ-MY20 disease symptom scores in Cohort A of MagnetisMM-3



Key: BL, baseline; C, Cycle; D, Day; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Multiple Myeloma Quality of Life Questionnaire; GHS, global health status; LSM, least square mean; QoL, quality of life.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Lower scores in the QLQ-MY20 disease symptom domain indicate an improvement in symptoms. * $p < 0.05$.
Source: MagnetisMM-3 15-month data-cut, 2023.[28]

Figure 6: (Figure 13, Document B) LSM change from baseline in EQ-5D index scores in Cohort A of MagnetisMM-3

Key: BL, baseline; C, Cycle; D, Day; LSM, least square mean; PRO, patient-reported outcomes; QoL, quality of life.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment. Higher scores in the EQ-5D disease symptom domain indicate an improvement in symptoms. * $p < 0.05$.
Source: MagnetisMM-3 15-month data-cut, 2023.[28]

Figure 7: (Figure 13, Document B) Distribution of Patient Global Impression of Change in Cohort A of MagnetisMM-3

Key: C, cycle; D, day.
Notes: PRO analysis set included all patients who completed baseline and at least one post-baseline assessment.
Source: MagnetisMM-3 15-month data-cut, 2023.[28]

A9. Document B, Table 15/Figure 18, p67-68. Please can you explain the discrepancy between the effective sample sizes (ESS) presented in Table 15 and

the starting numbers at risk in Figures 18 and 19. Perhaps the ESS might be incorporated into Appendix D Table 8, p41.

Document B, Table 15 lists the effective sample size (ESS). The ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. Mathematically, the ESS was derived following the formula:

$$ESS = \left(\sum_{t=A,B}\sum_{i=1}^{N_{t(AB)}} \hat{w}_{it}\right)^2 \Big/ \sum_{t=A,B}\sum_{i=1}^{N_{t(AB)}} \hat{w}_{it}^2$$ (NICE DSU 18).[29]

To visualize the effect of the weighting compared to the unadjusted data, Kaplan-Meiers were plotted in Document B, Figure 18.

Please note the number at risk at the start of the Kaplan-Meier plot in the weighted population is equivalent to the sum of the weights. This will be different to the ESS.

Multiple MAICs were conducted, these have been added to Table 5 below (taken from Table 15 in Doc B). ESS for PFS unanchored MAIC was 76 and for OS unanchored MAIC ESS was 75.

Table 5: Baseline characteristics before and after matching

		MagnetisMM-3 (Cohort A) (n = 123)	**MM-003, POM+DEX (n = 302)**	**MagnetisMM-3, after adjustment (ESS=76 [for PFS] and 75 [for OS])**
Age, n (%)	Median	68	64	
	>75 years	21 (17)	24 (8)	
Sex	Male	68 (55)	181 (60)	
Time from initial diagnosis (median, years)		6.1	5.3	
ISS disease stage	Stage I – Stage II	82 (67)	197 (65)	
	Stage III	24 (20)	93 (31)	
Number of prior lines	Median	5	5	
	More than 2 lines		285 (94)	
ECOG status	0	45 (37)	110 (36)	
	1	71 (58)	138 (46)	
	2	7 (6)	52 (17)	
Creatinine clearance	<60		95 (31)	

	MagnetisMM-3 (Cohort A) (n = 123)	MM-003, POM+DEX (n = 302)	MagnetisMM-3, after adjustment (ESS=76 [for PFS] and 75 [for OS])
Key: ECOG, Eastern Cooperative Oncology Group; IgG, immunoglobulin G; ISS, The International Staging System. **Source:** Lesokhin et al. 2023[30]; Miguel et al. 2013.[6]			

A10. Appendix M.6.4, p175-176. Please confirm whether any adverse events reported for MagentisMM-1 were considered treatment-related. If there were any treatment-related adverse events, please report these events by grade and the proportions of patients for each event.

Included below Table 5 - Table 10 are the treatment related adverse events (TRAEs) from the MagnetisMM-1 study, reported by grade and proportions of patients for each event.

This was a Phase 1 open-label, multi-dose, multi-centre, dose escalation, safety, PK and PD study of elranatamab as monotherapy and in combination with lenalidomide, pomalidomide or dexamethasone in adult patients with advanced MM who had relapsed from or were refractory to standard therapy. This study was divided into dose escalation/finding part (Part 1) and dose expansion part (Part 2).

Data from the following MagnetisMM-1 cohorts are displayed for elranatamab (PF-06863135):

- Dose escalation: subcutaneous (SC) cohorts (without priming) 215-1000 µg/kg elranatamab SC once weekly (QW)
- Dose expansion: SC 1000 elranatamab SC QW
- Part 1.1: cohorts (with priming) 600 µg/kg elranatamab SC priming dose followed by 1000 µg/kg SC either QW or biweekly (Q2W)
- Part 2a: elranatamab monotherapy expansion (with priming), 44 mg SC priming dose followed by 76 mg SC QW

Table 6: Overview of Treatment-Emergent Adverse Events (All Causality) - Safety Analysis Set (Protocol C1071001)

Number (%) of participants	PF-06863135 SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A Total n (%)	PF-06863135 SC 1000 ug/kg, Part 1.1, and Part 2A n (%)	PF-06863135 SC 1000 ug/kg, Part 1.1 Q1W, and Part 2A n (%)	PF-06863135 SC (44mg to 76mg) Part 2A n (%)
Participants evaluable for adverse events	[redacted]	[redacted]		[redacted]
Number of adverse events	[redacted]	[redacted]		[redacted]
Participants with adverse events	[redacted]	[redacted]		[redacted]
Participants with serious adverse events	[redacted]	[redacted]		[redacted]
Participants with Maximum Grade 3 or 4 adverse events	[redacted]	[redacted]		[redacted]
Participants with Maximum Grade 5 adverse events	[redacted]	[redacted]		[redacted]
Participants discontinued from study due to adverse events (a)	[redacted]	[redacted]		[redacted]
Participants discontinued study drug due to AE and continue Study (b)	[redacted]	[redacted]		[redacted]
Participants with dose reduced due to adverse events	[redacted]	[redacted]		[redacted]
Participants with temporary discontinuation due to adverse events	[redacted]	[redacted]		[redacted]

Includes all data since first dose of study drug, and up to 90 days (28 days for patients who completed the trial prior to approval of PA8 in June 2021) of last dose of study drug or start of new anti-cancer therapy, whichever occurs first.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
(b) Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE
did not cause the participant to be discontinued from Study
Cytokine release syndrome as defined based on ASTCT consensus criteria[28] except for IV cohorts, which are based on Lee et al. 2014[31] criteria.
MedDRA v25.0 coding dictionary applied.
PF-06863135 (Elranatamab)

Table 7: Overview of Treatment-Emergent Adverse Events (Treatment Related) - Safety Analysis Set (Protocol C1071001)

Number (%) of Participants	PF-06863135 SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A Total n (%)	PF-06863135 SC 1000 ug/kg, Part 1.1, and Part 2A n (%)	PF-06863135 SC 1000 ug/kg, Part 1.1 Q1W, and Part 2A n (%)	PF-06863135 SC (44mg to 76mg) Part 2A n (%)
Participants evaluable for adverse events	[redacted]	[redacted]		[redacted]
Number of adverse events	[redacted]	[redacted]		[redacted]
Participants with adverse events	[redacted]	[redacted]		[redacted]
Participants with serious adverse events	[redacted]	[redacted]		[redacted]
Participants with Maximum Grade 3 or 4 adverse events	[redacted]	[redacted]		[redacted]
Participants with Maximum Grade 5 adverse events	[redacted]	[redacted]		[redacted]
Participants discontinued from study due to adverse events (a)	[redacted]	[redacted]		[redacted]
Participants discontinued study drug due to AE and continue Study (b)	[redacted]	[redacted]		[redacted]
Participants with dose reduced due to adverse events	[redacted]	[redacted]		[redacted]
Participants with temporary discontinuation due to adverse events	[redacted]	[redacted]		[redacted]

Includes all data since first dose of study drug, and up to 90 days (28 days for patients who completed the trial prior to approval of PA8 in June 2021) of last dose of study drug or start of new anti-cancer therapy, whichever occurs first.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study
(b) Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE
did not cause the participant to be discontinued from Study
Cytokine release syndrome as defined based on ASTCT consensus criteria (Lee at al, 2019)[32] except for IV cohorts, which are based on Lee et al. 2014[31] criteria.
MedDRA v25.0 coding dictionary applied.
PF-06863135 (Elranatamab)

Table 8: Treatment Emergent Adverse Events by MedDRA PT Reported with >=20% of Participants (All Causality) - Safety Analysis Set (Protocol C1071001)

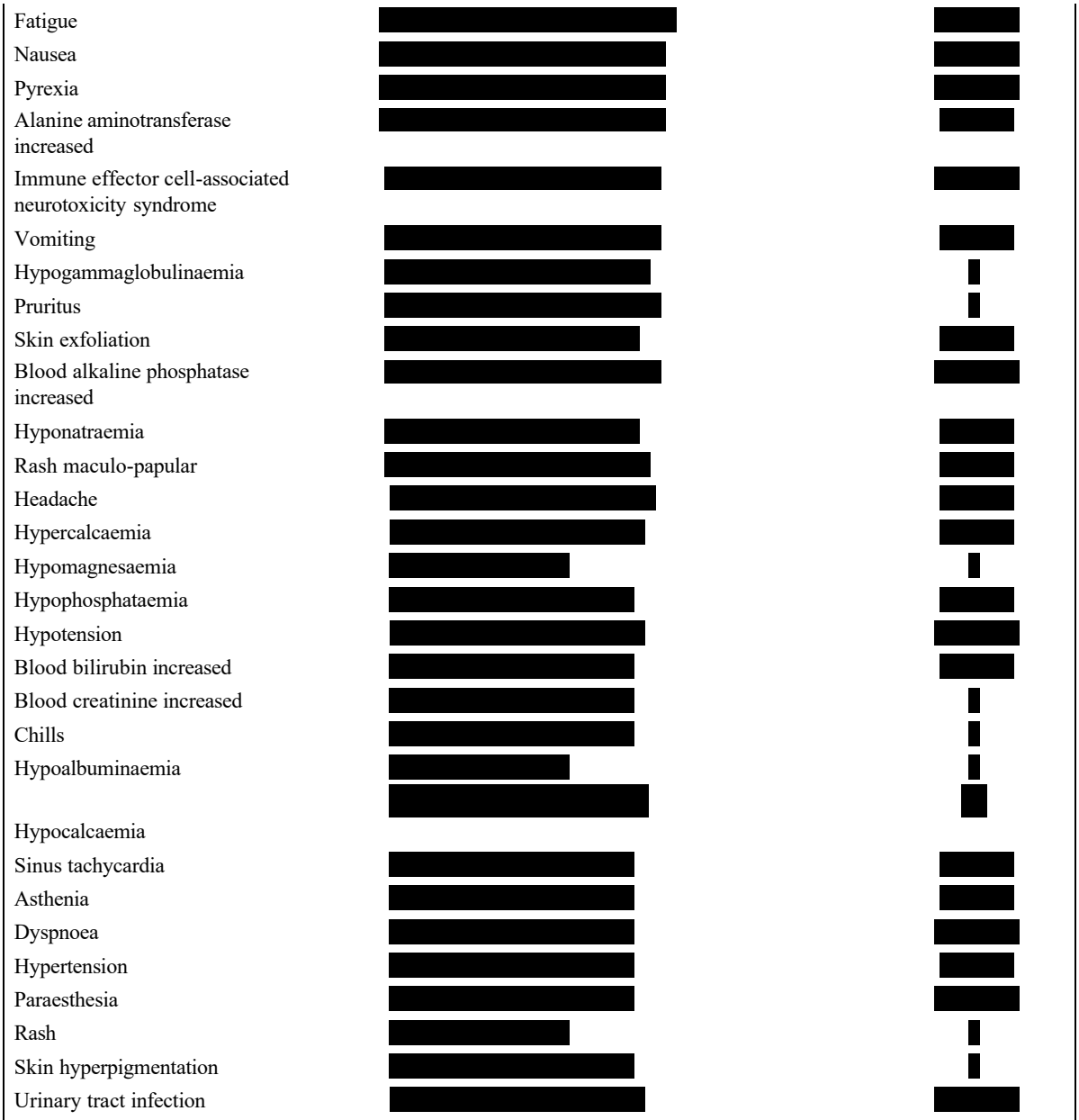
Number of Participants Evaluable for AEs	PF-06863135 SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A Total (N=55)	PF-06863135 SC 1000 ug/kg, Part 1.1, and Part 2A (N=41)	PF-06863135 SC 1000 ug/kg, Part 1.1 Q1W, and Part 2A (N=28)	PF-06863135 SC (44mg to 76mg) Part 2A (N=15)
	Total	Total	Total	Total
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]
Cytokine release syndrome				
Neutropenia				
Anaemia	[redacted]	[redacted]	[redacted]	
Injection site reaction	[redacted]	[redacted]	[redacted]	
Lymphopenia	[redacted]	[redacted]	[redacted]	
Thrombocytopenia	[redacted]	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	[redacted]	
Dry skin	[redacted]	[redacted]	[redacted]	
Hypophosphataemia	[redacted]	[redacted]	[redacted]	
Decreased appetite	[redacted]	[redacted]	[redacted]	
Nausea	[redacted]	[redacted]	[redacted]	
Leukopenia	[redacted]	[redacted]	[redacted]	
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	[redacted]	
Hypokalaemia	[redacted]	[redacted]	[redacted]	
Pain in extremity	[redacted]	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	[redacted]	
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	
Back pain	[redacted]	[redacted]	[redacted]	
Arthralgia	[redacted]	[redacted]	[redacted]	
Weight decreased	[redacted]	[redacted]	[redacted]	
Cough	[redacted]	[redacted]	[redacted]	
Headache	[redacted]	[redacted]	[redacted]	

Number of Participants Evaluable for AEs	PF-06863135 SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A Total (N=55)	PF-06863135 SC 1000 ug/kg, Part 1.1, and Part 2A (N=41)	PF-06863135 SC 1000 ug/kg, Part 1.1 Q1W, and Part 2A (N=28)	PF-06863135 SC (44mg to 76mg) Part 2A (N=15)
	Total	Total	Total	Total
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)	n (%)

@@ Uncoded term
Includes all data since first dose of study drug, and up to 90 days (28 days for patients who completed the trial prior to approval of PA8 in June 2021) of last dose of study drug or start of new anti-cancer therapy, whichever occurs first.
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), Hyperphosphataemia (PT=Blood phosphorus increased), Hypertension (PT=Blood pressure increased) are used.
Cytokine release syndrome as defined based on ASTCT consensus criteria (Lee at al, 2019)[32] except for IV cohorts, which are based on Lee et al. 2014[31] criteria.
MedDRA v25.0 coding dictionary applied. Frequencies ordered by occurrence in the group SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A.
PF-06863135 (Elranatamab)

Table 9: Treatment Emergent Adverse Events by MedDRA PT Reported with >=5% of Participants (Treatment Related) - Safety Analysis Set (Protocol C1071001)

Number of Participants Evaluable for AEs	PF-06863135 SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A Total (N=55)	PF-06863135 SC 1000 ug/kg, Part 1.1, and Part 2A (N=41)	PF-06863135 SC 1000 ug/kg, Part 1.1 Q1W, and Part 2A (N=28)	PF-06863135 SC (44mg to 76mg) Part 2A (N=15)
	Total	Total	Total	Total
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	[redacted]		[redacted]	[redacted]
Cytokine release syndrome	[redacted]		[redacted]	[redacted]
Neutropenia	[redacted]			[redacted]
Injection site reaction	[redacted]			[redacted]
Lymphopenia	[redacted]			[redacted]
Anaemia	[redacted]			[redacted]
Thrombocytopenia	[redacted]			[redacted]
Leukopenia	[redacted]			[redacted]
Dry skin	[redacted]			[redacted]
Decreased appetite	[redacted]			[redacted]
Aspartate aminotransferase increased	[redacted]			[redacted]
Diarrhoea	[redacted]			[redacted]



@@ Uncoded term
Includes all data since first dose of study drug, and up to 90 days (28 days for patients who completed the trial prior to approval of PA8 in June 2021) of last dose of study drug or start of new anti-cancer therapy, whichever occurs first.
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), Hyperphosphataemia (PT=Blood phosphorus increased), Hypertension (PT=Blood pressure increased) are used.
Cytokine release syndrome as defined based on ASTCT consensus criteria (Lee at al, 2019)[32] except for IV cohorts, which are based on Lee et al. 2014[31] criteria.
MedDRA v25.0 coding dictionary applied. Frequencies ordered by occurrence in the group SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A.
PF-06863135 (Elranatamab)

Table 10: Treatment Emergent Serious Adverse Events by MedDRA PT Reported with >=2% of Participants (All Causality) - Safety Analysis Set (Protocol C1071001)

Number of Participants Evaluable for AEs	PF-06863135 SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A Total (N=55)	PF-06863135 SC 1000 ug/kg, Part 1.1, and Part 2A (N=41)	PF-06863135 SC 1000 ug/kg, Part 1.1 Q1W, and Part 2A (N=28)	PF-06863135 SC (44mg to 76mg) Part 2A (N=15)
	Total	Total	Total	Total
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	[redacted]	[redacted]	[redacted]	
Cytokine release	[redacted]	[redacted]	[redacted]	
Muscular weakness	[redacted]	[redacted]	[redacted]	
Myelodysplastic syndrome	[redacted]	[redacted]	[redacted]	
Acute kidney injury	[redacted]	[redacted]	[redacted]	
Bacteraemia	[redacted]	[redacted]	[redacted]	
COVID-19	[redacted]	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	[redacted]	
Febrile neutropenia	[redacted]	[redacted]	[redacted]	
Herpes zoster	[redacted]	[redacted]	[redacted]	
Hypercalcaemia	[redacted]	[redacted]	[redacted]	
Malaise	[redacted]	[redacted]	[redacted]	

@@ Uncoded term
Includes all data since first dose of study drug, and up to 90 days (28 days for patients who completed the trial prior to approval of PA8 in June 2021) of last dose of study drug or start of new anti-cancer therapy, whichever occurs first.
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), Hyperphosphataemia (PT=Blood phosphorus increased), Hypertension (PT=Blood pressure increased) are used.
Cytokine release syndrome as defined based on ASTCT consensus criteria (Lee at al, 2019)[32] except for IV cohorts, which are based on Lee et al. 2014[31] criteria.
MedDRA v25.0 coding dictionary applied. Frequencies ordered by occurrence in the group SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A.
PF-06863135 (Elranatamab)

Table 11: Treatment Emergent Serious Adverse Events by MedDRA PT Reported with >=2% of Participants (Treatment Related) - Safety Analysis Set (Protocol C1071001)

Number of Participants Evaluable for AEs	PF-06863135 SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A Total (N=55)	PF-06863135 SC 1000 ug/kg, Part 1.1, and Part 2A (N=41)	PF-06863135 SC 1000 ug/kg, Part 1.1 Q1W, and Part 2A (N=28)	PF-06863135 SC (44mg to 76mg) Part 2A (N=15)
	Total	Total	Total	Total
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	[redacted]	[redacted]	[redacted]	
Cytokine release syndrome	[redacted]	[redacted]	[redacted]	
Febrile neutropenia	[redacted]	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	[redacted]	

@@ Uncoded term
Includes all data since first dose of study drug, and up to 90 days (28 days for patients who completed the trial prior to approval of PA8 in June 2021) of last dose of study drug or start of new anti-cancer therapy, whichever occurs first.
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), Hyperphosphataemia (PT=Blood phosphorus increased), Hypertension (PT=Blood pressure increased) are used.
Cytokine release syndrome as defined based on ASTCT consensus criteria (Lee at al, 2019)[32] except for IV cohorts, which are based on Lee et al. 2014[31] criteria.
MedDRA v25.0 coding dictionary applied. Frequencies ordered by occurrence in the group SC 215 ug/kg to 1000 ug/kg, Part 1.1, and Part 2A.
PF-06863135 (Elranatamab)

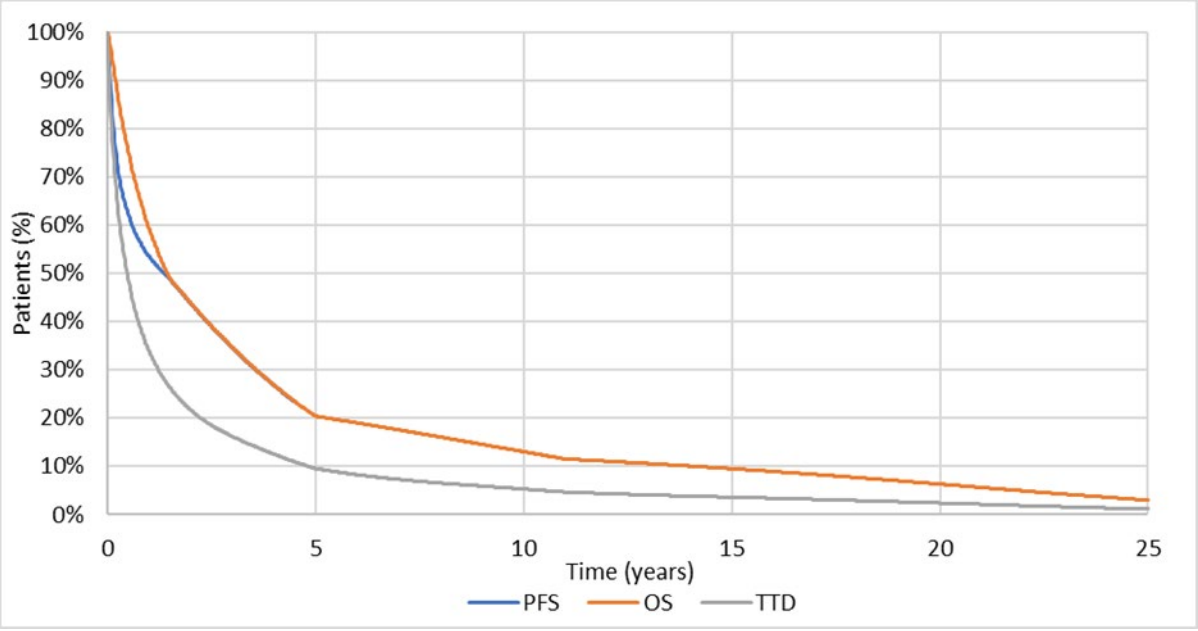
Section B: Clarification on cost-effectiveness data

Model structure

B1. Document B, Section B.3.3.2. (Figures 25 and 26). Figures 25 and 26 both show two figures (panels) with no explanation of how they differ and what they are showing. Please clarify.

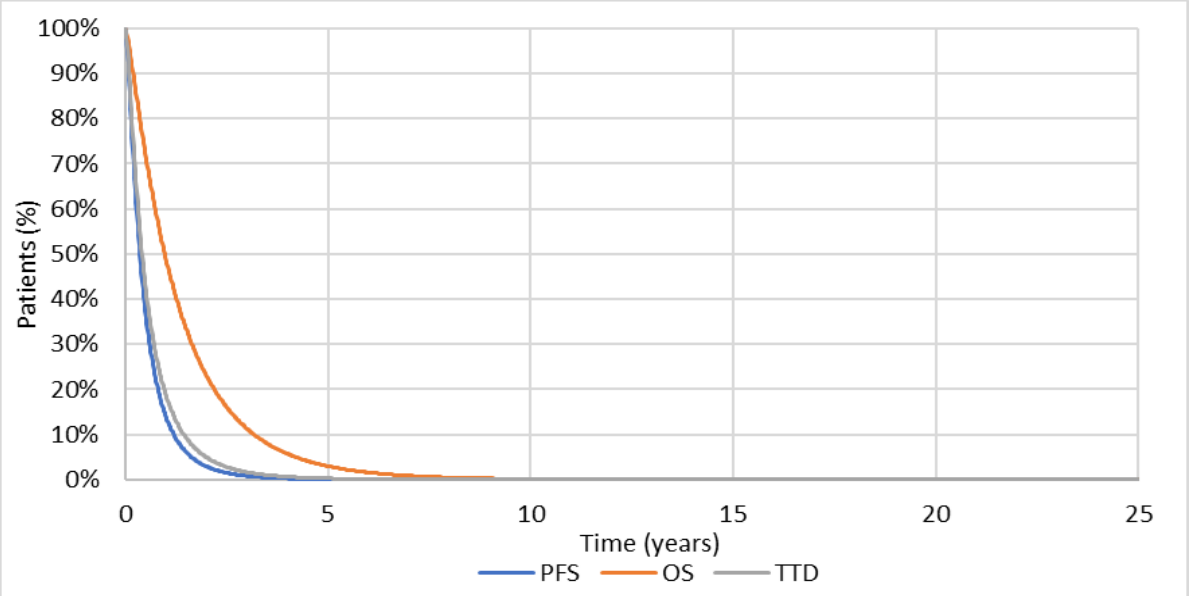
These duplicate figures were provided in error please see the correct figures below (Figure 8 and Figure 9)

Figure 8: Partitioned survival illustration for elranatamab - Correction to CS, Document B, Figure 25



Key: OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; TTD, time to treatment discontinuation.

Figure 9: Partitioned survival illustration, PFS and OS, for POM+DEX (MM-003) - Correction to CS, Document B Figure 26



Key: OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; TTD, time to treatment discontinuation.

Efficacy parameters

B2. Document B, Section B.3.3. Please clarify/clearly summarise the general approach to modelling comparative OS and PFS for elranatamab and POM-DEX in the base case and relevant scenarios. In particular, how does the MAIC with trial MM-003 feed into the economic modelling. It is unclear to the EAG from reading the submission, whether the parametric curves reported in document B for elaranatamab have been fitted to the raw Kaplan Meier data or MAIC adjusted Kaplan Meier data.

In the base case, adjusted Kaplan Meier data was used to derive long-term survival extrapolations in the elranatamab model arm, whilst unadjusted Kaplan Meier curves were used in the POM+DEX arm. Please see for a summary of the approach to modelling OS and PFS for elranatamab and POM-DEX.

Figure 10: Summary of base-case OS and PFS modelling

Model arm	Survival outcome	Base-case approach to survival modelling
Elranatamab	OS	Generalized gamma model fit to adjusted MM-003 data; PFS dominates OS.
	PFS	Generalized gamma model fit to adjusted MM-003 data; curves adjusted for excess mortality using SMR.
POM+DEX	OS	Generalized gamma model fit to unadjusted MM-003 data;
	PFS	Generalized gamma model fit to unadjusted MM-003 data; adjusted for excess mortality using SMR.
Key: DEX, dexamethasone; PFS, progression-free survival; POM, pomalidomide; OS, overall survival.		

B3. Document B, Section B.3.3.3.1 and Figure 41. It is stated that "….independent parametric models were fitted to the MAIC MM-003 data. Following the MAIC, standard parametric fits were calculated for MAIC MM-003 curves". Please explain the meaning of this statement. How have the MM-003 curves been altered/adjusted by the MAIC?

Prognostic variables and treatment effect modifiers were identified based on the clinical SLR (CS, Appendix D), and clinical opinion. These are summarized in CS, Document B, Table 14 (reproduced in Table 11**).**

Table 12: Prognostic variables and effect modifiers identified based on the SLR and clinical opinion (reproduced from CS, Document B Table 14)

	PFS	OS
Prognostic variables and effect modifiers	Age Time since initial diagnosis R-ISS or ISS (where available) High-risk cytogenetics Extramedullary disease Number of prior lines of therapy ECOG performance status Creatinine clearance Refractory/exposure status (penta-exposed; penta-refractory status) Type of MM (IgG, IgA, IgD, light-chain)	Age Sex Time since initial diagnosis R-ISS or ISS (where available) High-risk cytogenetics Extramedullary disease Number of prior lines of therapy ECOG performance status Creatinine clearance Refractory/exposure status (penta-exposed; penta-refractory status) Type of MM (IgG, IgA, IgD, light-chain)
Key: ECOG, Eastern Cooperative Oncology Group; EM, effect modifiers; OS, overall survival; PFS, progression-free survival; PV, Prognostic variables; R-ISS, Revised International Staging System. **Note:** R-ISS was prioritised as a PV/EM if it was reported in the comparator's trial.		

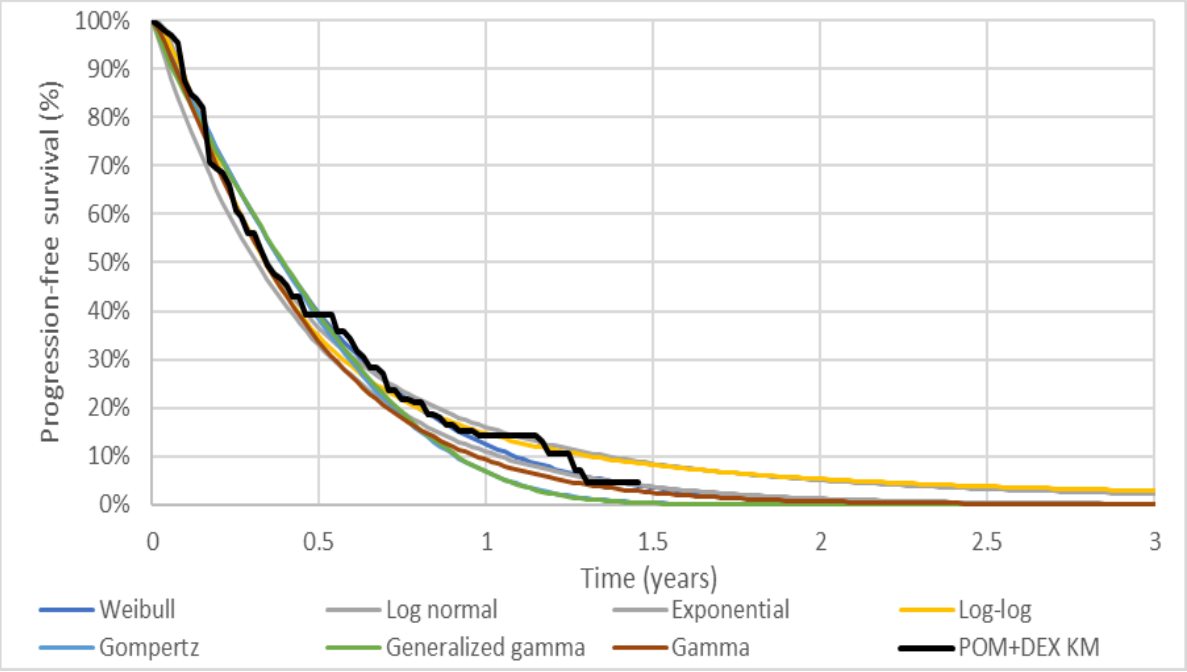
Based on these variables, MagnetisMM-3 data were reweighted to the aggregated data from MM-003 so that effect modifiers and prognostic variables in the elranatamab arm were the same as those reported for POM+DEX in the MM-003 study. Baseline characteristics before and after matching are described in response to A9 in Table 5..

Full details of the MAIC are available in CS Document B, Section B.2.9.1 and Appendix O.

B4. Document B, Section B.3.3.3.1 (Figure 41) and Section B.2.9.1.2 (Figure 18). Related to question B3, Figure 41 shows the PFS KM data from MM-003 terminating before one year of follow-up, yet the data in the clinical effectiveness section (Figure 18) shows follow-up to beyond 16 months. Please explain and justify this discrepancy.

The curve in CS Document B, Section B.3.3.3.1, Figure 41 was provided in error. A corrected version of the figure is provided below (Figure 4).

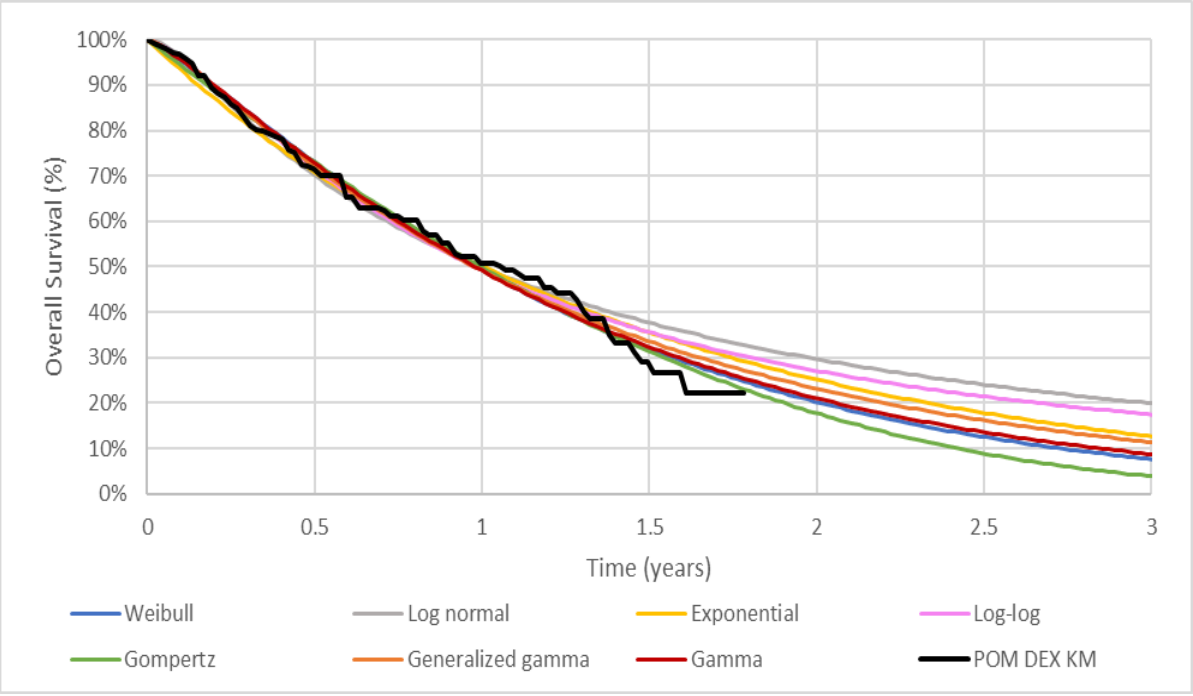
Figure 11: Standard parametric fits of PFS, POM+DEX (MM-003 parametric fits) – adjusted for excess mortality (3 -year time horizon) - Correction to CS, Document B, Figure 41



B5. Document B, section B.3.3.3.2. Figure 43. Figure 43 shows two figures (panels) with no explanation. Please clarify what each is showing and the relevance of the each to the economic case.

These figures were provided in error. Please see Figure 5 for a corrected graph of parametric fits to MAIC MM-003 OS Kaplan-Meier data.

Figure 12: Standard parametric fits of OS, POM+DEX (MAIC MM-003 parametric fits) – adjusted for excess mortality (3-year time horizon) - Correction of CS, Document B, Figure 43



B6. Document B, section B.3.3.3.2., Figure 43. Related to B5, Figure 43 shows the OS Kaplan Meier data for MM-003 terminating before 1.5 years, yet Figure 19 in the clinical effectiveness section shows the OS KM data from MM-003 out to about 22 months. Please explain and justify this discrepancy.

This curve was provided in error. Please see a corrected graph above (Figure 5), in response to B5.

B7. Document B, section B. 3.3.2.1. (Table 24). Table 24 indicates identical AiC and BiC for the Gompertz and log-normal distributions, with log-normal ranked second. Is this correct?

The AiC and BiC statistics for the Gompertz and log-normal distributions are similar and the difference does not show when they are presented to 2 decimal places. Please see Table 3 for AiC and BiC statistics presented to 3 decimal places

Table 13: AiC and BiC statistics of the standard parametric fits of PFS, elranatamab (MagnetisMM-3 15-month data-cut), 3 decimal places

Parametric model	AIC	BIC	Average	Rank
Weibull	413.295	418.919	416.107	5
Log-normal	403.916	409.540	406.728	2
Exponential	426.764	429.576	428.170	7
Log-logistic	408.937	414.562	411.750	4
Gompertz	403.917	409.541	406.729	3
Generalised gamma	396.879	405.315	401.097	1
Gamma	415.673	421.297	418.485	6

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation.

B8. Document B, Section B.3.3.5.1., Figure 49. Figure 49 shows two panels, with no explanation of what each panel is showing or how they differ. Please clarify.

These duplicate figures were provided in error. The correct figure is provided below (Figure 13).

Figure 13: Standard parametric fits of TTD, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (3-year time horizon) (CS, Document B Figure 49)

B9. Document B, Section B.3.3.5.2 and B.3.3.5.3. Section B.3.3.5.2 states that "Given the indication that treatment continues beyond the point of progression (in both MagnetisMM-3 and the ECA study), the assumption of PFS:TTD ratio was applied in the base case analysis". This is contradicted in B.3.3.5.3, which states "TTD equal to PFS based on MM-003 was applied to POM+DEX". Please clarify and justify the preferred approach.

This is an error in CS Document B, Section B.3.3.5.3. The sentence should read "the assumption of PFS:TTD ratio was applied to POM+DEX."

B10. Document B, Section B.3.3.6. The calculation methods for incorporating adverse event in the model are not described clearly. Is Table 34 displaying rates per 100 person years, probabilities per cycle or the percentage of patients experiencing different types of event? Table 34 also reports grade 1 and 2 AEs. Please clarify the approach and calculation methods for incorporating AEs in the model.

CS Document B, Table 34 presents the percentage of patients experiencing each AE in MagnetisMM-3. These percentages are applied as a probability in the first cycle of the cost-effectiveness model. These probabilities are taken directly from the CSR for MagnetisMM-3 without additional calculation.

For most AEs included in the table, only Grade 3-4 events are included in the probabilities. Grade 1-2 CRS and neurotoxicity are expected to be associated with costs and utility decrements therefore these probabilities are included separately. The probabilities of a Grade 1-2 CRS or neurotoxicity event are calculated by subtracted the percentage of patients experienced a Grade 3-4 CRS or neurotoxicity event from the percentage of patients with any grade CRS or neurotoxicity event.

Health related quality of life

B11. Document B, Section B.3.4.1. Please provide details on the numbers of pre- and post-progression EQ-5D observations, and up to how long after progression do the progressive disease values apply.

In the utility analysis, the pre-progression stage included all EQ5D observations until the timepoint when a patient was assigned a censoring or event of progression. This leads to [redacted] observations in total.

The post-progression stage included all EQ5D observations after the timepoint when a patient was coded as progression-event (therefore excluding the observations if patients were censored for progression). This leads to [redacted] observations in total.

In the company cost-effectiveness model, post-progression utility was applied to patients in the post-progression health state. As discussed in Document B, Section B.3.2.2, for elranatamab, the post-progression health state utility (illustrated in Document B, Figure 25) is applied to the proportion of patients who enter the post-progression health state and applied from progression until death for a period equating to 0.12 Life years (see Appendices Table 37).

For POM+DEX patients, the post-progression health state utility is applied to the proportion of patients who enter the post-progression health state and applied from progression until death for a period equating to 0.82 Life years (see Appendices Table 37).

B12. Document B, Section B.3.4.1. It is stated that “To determine the best-fitting model, the appropriateness was also assessed by evaluating the AIC”. Please can you provide details of the different multivariate models explored, and the corresponding AiC/BiC values.

In the univariate regression analysis, only the dummy variable indicating the “Common AE, Grade 3–4, treatment emergent’ and the dummy variable indicating “pre-or post-progression” were significant (p<=0.05).

Next, all the statistically significant covariates from the univariate analysis together with the corresponding interaction terms were considered in multivariate analyses. A

backwards stepwise approach was used to remove non-significant predictors at each step until a final model containing only the significant terms was left. Table 14 presents the results from the starting model.

[redacted]

Coefficient	Estimate	SE	p value	Significance	AIC	BIC
(Intercept)	[redacted]	[redacted]	[redacted]	***	[redacted]	[redacted]
Pre-progression or post-progression status indicator (1 or 0)	[redacted]	[redacted]	[redacted]	**		
Common AE, Grade 3–4, treatment emergent	[redacted]	[redacted]	[redacted]			
Interaction term: Pre-progression or post-progression status indicator (1 or 0) * Common AE, Grade 3–4, treatment emergent	[redacted]	[redacted]	[redacted]			

Key: AE, adverse events; AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival; SE, standard error.
Notes: *statistically significant (≤ 0.05), **statistically significant (≤ 0.01), *** statistically significant (≤ 0.001).

Next, the interaction term between progression state and common AE grade 3-4 was eliminated as it was the most insignificant one. All covariates became significant in the derived model ($p<0.05$), and AIC/BIC are lower than the starting model, as shown in Table 15. This model was selected as the final model for the health-state utility values and the AE disutility.

Please note an error was identified in Table 36 from Document B where 12-month data was not updated to the 15-month data cut. A corrected Table 15 is included below. Please note the cost-effectiveness model was updated with the 15-month data and is correct at submission.

Table 1516: Results of multivariate analyses for utility analysis

Coefficient	Estimate	SE	p value	Significance	AIC	BIC
(Intercept)	[redacted]	[redacted]	[redacted]	***	[redacted]	[redacted]
Pre-progression or post-progression status indicator (1 or 0)	[redacted]	[redacted]	[redacted]	**		
Common AE, Grade 3–4, treatment emergent	[redacted]	[redacted]	[redacted]	*		

Key: AE, adverse events; AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival; SE, standard error.
Notes: *statistically significant (≤ 0.05), **statistically significant (≤ 0.01), *** statistically significant (≤ 0.001).

In addition, following this clarification question we have undertaken a review of CS Document B to check all data related to the 12-month vs. 15-month data cut. The values are all correct in the cost-effectiveness model and do not impact the analysis results. However, during our checks we have noticed a minor error in the 95% CI for the utility values used in the cost effectiveness analysis (Table 40, Document B). The correct values are in Table 16 below.

Table 1718: (Table 40 Document B): Summary of utility values for cost effectiveness analysis

State		Utility value: mean	95% CI	Justification
PFS (on and off treatment)		0.71	[0.64,0.79]	Estimated directly from systematic analysis, mapping EQ-5D-5L to EQ-5D-3L data from patients informing effectiveness estimates, in line with the NICE reference case[103]
PPS		0.63	[0.59,0.67]	
AE disutility	Elranatamab	-0.0051*		
	POM+DEX	-0.0034*		

Key: AE, adverse events; CI, confidence interval; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; PPS, post-progression survival.
Note: *Calculated in the cost effectiveness model

B13. Document B, Section B.3.4.1. Please could you clarify how the variable "Common AE, Grade 3–4, treatment emergent" was defined in the EQ-5D regression (i.e. did it capture all grade 3-4 AEs or only those included in the model). And how many EQ-5D observations were considered to occur during these AEs?

The variable "Common AE, Grade 3–4, treatment emergent" captured all grade 3-4 common AEs in the MagnetisMM-3 trial (i.e., except for the CRS and neurotoxicity). Separate variables were generated for CRS and neurotoxicity respectively.

In total, there were [redacted] EQ-5D observations experiencing treatment emergent grade 3-4 common AEs in the analysis.

Costs

B14. Document B, section B.3.3.6. It is stated that 43.1% of Cohort A patients received intravenous immunoglobulin (IVIG) in the MagnetisMM-3 study (Document B page 81). Could you please consider and give an opinion on the following:

- What impact would this have had on the infection rates observed in the trial?
- What impact could this have had on the observed treatment discontinuation rate?

A recent post hoc analysis of the MagnetissMM-3 trial has explored the potential impact of hypogammaglobulinemia and immunoglobulin replacement on infection rates.[33] Patients treated with IVIG or who do not develop hypogammaglobulinemia develop fewer infections (including grade 3). The company believes no data currently exists on the impact this might have on discontinuation although it would be clinically plausible to expect that a reduction in infection rates might lead to a reduction in discontinuation.

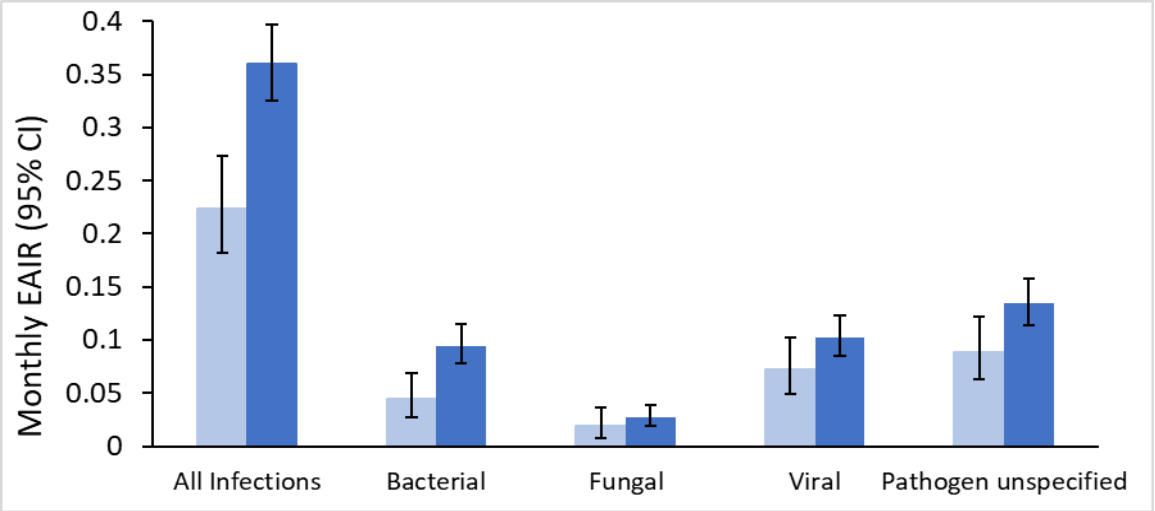
The key findings are:

- Lower monthly EAIRs were observed in patients "on" vs "off" Ig replacement therapy (0.22 [95% CI, 0.18-0.27] vs 0.36 [95% CI, 0.33-0.40]), with similar trends observed regardless of infection type

- Lower monthly EAIRs were observed in patients without vs with hypogammaglobulinemia (0.23 [95% CI, 0.19-0.27] vs 0.36 [95% CI, 0.32-0.40]); similar trends were seen across infection types.

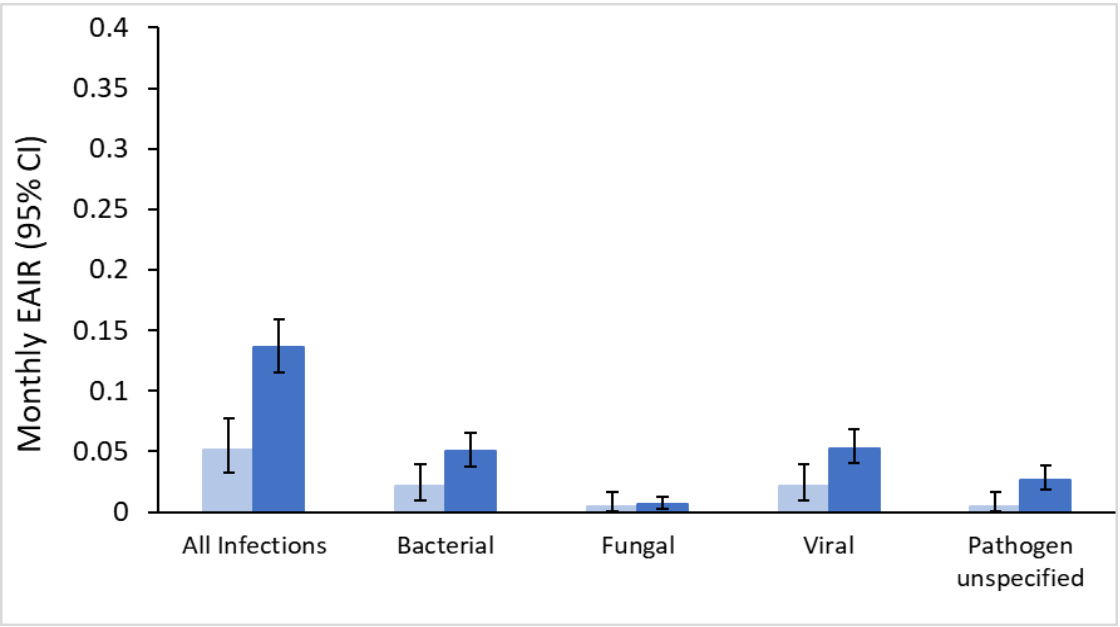
Figure 14: Infections of any grade (A) and grade ≥3 (B) in patients with or without Ig replacement therapy in MagnetisMM-3.

A



Rates with Ig replacement	0.22413	0.04436	0.01868	0.07238	0.08872
Rates without Ig replacement	0.35951	0.09480	0.02772	0.10284	0.13414
Cases with Ig replacement	96	19	8	31	38
Cases without Ig replacement	402	106	31	115	150

B.

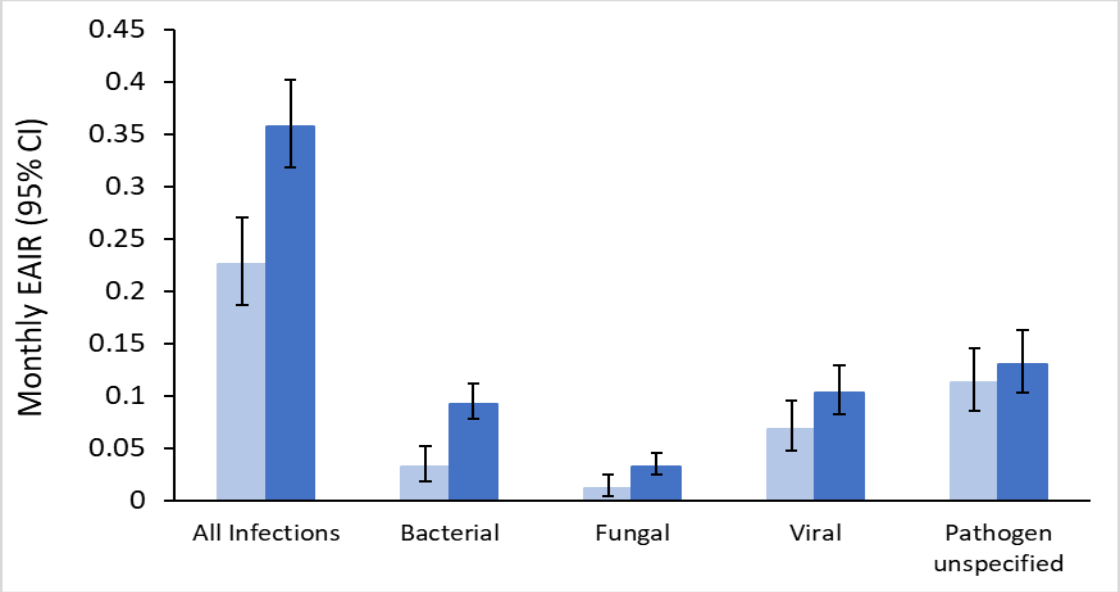


Rates with Ig replacement	0.05136	0.02101	0.00467	0.02101	0.00467
Rates without Ig replacement	0.13593	0.05008	0.00626	0.05276	0.02683
Cases with Ig replacement	22	9	2	9	2
Cases without Ig replacement	152	56	7	59	30

Ig=Immunoglobulin
EAIR=exposure-adjusted infection rate

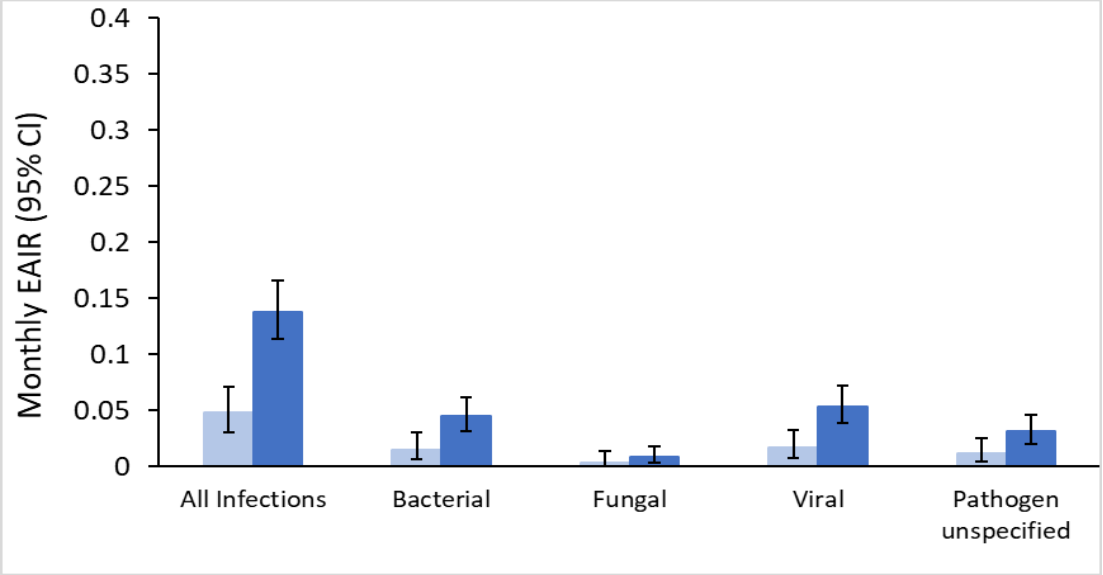
Figure 15: Infections of any grade (A) and grade ≥3 (B) in patients without or with hypogammaglobulinemia in MagnetisMM-3.

A



Rates without HGG	0.22589	0.03254	0.01149	0.06892	0.11294
Rates with HGG	0.35759	0.09188	0.03228	0.10306	0.13037
Cases with Ig replacement	118	17	6	36	59
Cases without Ig replacement	288	74	26	83	105

B



Rates without HGG	0.04786	0.01531	0.00383	0.01723	0.01149
Rates with HGG	0.13782	0.04470	0.00869	0.05339	0.03104
Cases with Ig replacement	25	8	2	9	6
Cases without Ig replacement	111	36	7	43	25

HGG=Hypogammaglobulinemia
EAIR=exposure-adjusted infection rate

B15. Document B, Page 158, Table 47. The cost of IVIG used in the model (£1,573.58) is based on the list price. It is not clear whether this includes the administration cost of the treatment. Please clarify whether this is included and if necessary, provide an updated cost to include it.

The model uses the list price for IVIg based on NHS a published clinical commissioning policy (£1,573.58) which does not include administration costs. However, a previous NICE appraisal, NICE TA872, used £1256.93 (NHS Reference Costs 2016/2017, XD34Z, Immunoglobulins Band 1 – Admitted patient care). Inflated to the current cost year using PSSRU NHSCII pay and prices inflation indices this would reflect a cost of £1,390.92.

As IVIG is administered for the management of certain adverse events, the administration cost could be accounted for within the AE costs, so if we were to include the admin costs, there is a risk of double counting. Therefore, we have presented the cost of IVIG separately as it is a high-cost item, and we are uncertain if the cost of IVIG is reflected fully in NHS reference costs.

B16. Document B, Section B.3.3.6. The dosage of IVIG used for the economic model is 0.5mg/kg. Please clarify which indication detailed in reference 97 this is for. What was the typical dosage of IVIG (given to those developing bacterial infections) in the MagentisMM-3 study?

Indication and dose

The use of IVIG in England is governed by the Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, Prepared by NHS England Immunoglobulin Expert Working Group.[34]

The use of IVIG in patients on elranatamab would fall into the “secondary antibody deficiency – long term use” category (page 5, Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021). This recommends a dose of 0.4-0.6g/Kg/month.[34]

Long-term IVIG dosing is not defined in published papers or guidance. UK clinicians have informed the company that patients are typically treated monthly for 6 months, after which the frequency can be dropped depending on adequate antimicrobial prophylaxis, incidence of infections, the season, and IgG trough levels.[20]

Dosage of IVIG in MagnetisMM-3

- We have attempted to source this information. However, IVIG dose data were not captured in MagnetisMM-3, so these data are not available.
- Regardless of the MagnetisMM-3 data, IVIG use in the UK would have to follow national guidelines, i.e. Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England.[34]
- Pfizer has sought clinical validation for IVIG dosing. A leading UK KOL stated that 0.4g/Kg/month is the usual dose used in his clinical practice. [20]

B17. Document B, section B.3.3.6. The mean treatment duration of [redacted] observed during the MagnetisMM-3 study was applied to those modelled to receive IVIG

treatment. Is this estimate derived from all patients who received IVIG in Cohort A (43.1%) or the [redacted] who received it for treatment emergent infections?

43.1% of cohort A patients received IVIG during the study. The median duration of IVIG treatment was [redacted], mean was [redacted].

Pfizer performed a post-hoc analysis of the IVIG data by indication and incidence of infection. [redacted] of patients received IVIG as a result of a bacterial infection, or developed a bacterial infection whilst on-IVIG. The median duration on-IVIG treatment in these patients was [redacted] months whilst the mean was [redacted] months.

B18. Document B, section B.3.5.1. Drug acquisition costs are based on a relative dose intensity of [redacted]. Please clarify how this was calculated and whether it is generalisable to UK clinical practice.

Relative dose intensity was calculated using standard methodology as detailed in Magnetis CSR Table 14.4.1.1. For reference, this was calculated based on the following formula:

- Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] *100

As part of the process of developing the responses to these clarification questions, Pfizer undertook a 1-hour paid consultancy with a key opinion leader, practicing UK clinician. This doctor confirmed that the RDI [redacted]% was generalisable to the UK. This is because the Q2W step-down was in our trial protocol and subsequent data has been presented for it's effectiveness. Furthermore, the draft SmPC has a lower threshold for QW to Q2W step-down than the MagnetisMM-3 protocol, potentially allowing a greater proportion of patients to step-down to Q2W dosing.

The same key opinion leader, practicing UK clinician also suggested RDI could be even lower than [redacted]% in clinical practice. They explained this could be due to step down to Q2W earlier than what is in the label, or dosing that is less frequent than Q2W. Continuous BsAb exposure has been shown to induce an exhausted T-cell phenotype, with less frequent dosing or treatment pauses potentially helping to avoid this outcome.[35, 36] Alternative BsAbs are already being investigated or used with dosing that is the same or less frequent than Q2W.[37-39] Pfizer are also exploring less

frequent dosing, with future elrantamab protocol amendments to allow for Q4W dosing.

B19. Document B, section B.3.5.1. It is stated that “vials are a fixed dose (i.e., not weight-based), thus wastage will not occur”. However, the step-up doses are less than the 44mg vial, please clarify how wastage is accounted for in the model.

The company cost effectiveness model assumes that Elranatamab wastage is modelled for the 44 mg, i.e., a single dose 44 mg vial is used for the 12 mg dose, and another is used for the 32 mg dose. No wastage is assumed for the 76 mg vial dose, as this is equivalent to the single dose 76 mg vial.

The wastage assumption is linked to a Yes/No switch in the settings tab of the company cost effectiveness model.

Yes =1 = Cost per dose (with wastage), this means that when a 12 mg dose is used, the cost of a 44 mg is included in the model and the same for a 32 mg dose i.e. the left amount of the vial is wasted.

No = 2, Cost per dose (no wastage), this means that when a 12 mg or 32mg dose is used, the cost of 12 mg or 32mg only is included i.e., there is assumed to be no wastage of elranatamab.

Please note these assumptions also impact Bortezomib calculations.

B20. Document B, Section B.3.5.2., table 46. The health state specific resource use costs are multiplied by 0.23 to account for frequency. Please clarify the units of this frequency measure and justify its use.

The health state resource use frequencies used in the cost-effectiveness analysis were derived from NICE TA658 which used a 1-month model cycle length. However, the cost-effectiveness model in this submission adopts a 1-week cycle length. Therefore, resource use frequencies were adjusted by 0.23 to generate resource use per week rather than per month.

References

1. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of epidemiology and community health. 1998;52(6):377-84.
2. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. University of Sheffield: NICE Decision Support Unit; 2016. 82 p.
3. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-Adjusted Indirect Comparisons: A New Tool for Timely Comparative Effectiveness Research. Value in Health. 2012;15(6):940-7.
4. Pfizer Inc. MagnetisMM-3: Study Of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One PI, One IMiD and One Anti-CD38 mAb. 2023.
5. Pfizer Inc. MagnetisMM-3: Trial Protocol of C1071003. 2020.
6. Miguel JS, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2013;14(11):1055-66.
7. Richardson PG, Siegel DS, Vij R, Hofmeister CC, Baz R, Jagannath S, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123(12):1826-32.
8. Richardson PG, Perrot A, San-Miguel J, Beksac M, Spicka I, Leleu X, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. The Lancet Oncology. 2022;23(3):416-27.
9. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. New England Journal of Medicine. 2018;379(19):1811-22.
10. Dimopoulos MA, Schjesvold F, Doronin V, Vinogradova O, Quach H, Leleu X, et al. Oral ixazomib-dexamethasone vs oral pomalidomide-dexamethasone for lenalidomide-refractory, proteasome inhibitor-exposed multiple myeloma: a randomized Phase 2 trial. Blood Cancer J. 2022;12(1):9.
11. Schjesvold FH, Dimopoulos MA, Delimpasi S, Robak P, Coriu D, Legiec W, et al. Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study. Lancet Haematol. 2022;9(2):e98-e110.
12. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. British journal of haematology. 2016;175(2):252-64.
13. Gandhi UH, Cornell RF, Lakshman A, Gahvari ZJ, McGehee E, Jagosky MH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-75.
14. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20.

15. Hanamura I. Multiple myeloma with high-risk cytogenetics and its treatment approach. Int J Hematol. 2022;115(6):762-77.
16. Bladé J, Beksac M, Caers J, Jurczyszyn A, von Lilienfeld-Toal M, Moreau P, et al. Extramedullary disease in multiple myeloma: a systematic literature review. Blood Cancer J. 2022;12(3):45.
17. Goel U, Charalampous C, Kapoor P, Binder M, Buadi FK, Dingli D, et al. Defining drug/drug class refractoriness vs lines of therapy in relapsed/refractory multiple myeloma. Blood Cancer J. 2023;13(1):11.
18. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012;15(6):940-7.
19. Pfizer. HTA Advisory Board for Elranatamab for Treating Relapsed or Refractory Multiple Myeloma after Three Therapies 2023.
20. Pfizer. Clinical Validation Interview Report for the NICE Submission of Elranatamab for Treating Relapsed or Refractory Multiple Myeloma after Three Therapies. 2023.
21. National Institute for Health and Care Excellence (NICE). Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable [TA763] 2022 [Available from: https://www.nice.org.uk/guidance/ta763.
22. Digital N. Cancer Registration Statistics, England 2019 - NHS Digital C90 Multiple myeloma and malignant plasma cell neoplasms age 20 and over 2019 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2019/content.
23. Pfizer. Routes to TCR in the NICE pathway. 2023.
24. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17(8):e328-e46.
25. Pfizer. 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
- PROTOCOL 2023 16.06.2023.
26. Rajkumar SV, Harousseau J-L, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-5.
27. Durie BGM, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73.
28. Pfizer. MagnetisMM-3 15 Month Study Report Output. 2023.
29. National Institute for Health and Care Excellence (NICE) Decision Support Unit. Technical Support Document 18: Methods for population-adjusted indirect comparisons 2016 [Available from: https://research-information.bris.ac.uk/ws/portalfiles/portal/94868463/Population_adjustment_TSD_FINAL.pdf.
30. Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ, Miles Prince H, Niesvizky R, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nature Medicine. 2023.

31. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.
32. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.
33. Leleu X, Bahlis N, Rodriguez-Otero P, Quach H, Touzeau C, Depaus J, et al. P-286 Impact of hypogammaglobulinemia and immunoglobulin replacement therapy on infection rate in patients with RRMM treated with elranatamab: post-hoc analysis from MagnetisMM-3. Clinical Lymphoma Myeloma and Leukemia. 2023;23:S194.
34. England N. Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021. 2021.
35. Philipp N, Kazerani M, Nicholls A, Vick B, Wulf J, Straub T, et al. T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. Blood. 2022;140(10):1104-18.
36. Florian Eisele NA, Emilia Stanojkovska, Mara John, Moutaz Helal, Lars Grundheber, Philipp Weis, Christine Riedhammer, Sofie-Katrin Kadel, Max Steinhardt, Johannes Duell, Johannes M Waldschmidt, Hermann Einsele, Angela Riedel, K. Martin Kortüm, and Leo Rasche. 1938 The Impact of Treatment-Free Intervals on T-Cell Exhaustion and Clonotypic Diversity in Myeloma Patients Treated with BCMA Bispecific Antibodies. American Society of Haematology; Saturday, December 9, 2023, 5:30 PM-7:30 PM; San Diego: ASH; 2023.
37. Sandy W. Wong NB, Laura Paris, Craig C Hofmeister, Markus Hansson, Armando Santoro, Maria-Victoria Mateos, Paula Rodríguez-Otero, MD, Johan Lund, Cristina Encinas, Andrew J. Yee, Albert Oriol, Claudio Cerchione, Javier de la Rubia, Barbara Ferstl, Kristina Carlson, Paz Ribas, Arancha Bermúdez, Isaac W. Boss, Allison Gaudy, Shaoyi Li, Kevin Hsu, Colin D. Godwin, Michael R. Burgess, Jesús San-Miguel,and Luciano J. Megala Costa. Alnuctamab (ALNUC; BMS-986349; CC-93269), a B-Cell Maturation Antigen (BCMA) x CD3 T-Cell Engager (TCE), in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Results from a Phase 1 First-in-Human Clinical Study. Blood 2022; 140 (Supplement 1): 400–402. ASH 2022 - 64th American Society of Hematology Annual Meeting and Exposition; New Orleans: Blood 2022; 140 (Supplement 1): 400–402; 2022.
38. Johnson Ja. European Commission Approves Reduced Dosing Frequency for Janssen's Bispecific Antibody 2023 [Available from: https://www.jnj.com/european-commission-approves-reduced-dosing-frequency-for-janssens-bispecific-antibody-tecvayli-teclistamab.
39. Lee HC BN, Richter J, Dhodapkar M, Hoffman JE, Suvannasankha A, Zonder J, Shah MR, Lentzsch S, Maly JJ, Ye JC, Wu KL, Deveaux M, Chokshi D, Boyapati A, Hazra A, Lorenc KR, Kroog G, Houvras Y, Jagannath S. S197: LINKER-MM1 STUDY: LINVOSELTAMAB (REGN5458) IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA. Hemasphere. 2023;8;7(Suppl).

Appendix A

Systematic Literature Review (2021) – Clinically Important Prognostic Variables and Effect Modifiers in RRMM

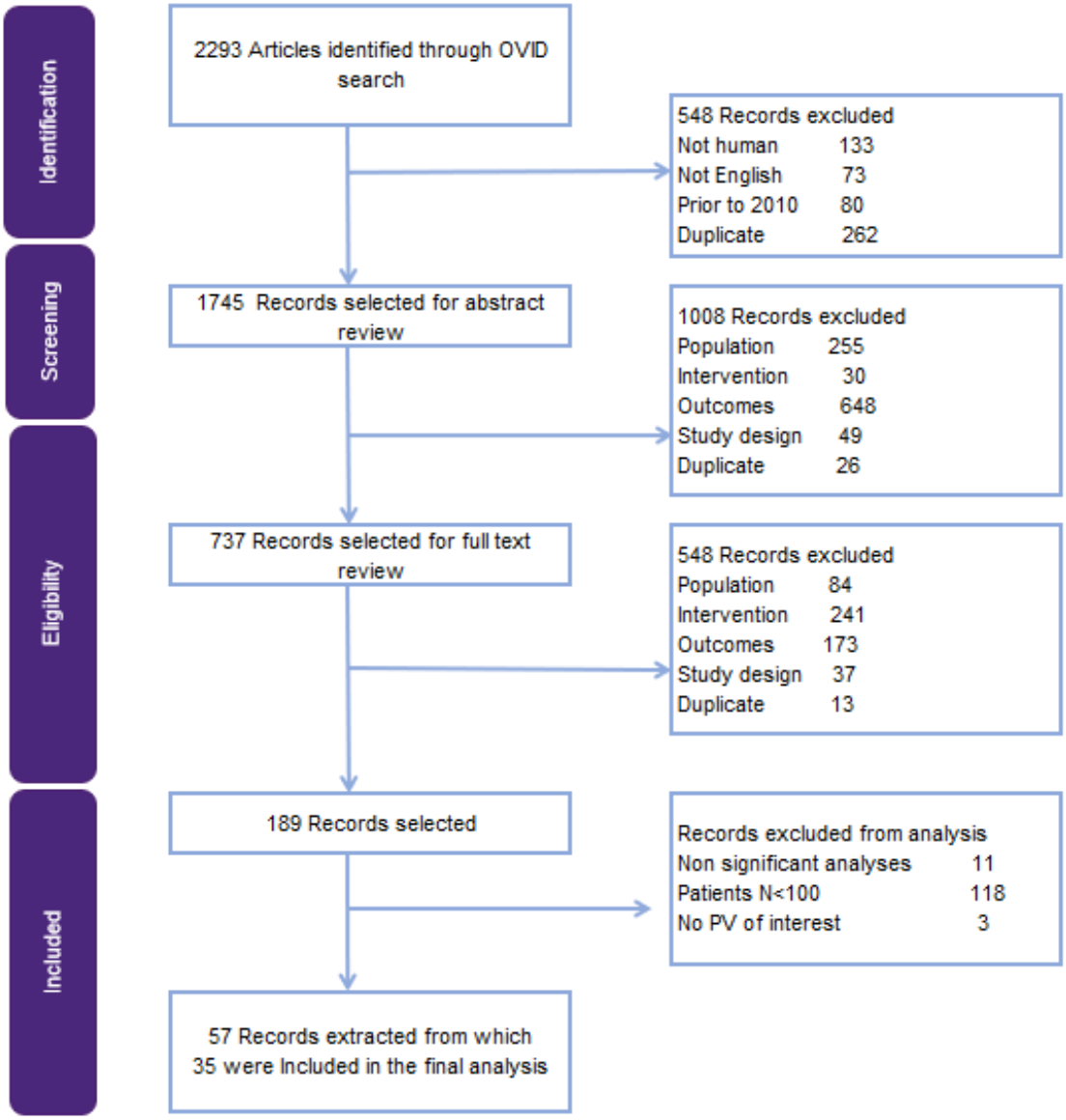
In June 2021, an SLR was conducted to identify the clinically important PVs and EMs in patients with RRMM from RWE studies. The PICOS is shown in **Table 1**.

Table 19: PICOS statement

Category	Inclusion criteria
Patient population	Patients diagnosed with relapsed or refractory multiple myeloma (RRMM) in any line
Intervention and comparators	Bortezomib, lenalidomide, carfilzomib, ixazomib, daratumumab, pomalidomide, panobinostat, elotuzumab, selinexor, melflufen, vorinostat, isatuximab, bendamustin, TJ202/MOR202 (felzartamab), encorafenib, binimetinib, pembrolizumab, nivolumab, erdafitinib, RAPA-201, belantamab mafodotin, idecabtagene vicleucel, ciltacabtagene autoleucel, CAR-T
Outcomes measures	• Overall survival (OS) • Progression-free survival (PFS) • Response rates (ORR/CR/sCR/VGPR) • Time to Progression (TTP), duration of response (DOR) • Minimal Residual Disease (MRD) • Other time-to-event measurements (event-free survival, time-to-next treatment, treatment-free survival, duration of response) • Patient reported outcomes (PRO) (EORTC-QLQ C30, MY20, FACT) • Utility values (EQ-5D, SF-36, VAS, etc.) • Safety (SAE, Grade 3/4 AE, special interest AE)
Study design	• Real world evidence (prospective, observational, longitudinal, retrospective) • Indirect treatment comparisons • Systematic reviews, meta-analyses and indirect comparisons • Pooled Analyses (for cross-checking only)

Figure 8 shows the PRISMA diagram of the SLR. Thirty-five studies with multivariate analyses were extracted and analysed, which 22 studies with univariate analyses were extracted.

Figure 16: PRISMA diagram



The SLR identified two categories for PVs and EMs: 'likely' and 'potential' PVs and EMs. We only carried the 'likely' PVs and EMs into the MAIC for adjustment.

- 'Likely' PVs and EMs were defined if the variables were reported in 3 or more studies which support the association between the variable and outcome
- 'Potential' PVs and EMs were defined if the variable were reported in less than 3 studies with conflicting evidence to support an association between the variable and the outcomes

DataSAT assessment: UK external control arm study

Research question

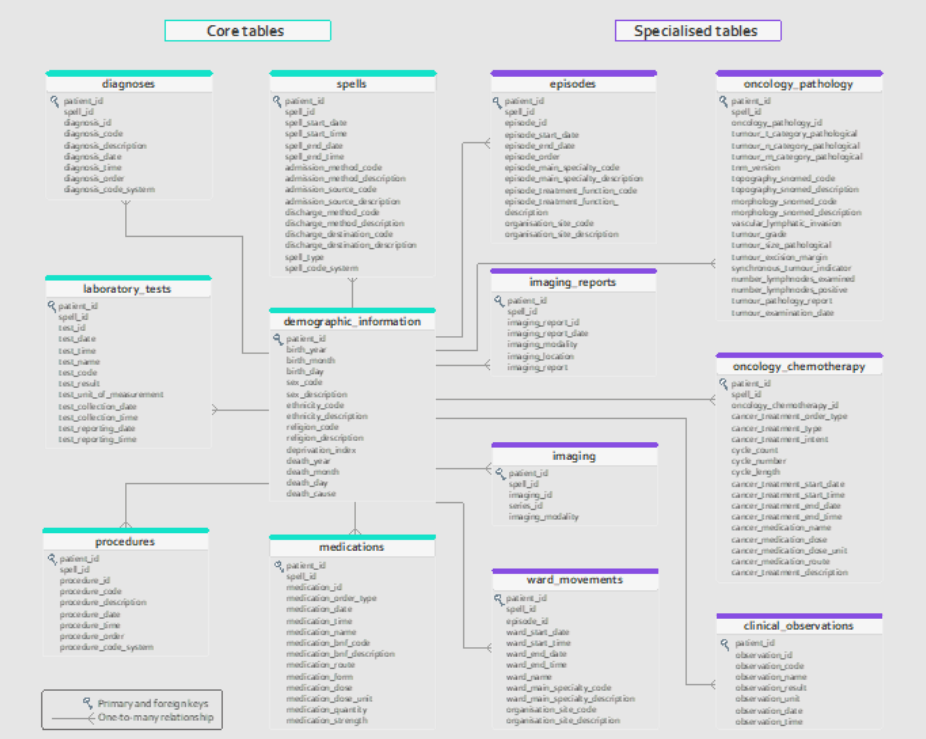
This study estimated the treatment effect of elranatamab in patients with relapsed and refractory multiple myeloma (RRMM) by comparing patients treated with elranatamab in Clinical Study C1071003 (MagnetisMM-3, MM-3) with an external control arm (ECA) of patients treated in real world UK clinical practice.

Data provenance

Item	Response
Data sources	Source 1, MagnetisMM-3 (MM-3): Clinical Study C1071003 – multicentre, open-label, single-arm, phase 2 study. Date of data cut 14th April 2023 https://clinicaltrials.gov/study/NCT04649359 Source 2, RWE: is comprised of multiple data cuts over time containing anonymised data from NHS centres partnered with Arcturis Data. OSF Registries | Comparative effectiveness of elranatamab (PF 06863135) in Clinical Study C1071003 (MagnetisMM-3) versus real world treatments for relapsed and refractory multiple myeloma (RRMM) Trusts deliver data following submission of a Data Processing Protocol (DPP): a document which specifies the rationale for and requirements of data to be acquired from each centre. Some cenres provide data cuts as partial cuts: appending previously provided data; whilst others provide full database cuts but submit additional data to Arcturis as it becomes available. As such, a range of data cuts are included from multiple centres which are then transformed and pooled into the Arcturis common data model (CDM). Anonymised, individual patient data were provided by the following NHS centres under the partnership with Arcturis Data: Chelsea and Westminster Hospital NHS Foundation Trust (01/1999 to 07/2023), Oxford University Hospitals NHS Foundation Trust (10/2010 to 08/2023), and Hampshire Hospitals NHS Foundation Trust (10/2003 to 05/2023). See Appendix 1 for all data tables provided from the English NHS centres. Data from Greater Glasgow and Clyde Health Board (01/2000 to 02/2023) was first accessed through the SafeHaven Secure Data Environment, and then a tailored analytical dataset including the relevant patients and data variables were sent to Arcturis Data to pool with the English NHS centre data under a Data Sharing Agreement.
Data linkage and data pooling	Source 2, RWE: Deterministic linkage using patient identifiers was performed by each centre to collate information about each patient from multiple systems. This may be required as data does not exist on one single database or system (for example: chemotherapy data was recorded on a different system to laboratory or pathology data). The

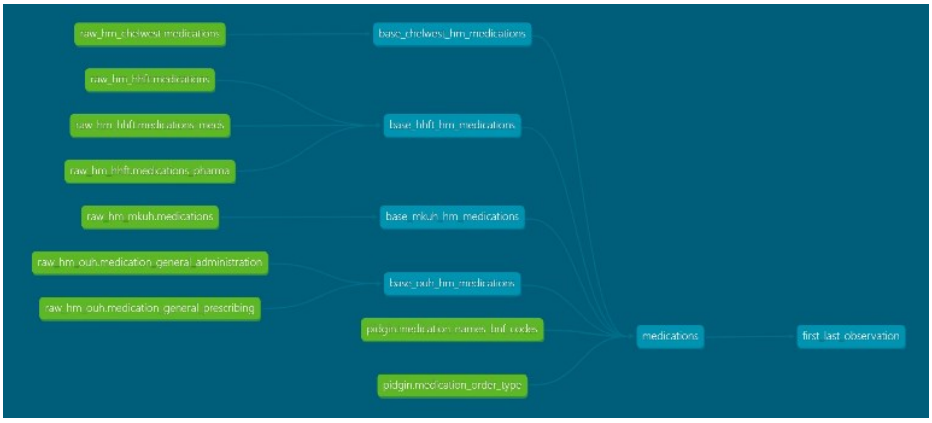
	centres undertook this activity as patient identifiable information was subsequently removed to create an anonymised data set which could be shared with Arcturis Data. Therefore, no linkage was performed by Arcturis Data. Data pooling was performed by Arcturis Data into a Common Data Model (CDM): combining anonymised patient data from multiple trusts into standardised tables. Pooling of source 1 MM-3 and source 2 RWE: Specific datasets from the MM-3 trial, identified according to analysis requirements, were shared with Arcturis Data. The final analysis dataset from the RWE source was then aligned to match the data specification of the MM-3 trial. Data were then pooled together into a single analytical dataset, where pseudo-IDs were generated to create a blinded dataset for the main analyst to conduct the comparative analysis.
Type of data source	Source 1, MM-3: Clinical trial data from 47 study sites in 10 countries Lesokhin et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med 29, 2259–2267 (2023). https://doi.org/10.1038/s41591-023-02528-9 Source 2, RWE: A combination of electronic health record (EHR) data (constituted of medication administration records, clinical observations, procedures, spells, imaging reports, pathology reports, ward movements, laboratory and microbiology tests) and administrative records (demographic data and diagnoses [ICD-10 codes] from clinical coders) along with systemic anti-cancer therapy data.
Purpose of data collection	Source 1, MM-3: Research study (phase 2 clinical trial). Source 2, RWE: Data collected as part of routine clinical care, reimbursement, and population health monitoring.
Data collection	Source 1, MM-3: Demographics, medical history including clinical diagnoses, procedures, treatments, clinical outcomes and patient experience (patient reported outcomes), as reported in https://clinicaltrials.gov/study/NCT04649359 and https://doi.org/10.1038/s41591-023-02528-9 Data were collected by investigators or their designee, or self-reported by patients, specifically to answer pre-determined research questions from clinical coding systems, free text records and from surveys. Data were collated in the Pfizer InForm EDC platform. Source 2, RWE: Demographics, medical history, treatments, clinical observations, diagnoses, procedures, and investigations. Data that had already been collected were accessed and this consisted of data were recorded by healthcare professionals in HER systems; and administrative data recorded by clinical coders at each NHS centre.

	The nature of data collection did not change: routinely collected information was utilised for all time. No additional data collection was performed for source 2.
Care setting	Source 1, MM-3: Secondary care clinical trial. Source 2, RWE: Secondary care routine clinical care.
Geographical setting	Source 1, MM-3: Multi-country, including UK. Source 2, RWE: UK – England and Scotland.
Population coverage	Source 1, MM-3: As participants of this clinical trial were enrolled from multiple countries, the data partially reflects the target population but may not be fully representative of it. Source 2, RWE: Data were obtained four NHS centres in the UK and therefore may not be fully representative of the target population. However, comparison of the population covered by the centres used in this RWE study relative to the broader UK population based on 2021 census data indicated a strong overlap in demography across age, sex and ethnicity categories, suggesting these centres are representative of the general UK population (assessment undertaken by Arcturis Data independently and outside of the scope of the current project).
Time period of data	Source 1, MM-3: February 2021 to April 2023 (15 month data cut). Source 2, RWE: January 2000 to August 2023.
Data preparation	Source 1, MM-3: Data were processed to Level 2 quality and shared a coded information (pseudonymised). Source 2, RWE: Centres provided data to Arcturis Data following extraction from their main and specialist EHR systems. Both raw data as provided by the centres and data transformed to the Arcturis Data CDM were utilised within the analysis. Both were required as some elements of the data, concretely the System Anti-Cancer Therapy (SACT) data, are not included within the CDM model. Version 4.1 of the CDM was utilised, the schema of which is here:



The transformation performed by Arcturis Data included multiple steps to combine data from multiple centres into a proprietary CDM.

An example of the flow of data from respective sources (centres) into one common table ‘medications’ is as below. Multiple tables may be required to extract all relevant information. Included within this process are so called “pidgins”: which are files that contain information of how data should be mapped to standardise data into the Arcturis CDM.



Data governance	Source 1, MM-3: Data are proprietary to the study sponsor (Pfizer Inc). Upon request, and subject to review, Pfizer will provide the data that support the findings of this study (MM-3). Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified patient data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. Source 2, RWE: For the data from Oxford University Hospitals NHS Foundation Trust and Chelsea and Westminster Hospital NHS

	Foundation Trust, Arcturis Data is the Data Processor. For data from Hampshire Hospitals NHS Foundation Trust and NHS Greater Glasgow and Clyde, Arcturis Data is the Joint Data Controller.
Data specification	Source 1, MM-3: Data specification document available internally at Pfizer, developed for clinical study report (CSR). Source 2, RWE: ECA study phase 2 study protocol and SAP (submitted to NICE and the EAG).
Data management plan and quality assurance methods	Source 1, MM-3: A data management plan was maintained by the study sponsor (Pfizer Inc), along with a clinical monitoring plan data. Source data verification was undertaken at study sites and verification records are maintained at each study site by the investigator). Source 2, RWE: Arcturis Data does not have access to the source data quality assurance methods but once the raw data were received, Arcturis data performs tests on data provided by trusts as part of its transformation pipeline and data quality testing. The study data was based on secondary care data collected by the centres as part of routine clinical care. Upon receiving the data from each of the sponsor's partner NHS organisations, the data goes through rigorous quality control checks before any analysis is conducted. The quality control checks are broadly categorised into the following three groups: data conformance, data plausibility, and data completeness. Full descriptions of each group of quality control checks are provided in the ECA study protocol.
Other documents	None

Data quality

For source 1, MM-3: the quality of data entered in case report forms was assessed by ongoing source data verification at each study site to ensure data are accurate, complete, and verifiable from source documents and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

For source 2, RWE: a feasibility assessment was undertaken during phase 1 of the study (to characterise patients with TCE/TCR MM, their treatments and clinical outcomes) and consisted of the following elements:

- A first feasibility criteria was used to assess whether enough TCE patients with at least one subsequent line of therapy would be available to allow for matching of patients in MM-3 with a real-world population. Identification of at least 75 patients was required for the project to be considered feasible. A total of 168 patients who were TCE with at least one subsequent line of therapy were identified, before the application of any inclusion/exclusion criteria from C1071003, resulting in the first feasibility criteria being met.

- A second feasibility criteria was used to assess whether a sufficient coverage of key laboratory markers (quantified serum paraprotein (or IgA) and kappa/lambda free light chain assay) recorded across the line of therapy following TCE eligibility would be available. This data was required for follow up, to define outcomes and allow for a comparative effectiveness analysis. At least 50% of TCE patients identified in the first feasibility assessment would be required to have sufficient data available for key laboratory markers for phase 2 comparative effectiveness analyses to be considered feasible. A total of 119 patients with sufficient key laboratory markers were identified, before the application of inclusion and exclusion criteria from MM-3, resulting in the second feasibility criteria being met.

In phase 2 of the study (comparative effectiveness analyses), study variables were operationally defined in the study protocol and SAP. Formal quality assessment was not undertaken beyond the data quality steps described in the previous section ("Data management plan and quality assurance methods").

Data relevance

Item	Response
Population	Source 1, MM-3 is a clinical trial in 10 countries including the UK, and therefore it is possible that given the eligibility criteria applied, the trial sample may not fully reflect the MM population in the UK. However, participants were recruited from real world clinical practice. For source 2, RWE the study sample was defined as patients with RRMM who also met the inclusion and exclusion criteria of the MM-3 clinical trial. However, it was not possible to assess the following MM-3 criteria due to unavailability of the respective data items in the real world dataset: • Left ventricular ejection fraction ≥40% • Safety risks due to adverse events of prior therapies • Smouldering multiple myeloma, • Systemic amyloid light chain amyloidosis, • POEMS syndrome • Active GVHD • Ongoing peripheral or motor neuropathy • Suicidal ideation/behaviour • Live vaccine
Care setting	Although source 1, MM-3 is a clinical trial, the study centres in 10 countries were hospitals where the target population would be managed in routine care. Source 2, RWE reflects routine care in the NHS as all study centres were NHS hospitals that routinely manage the target population.

Treatment pathway	Source 1, MM-3 captures treatment pathways outside of the UK, and also within the UK given the international setting of the study but as this is a single-arm clinical trial, participants are treated along an investigational pathway. Source 2, RWE was reflective of routine treatment of MM in the UK as study data were recorded during routine clinical care.
Availability of key study elements	The ECA study was based on the data items/covariates, criteria and outcomes in source 1: MM-3. Data availability are reported in Lesokhin et al. https://doi.org/10.1038/s41591-023-02528-9 For source 2, RWE: *Population Eligibility Criteria* Longitudinal systemic anti-cancer therapy data were analysed using propriety line of therapy algorithms in order to determine patients with RRMM. Availability of historical diagnosis data ensures capture of comorbidities for eligibility. Comprehensive capture of all laboratory testing undertaken in the secondary care setting allowed for assessment of hepatic, renal and bone marrow function. *Outcomes* Data were available to estimate the clinical outcomes of interest. However, urine paraprotein, which is used in the International Myeloma Working Group (IMWG) criteria for progressive disease, was missing for all patients as this test is not routinely conducted in the NHS. *Covariates* Cytogenetic risk and disease staging (international Staging System) were not well recorded in the dataset.
Study period	Source 1, MM-3 is an ongoing single-arm clinical trial of an investigational treatment. Source 2, RWE included data up to until August 2023 and therefore reflects contemporary treatment pathways in the UK.
Timing of measurements	Data collection in source 1, MM-3 was according to the trial's Schedule of Activities. Source 2, RWE data collection was according to routine patient interactions with the healthcare service in real world practice.
Follow up	Source 1, MM-3 data were available up to 15 months follow up at the time of analysis. Source 2, RWE data were available for a longer period but was restricted to the same maximum follow up period of 15 months to ensure comparability of outcomes measured in the ECA study. The available follow up period of 15 months was sufficient to estimate the clinical outcomes of interest, but further follow up will

	be required to determine longer term outcomes as median OS and PFS were not reached in MM-3 at 15 months.
Sample size	The MM-3 study (source 1) recruited 123 patients into Cohort A (the cohort that was analysed in the ECA study). From source 2, RWE [redacted] patients were identified as RRMM and met the eligibility criteria of the MM-3 study. From these [redacted] patients, [redacted] received pomalidomide and dexamethasone as their index treatment. Statistically significant differences in progression-free survival (primary outcome) for weighted analysis indicated that sufficient sample was present to detect the treatment effect estimate.

Appendix 1 Data tables from NHS centres in the ECA cohort

Trust	Source Table
raw_automated_ouh	inpat_spell_2023_01_05_17_18_00_d03f054c
raw_automated_ouh	inpat_procedures_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	outpat_procedures_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	inpat_movements_2023_01_05_17_18_00_d03f054c
raw_automated_ouh	vitals_2023_01_05_17_18_00_d03f054c
raw_automated_ouh	outpat_diagnosis_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	bmi_and_related_measurements_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	inpat_episodes_2023_01_05_17_18_00_d03f054c
raw_automated_ouh	pathology_reports_2023_01_13_10_25_50_22ed43da
raw_automated_ouh	pathology_synoptic_2023_01_05_17_18_00_d03f054c
raw_automated_ouh	medication_chemo_admin_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	biochemistry_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	medication_general_prescribing_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	medication_general_administration_2023_08_23_14_14_30_48ae056d
raw_automated_ouh	outpat_attendance_2023_01_05_17_18_00_d03f054c
raw_automated_ouh	inpat_diagnosis_2023_08_23_14_14_30_48ae056d
raw_automated_hhft	clinical_observations_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	medications_meds_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	laboratory_tests_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	medications_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	procedures_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	medications_pharma_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	spells_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	diagnoses_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	oncology_chemotherapy_2023_05_11_15_35_10_d1f76800
raw_automated_hhft	oncology_pathology_2023_05_11_15_35_10_d1f76800
raw_automated_chelwest	clinical_observations_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	clinical_laboratory_tests_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	laboratory_tests_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	medications_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	ward_movements_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	diagnoses_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	procedures_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	spells_2023_07_18_15_11_19_c1fb6a0c
raw_automated_chelwest	raw_data_20220516_oncology_chemotherapy_patched_20220519

Methods to address bias: UK external control arm study

Study description: This study estimated the treatment effect of elranatamab in patients with relapsed and refractory multiple myeloma (RRMM) by comparing patients treated with elranatamab in Clinical Study C1071003 (MagnetisMM-3, MM-3) with an external control arm (ECA) of patients treated in real world UK clinical practice.

Type of bias	How bias was addressed or assessed
1. Selection bias at study entry	This comparative effectiveness study had two arms. One arm was obtained from Clinical Study C1071003 (MagnetisMM-3, MM-3) which recruited patients according to a set of inclusion and exclusion criteria, and a second external control arm (ECA) obtained from existing healthcare data, i.e. electronic healthcare records, in which no criteria were required for patients to be followed up (except for ongoing interactions with healthcare services). To mitigate the presence of systematic differences across key potentially confounding covariates, the inclusion and exclusion criteria from MM-3 were applied to the ECA to limit the real world cohort to only those patients who would also be eligible to participate in MM-3. As the types of data collected in routine clinical practice and clinical trials can vary, it was necessary to apply real world analogues of several of the MM-3 inclusion and exclusion criteria to the ECA dataset. This work was described in the ECA study protocol and SAP. Despite best efforts to harmonise criteria between the two data sources, inevitably some discrepancies will remain. Similarly, some inclusion and exclusion criteria could not be applied to the ECA dataset in any form due to the data not being collected in routine clinical practice (e.g. urine paraprotein). Consequently, residual differences in key potential confounders may remain between both arms, potentially introducing bias when comparing outcomes across both arms.
2. Selection bias at study exit	Informative censoring cannot be ruled out across all outcomes, although it was more likely to be present in progression-free survival (PFS) than in outcomes considered in the study. As censoring in PFS occurred on initiation of a new therapy regimen, if there was an underlying process driving termination of the index therapy which is different across the two arms then informative censoring may have occurred.
3. Addressing confounding	Measured confounding was addressed through the use of inverse probability treatment weights (IPTW) derived from propensity models. A selection of priority confounding variables were determined *a priori* (documented in the study protocol), that were identified through a published literature review, National

	Comprehensive Cancer Network (NCCN) guidelines, an unpublished targeted literature review conducted by Pfizer, and expert clinical opinion from a myeloma expert who is a practising haematology consultant in the NHS (as referenced in the study protocol). These variables were categorised as priority or secondary variables. Those in the priority list were considered to be the most important to ensure unbiased estimation of the treatment effect between the ECA and MM-3 study populations. The secondary variables list contains additional variables that were included in the analysis based on existing evidence and/or expert clinical opinion and were used in an extended propensity score sensitivity analysis.
4. Detection bias	As this study was observational, there is a possibility that unmeasured confounding induced bias in estimated effects, even after adjustment, as the 'no-unmeasured confounding' assumption required to achieve ignorability of treatment assignment is effectively un-testable. Due to geographic differences in the sources of data contributing to each arm of the study it was likely that baseline confounding covariate differences would be present, with ECA data sourced entirely from the UK and MM-3 data collected from multiple countries. The presence of such imbalances was confirmed by comparing summary statistics and standardised mean differences across the two study arms. Key confounders (cytogenic risk status, type of prior therapy) could not be included in any propensity score model due to lack of data availability and the presence of unique categories in one arm only, respectively. The absence of these covariates in the propensity score model may have resulted in imbalance across the two arms, but this cannot be assessed due to lack of availability of the required data. Analysis was performed with both a Cox-PH model and difference in RMST, providing suitable estimated treatment effects for cases where the proportional hazards assumption was supported by the data and also where the assumption was rejected. As the pre-specified definition of acceptable covariate balance was not reached for a few covariates, quantitative bias analysis was used to investigate the extent of a potential causal relationship for an omitted covariate to reverse the direction of estimated treatment effects. Detection bias may induce bias in PFS analyses due to differences in frequency of disease assessment in the clinical trial setting of MM-3 and real world clinical practice in the ECA. Consequently, progression events may be observed at different rates in the two arms due to study design and not a treatment effect.

5. Measurement error and misclassification	Misclassification bias is unlikely to affect the MM-3 arm given the clinical trial processes for recruitment, data collection and analyses. Misclassification of outcome data is possible in the ECA arm, particularly as harmonising the definition of each outcome between the two data sources was complex. PFS in the ECA was defined as a real world analogue of PFS, which was necessitated by the lack of key progression data items (e.g., 24-hour UPEP, plasma cell %, bone trephine results) due to their relatively infrequent assessments in UK routine clinical care. Consequently, progression events which were defined purely by these missing data items may be missed or delayed in the ECA arm, with progression only identified when it manifested in biochemistry test data. As this phenomenon does not affect the MM-3 arm, a bias toward the null may have been introduced in which PFS was artificially lengthened in the ECA arm, relative to the MM-3 arm. Due to the lack of a 'gold-standard' of PFS in the ECA arm in which all required data sources were utilised to construct PFS in a subset of the ECA population, it was not possible to explicitly account for the use of real world PFS or to perform calibration or sensitivity analyses. Despite this, the median PFS in this study was similar to the (propensity score weighted) median PFS obtained from real world RRMM patients in the KarMMa-RW study ((Jagannath et al, 2021), which also used International Myeloma Working Group (IMWG) progression criteria but with no reference to any limitations in real world application of these criteria. Misclassification in OS was possible in the ECA but not as likely as PFS. Occasionally mortality data was provided by an NHS centre with the day of death missing, but the month and year were present. In such cases, the date of death was imputed to the 15th day of the provided month. The presence of a small number of such deaths in the ECA group may have induced bias when comparisons were made to the MM-3 cohort.
6. Missing data	As this study utilised electronic healthcare records there was a considerable amount of missing data present in the analysed ECA dataset. This missingness reflected the types of data that were (or were not) generated in routine clinical care. When reporting on study results, the percentage of each covariate that was missing in the ECA cohort was provided. Missingness was particularly common in a selection of key potentially confounding covariates such as ECOG and ISS disease staging. Due to the lack of structured cytogenetic risk status for ECA cohort members, this covariate was missing entirely from the ECA arm of the study and had to be dropped from all analyses. No outcome data was missing.

	Multiple Imputation by Chained Equations (MICE) was used to perform all adjusted analyses. MICE assumes that the distribution of missing data is at random, and if missing data are not distributed in this manner, imputation may induce bias in subsequent estimated treatment effects. A pre-specified sensitivity analysis in which missing categorical data was assigned a new 'missing' category when used to estimate propensity scores could not be performed. The restricted distribution of missing categorical data in the ECA arm (but not in the MM-3 arm) resulted in categorical covariates that were perfectly separated between arms when applied in a logistic regression model with the extra 'missing' category included. Consequently, the sensitivity of these analyses to assumptions regarding the missing at random assumption were not assessed. Interpretation of all adjusted results presented in this study must also consider the potential biases induced by the application of imputation in data that may not be missing at random.
7. Reverse causation	As follow up in the ECA study began at the point an individual received the intervention (elranatamab) or control (real world treatments), the potential effect of reverse causation on comparative effectiveness estimates in this study is likely to be small. Patients in both arms were followed up longitudinally to assess whether they remained exposed to their baseline exposure.

References

Jagannath, S. et al., 2021. KarMMa-RW: comparison of idecabtagene vicleucel with real-world outcomes in relapsed and refractory multiple myeloma. Blood Cancer Journal, 11(116).

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elranatamab for treating refractory multiple myeloma after 3 standard therapies [ID4026]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

<table>
<tr><td>1.Your name</td><td>[redacted]</td></tr>
<tr><td>2. Name of organisation</td><td>Myeloma UK</td></tr>
<tr><td>3. Job title or position</td><td>[redacted]</td></tr>
<tr><td>4a. Brief description of the organisation (including who funds it). How many members does it have?</td><td>Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and related conditions. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We are not a membership organisation and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies.</td></tr>
<tr><td>4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]
If so, please state the name of the company, amount, and purpose of funding.</td><td>We has received funding from the manufacturer of the technology (Pfizer) in the last 12 months.
In 2022, 5.7% of Myeloma UK’s income came from pharmaceutical companies.
The table below shows the 2022 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, and gifts, honoraria or sponsorship.
<table>
<tr><th>Company</th><th>Core grant</th><th>Research / Project</th><th>Donation</th><th>Honoraria</th><th>Fundraising Events</th><th>Total (£)</th></tr>
<tr><td>AbbVie Ltd</td><td></td><td></td><td>10,000</td><td></td><td></td><td>10,000</td></tr>
<tr><td>Amgen Ltd</td><td></td><td>25,000</td><td></td><td></td><td>10,000</td><td>35,000</td></tr>
<tr><td>Amgen (Europe) GmbH</td><td></td><td></td><td></td><td></td><td>8,000</td><td>8,000</td></tr>
<tr><td>The Binding Site Ltd</td><td>20,000</td><td></td><td></td><td></td><td></td><td>20,000</td></tr>
<tr><td>Celgene Ltd</td><td></td><td></td><td></td><td></td><td>15,000</td><td>15,000</td></tr>
<tr><td>Bristol Myers Squibb - Celgene</td><td>20,000</td><td></td><td></td><td></td><td></td><td>20,000</td></tr>
<tr><td>GSK</td><td></td><td>20,444</td><td></td><td>1,386</td><td>12,000</td><td>33,830</td></tr>
<tr><td>ITECHO</td><td></td><td>6,600</td><td></td><td></td><td></td><td>6,600</td></tr>
<tr><td>Janssen-Cilag Ltd</td><td></td><td></td><td></td><td>180</td><td></td><td>180</td></tr>
<tr><td>Janssen Pharmaceutica JW</td><td></td><td>25,000</td><td></td><td></td><td></td><td>25,000</td></tr>
<tr><td>Pfizer</td><td></td><td>19,259</td><td></td><td></td><td></td><td>19,259</td></tr>
<tr><td>Sanofi</td><td></td><td></td><td></td><td></td><td>48,980</td><td>48,980</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Takeda UK Limited</td><td></td><td>40,000</td><td></td><td></td><td>17,000</td><td>57,000</td></tr><tr><td></td><td>40,000</td><td>136,303</td><td>10,000</td><td>1,566</td><td>110,980</td><td>298,849</td></tr></table> Between January-October 2023 we received £31,880 from Pfizer. £31,080 towards research project and £800 as honorarium.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission came from the myeloma patients and carers we engage with through our research and services programmes, including: - Semi-structured interviews in September-October 2023 with relapsed/refractory myeloma patients. These interviews provide valuable experience and insight data from patients who have either had elranatamab via clinical trials or who are multiply relapsed and view this technology as a potential next step in their treatment pathway. - A Myeloma UK-funded, multi-criteria decision analysis study of 560 myeloma patients run by the European Medicines Agency (EMA) and the University of Groningen. The study explored patient preferences for different benefit and risk outcomes in myeloma treatment. - Analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays, posts to our online Discussion Forum and insights gathered for earlier appraisals.

Living with the condition

Current treatment of the condition in the NHS

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is no cure, but treatment can halt its progress and improve the quality of life. The complications of myeloma can be significant, debilitating, and painful; they include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system that can lead to increased infections. "Myeloma can make you feel very isolated. The risk of infection makes you scared of going out. Especially in large groups or crowed places. I don't like going to the supermarket. I am lucky I have a car and can drive. I don't need to rely on taxis or public transport – that adds risk." "For me the worst thing is fatigue. I've learnt to work around it. To do things when I have the energy and accept when I don't." In a survey of 1324 patients and carers, 72% of respondents reported that their myeloma had a high or moderate impact on their quality of life.1 "Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted." It is an incurable, relapsing and remitting cancer. The aim of treatment is to control the myeloma, slowing its progression, and reducing symptom burden. The constant possibility of relapse has a huge psychological impact on patients. Relapse completely disrupts the lives of patients and their families. Symptoms increase (e.g., pain, fatigue). Hospital visits and tests increase. They must switch treatments and adjust to different side effects and new routines for hospital visits/treatment administration. They also face the uncertainty of whether the new treatment will be effective and tolerable. They are aware that every time they need to change treatment, their options and life expectancy decrease. Therefore, the anxiety of relapse increases with each subsequent line. "There is a constant pressure of wondering what's going to happen to me next because myeloma is like that, it's not curable and it's going to come back, I'm sure every month there's the possibility of relapse and it's hard to ignore that. It's a massive relief every month when I'm told that my paraproteins haven't risen." "I think the most difficult thing, and this trumps fatigue by miles, is the relapsing and remitting nature of the disease. You never quite know what's around the corner. It's always in the back of my mind. And I'm sure it's the same for my family - How long is this treatment going to work and what is going to happen next? Once you get further down the lines of treatment like I am, that question becomes a bit more serious. When your options are becoming more limited."

[1] Myeloma UK (2022) A Life Worth Living The impact of a delayed diagnosis on myeloma patients' quality of life. Available at https://www.myeloma.org.uk/library/a-life-worth-living/ (Accessed September 2023)

	"The further you get along people write you off. They think the drugs are unlikely to work or they are not going to work as well. I feel like my life is in the hands of other people with preconceived ideas about patients at fourth or fifth line. I don't want to be written off. I want a chance to carry on living this life." The individual and heterogeneous nature of myeloma means that some patients may respond to or tolerate treatment well, and others may not. How well patient responds to or tolerates a drug impacts future treatment options. Myeloma also evolves and becomes resistant to treatment. In general, a drug that did not work, stops working or caused serious side effects would not be offered again, even when administered in a different combination. Therefore, it is essential to have a range of treatments with different mechanisms of action at all stages of the myeloma pathway to ensure patients have a treatment available when they need it. "I was diagnosed 18-20 months ago. Initially I joined the RADAR trial, but I ended up being hospitalised with renal insufficiency. Then I got several hospital infections. I was then moved onto conventional chemo. I only had a partial response. I went for a stem cell harvest, but they could collect enough stem cells. So, stem cell transplant wasn't an option. After this I was invited to join the MagnetisMM trial." "The more options the better chance of having one work and be compatible. Two previous ones have failed, or I reacted badly to." "I have many different treatments and my response to them has been disappointingly average. I have never really had a long remission – not like some patients. That's my hope. And elranatamab might be the one." Relapsed patients, the population covered in this appraisal, often experience a more significant disease burden due to the progressive nature of the disease and the cumulative effects of treatment, which can result in reduced quality of life.2 Treatment side effects and frequent hospital visits have a social and practical impact on patient's lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members also affect patients' sense of control. Living with myeloma is often extremely physically and emotionally challenging for carers, and family members. They are affected in many ways because of both caring and dealing with the day-to-day implications of myeloma. Many in this situation mention changes in their social life, relationships, income, and wider family dynamics. A Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact: - 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor - 25% of those in work had been unable to work or had to retire early to care for the person with myeloma - 84% always put the needs of their relative or friend with myeloma before their own

[2] Ramsenthaler, C., Osbourne, T.R. et al (2016) The impact of disease related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. BMC cancer 16:1 P.427

	- Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them3 "I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo." "Sometimes it's tiring. Sometimes I feel sad. Sometimes I think about all the hours I have spent at the hospital and how I might have used that time otherwise. But it's all the price of love."

[3] Myeloma UK (2012) A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK. Available at https://www.myeloma.org.uk/documents/a-life-in-limbo/ (Accessed September 2023

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers feel fortunate that although myeloma is incurable, it is treatable in most cases. However, patients and carers, especially those who have already experienced relapse, are acutely aware that the range of treatment options and the chance of deep responses with long remissions decreases every time they relapse. They know about treatment resistance and that an effective treatment will stop working at some point. They also know that the range of treatment options available at the fourth line and beyond is markedly narrower than those available at first or second line. However, there is hope that newer immunotherapies like CAR-T cell treatments or T-cell engagers could reverse this trend delivering good responses and long remission times at later lines. Multiply relapsed patients also know that every myeloma patient is different. They know every patient's experience of a treatment is different and sometimes unpredictable. They know that the level of effectiveness or side effects can differ, either from direct experience of treatments not working or causing unbearable side effects or through discussions with peers. Understandably, this can cause a great deal of worry for myeloma patients and their families. There is uncertainty about the future, whether the next treatment will work and if it will negatively affect their quality of life and the fear of reaching the 'end' of treatment options for their cancer. ***"Myeloma is currently incurable, so having a variety of available strategies/ options gives me and my partner some hope and time."*** All anti-myeloma treatments have side effects which affect quality of life. The most impactful side effects are the ones which limit daily activities or reduce independence. These include fatigue, peripheral neuropathy, and gastrointestinal disturbances. ***"Having myeloma is really hard. When you're first diagnosed, you just you just don't know what is going. I remember the sentence that the doctor used. "It's like a terminal type of cancer, it's not curable, it's just treatable." When somebody tells you've got something that's not curable, but it's treatable it wouldn't be so bad if the treatment was alright, but the treatment is horrible. The treatments intensive chemotherapy, a stem cell transplant which was absolutely hideous. And I now know that for the rest of my life, I'll be on treatment. Because it will come back if I'm not. I hope that the treatment I have is as easy on me as possible so I can live well, with it."*** ***"My initial treatment was a huge shock. It was VTD induction. I've never felt so ill. I know now what it feels like to be a very elderly person. I was just so ill."*** The use of steroids in most treatment combinations is seen as a big disadvantage of current treatment regimens. The mood swings, irritability and mania caused by dexamethasone is very challenging for patients and their families. ***"The treatment included steroids. I was wired on those. I was awake all night. I didn't go out much. I went to get my hair cut and I braced myself getting out the car. I never felt so ill before, my legs were so swollen, my stomach big and blown up, my ankles enormous. I was so tired all the time."***

8. Is there an unmet need for patients with this condition?	There is a clear need for innovative anti-myeloma treatments which deliver deep, durable responses for relapsed and refractory myeloma patients. Patients can be successfully retreated at relapse, but the probability of deep, durable responses decreases with every relapse. A retrospective study of patient outcomes across Europe showed that 32% of patients achieved a complete response in the first-line setting, compared with 4% at fourth line and 2% at fifth line or later. It also showed a decrease in overall response rates (ORR) with each line of treatment with 3 in 5 patients not responding to available treatments at fifth line. (ORR = 92% at first line, 84% at 2nd line, 73% at 3rd line, 64% at 4th line and 41% fifth line). [4] Relapse is caused by resistance to existing treatment. Myeloma is still incurable, and even after successful treatment, almost all patients eventually become resistant to existing treatment. Treatments that have worked well at earlier lines are no longer effective. Patients with relapsed and refractory myeloma are all too familiar with this scenario. Their disease is resistant to most existing treatments, and treatments with new mechanisms of action are needed to control their myeloma. New drugs are urgently needed to overcome treatment resistance. Data has shown that the life expectancy for multiply relapsed myeloma patients who are refractory to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody is typically less than 12 months.[5] Patients who are refractory to both a proteasome inhibitor and an immunomodulatory drug have median life expectancy of 8-9 months, and patients who are refractory to three or four of the common proteasome inhibitors and immunomodulatory drugs have a median life expectancy of only 3-5 months.[6] It is also important to note that more than a quarter of myeloma patients have high-risk disease at diagnosis. They either don't respond to existing treatments or relapse shortly after successful treatment. They move through the myeloma treatment pathway and run out of viable treatment options more quickly than standard-risk patients. Treatments with new mechanisms of action are a lifeline for high-risk patients with the potential to deliver significant remission times when other established classes of anti-myeloma drugs have not. Many patients needing effective treatment at fourth line and beyond are still fit and active, particularly patients who were diagnosed when they were younger or who have quickly moved through treatment lines due to side effects or poor response rates. ***"I would be keen to see something more out there for people like me who are young - I can't say healthy, but I feel healthy technically - and who are active. It wouldn't be nice not to give me some more treatment, given what I can contribute generally to society and my family. That's how I feel."*** ***"It is very difficult, frightening in a way to feel written off. I am quite fit. I am by no means disabled. I can walk, drive do the garden. I do everything by myself."***

	Given the heterogeneous and evolving nature of myeloma, there is a need for a wide range of options at each stage of the treatment pathway. However, treatment options are extremely limited and, in some cases, non-existent at the more advanced stages of this pathway. Although clinical trials and compassionate use programmes may be available at later stages of the pathway, they are not accessible to all patients. Clinical trials and compassionate use programmes are often limited to a few large, specialist, inner-city hospitals.

[4] Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.
[5] Lee, H. C.,et.al.. (2023). Treatment Patterns, Survival, Quality of Life, and Healthcare Resource Use Among Patients With Triple-Class Refractory Multiple Myeloma in US Clinical Practice: Findings From the Connect MM Disease Registry. Clinical lymphoma, myeloma & leukemia, 23(2), 112–122. https://doi.org/10.1016/j.clml.2022.11.008
[6] Gooding S, Lau IJ, Sjeikh M et al, Double Relapsed and/or Refractory Multiple Myeloma: Clinical Outcomes and Real World Healthcare Costs. PLoS ONE. 2015. 10 (9): e0136207)

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our research that patients value treatments which control their myeloma, keep them in remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life.[7] The MagnetisMM-3 clinical showed that elranatamab delivers these benefits. In the trial, the overall response rate of elranatamab was 61%. 35% of patients achieved a complete response or better, and 56% achieved a very good partial response (VGPR) or better. 51% of all patients and 90% of patients who achieved a complete response of better remained in remission/stable after 15 months of treatment. Elranatamab targets and kills myeloma cells in a different way compared to currently approved treatments. If approved, elranatamab will be the first NHS-commissioned t-cell engager and the first B cell maturation antigen (BCMA) targeted treatment for myeloma. Therefore, it has much potential to fulfil an unmet need for multiply relapsed/refractory myeloma patients. The patients we interviewed liked that elranatamab was a new class of drug with a unique way of killing myeloma cells. They were also happy to see that this treatment combination was for multiply relapsed, refractory patients, giving them hope that something would be available when their current treatment stopped working. ***"Elranatamab works in a different way. It is good to have the opportunity to try different things. It gives me hope. The response rates are great."*** ***"The treatment sounded quite groundbreaking. It doesn't poison the whole body. Just goes for the myeloma. it sounded exciting – I wanted to give it a try."*** ***"I wanted the latest state-of-the-art thing that would allow me to hopefully get a really good response and wouldn't feel too ill while I'm having it so I can actually carry on my life."*** The patients were also encouraged by the response rates observed in the trial or following treatment. They felt this made the treatment more appealing than some of the other options available to them. ***"The big difference between this treatment and my previous treatment is that I have reached complete response. My myeloma is controlled. The treatment is working. That gives me piece of mind. Knowing it is well controlled means a lot."*** The patients we interviewed also liked that the treatment did not include dexamethasone. The ability to access a novel treatment without steroids that can deliver effective remissions cannot be underestimated. **"I don't have to have dexamethasone with it every week because that always used to make me climb the wall. I had to have twice a week with my first batch of chemotherapy. It was horrible. You don't sleep, it affects your mood. It's just horrible."**

	The patients we spoke to who had received elranatamab felt the treatment side effects were more manageable than previous treatments. They felt normal and could get back to doing the things they wanted to. **"I felt normal. I am retired now but if I was working, I could have gone to work. I started treatment around Christmas and by 19th April I was in remission. Complete remission. There is no comparison between elranatamab and my previous treatment. I am living an absolutely normal life."** ***"After this I was invited to join the MagnetisMM trial. The treatment was a breeze. I had maybe one week in hospital. Everything went really well. I am now on fortnightly injections. They are no bother."*** ***"Now I go every week and I have the normal high dose, as a day patient. Now it's something easy to have. All it is an injection. Compared to the drips and all the horrible stuff that I had with the other chemotherapy; the treatment is quite nice. Initially they gave me lots of things in the first step doses. A little bit of dexamethasone, Piriton and paracetamol just in case you do have the cytokine reaction. But I'm past that now and I'm just having the weekly dose of elranatamab."*** Some patients felt the treatment administration as a single injection under the skin was an advantage. Having one injection fortnightly and ultimately monthly was easily manageable. They could get their treatment and then forget about it. The monthly injection often coincided with other regular appointments. ***"This treatment feels less intrusive to me. It is an injection once a fortnight instead of swallowing multiple pills every day.*** ***I don't have to think about it. I don't need to worry about missing a dose. I just pop into the hospital get the injection and it is done. It also much better than swallowing lots of pills. I hate swallowing pills."*** ***"My experience of this drug has been great. It is no bother getting to the hospital. I can drive myself. It is nothing. Where I live there is no transport. You can only drive. I don't think it interferes with life at all."*** ***"And I told myself that on a Tuesday I go to the hospital for the treatment and the rest of the time I can Get your life back, you know, get doing the things you love."***

[7] Postmus, D., et. al. (2018). Individual Trade-Offs Between Possible Benefits and Risks of Cancer Treatments: Results from a Stated Preference Study with Patients with Multiple Myeloma. The oncologist, 23(1), 44–51.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There are three factors that patients typically consider when thinking about treatments – efficacy, side effect profile and ease of administration. The order of priority varies based on personal preference.[8] As with all anti-myeloma treatments, side effects are a disadvantage. Patients value treatments with few mild side effects that stop when treatment ends. However, in practice, patients accept varying levels of toxicity in a treatment, depending on the stage of their myeloma and whether it delivers a good survival benefit. Most of the patients we interviewed felt that the side effects associated with elranatamab were like those they had experienced whilst taking other treatments. **"CRS doesn't sound very nice, but it wouldn't put me off. I have been through a stem cell transplant. You can't get anything more brutal than that. All the other side effects sound manageable. All normal. You just learn to live with them. The list is my life. It doesn't define me. It is just irritating. I have been doing this for 12 years. It is just more of the same."** **"Before the treatment started, I got a big document and when you start reading it you think holy moly because it covers absolutely everything. I just knew to step away from that. I just felt the alternative was the standard treatment that probably wouldn't keep it at bay for very long and would be quite nasty anyway, so I just felt like the state-of-the-art immunotherapy treatment was my best option and I still feel like that."** The main side effects patients would worry about were the potentially severe side effects like CRS or ICANs. However, they knew that these side effects only happened when starting treatment. They also felt there were similar risks associated with other treatments, especially high-dose therapy and stem cell transplantation. **Then in July/August last year it came back, and my consultant told me about this trial and would I be interested. At first it sounded risky. But then I thought – a stem cell transplant is risky, extremely risky. I decided to go for it.** The need for hospitalisation and specialised care during the set-up phase was seen as a slight disadvantage because this could limit the availability of the treatment. Limited availability could have a bigger impact on people who live further from the treatment centre and those who don't drive.

[8] Fifer, S, et. al. (2020) Myeloma Patient Value Mapping: A Discrete Choice Experiment on Myeloma Treatment Preferences in the UK, Patient Preference and Adherence, 14, 1283-1293

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues

13. Are there any other issues that you would like the committee to consider?	The patient cohort eligible for this treatment is small. There are around 1000 patients receiving fourth-line treatment and 450 receiving 5th line treatment every year. The myeloma treatment pathway is continually evolving. The treatment given to patients at each line depends on when they were diagnosed or relapsed and the treatment available via routine commissioning or clinical trials. NICE also introduced interim guidance during the pandemic. As a result, many patients at fourth line may not have followed the current approved pathway. Any recommendation should ensure clinicians have the flexibility to give the treatment when it is most beneficial to patients based on the characteristics of their disease and overall health.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a clear need for innovative anti-myeloma treatments which deliver deep, durable responses for relapsed and refractory myeloma patients. • There is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. If approved, elranatamab will be the first NHS-commissioned t-cell engager and the first B cell maturation antigen (BCMA) targeted treatment for myeloma. Therefore, it has much potential to overcome treatment resistance and fulfil an unmet need for multiply relapsed/refractory myeloma patients. • Insights from our patient interviews clearly show that patients who received elranatamab had a positive experience and would recommend it for approval on the NHS. • Clinical trial data and insights from our patient interviews confirm that elranatamab can deliver the most important benefits to patients: high response rates, good remission times and quality of life. • Patients consider the weekly, bi-weekly and eventually monthly subcutaneous injection without combination with steroids a distinct advantage of this treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elranatamab for treating refractory multiple myeloma after 3 standard therapies [ID4026]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Myeloma Society/ Royal college of Physicians/ Royal College of pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	UK Myeloma society is funded by philanthropic grants, conference fees and industry grants
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	UK Myeloma society receives educational grants from all myeloma drug and diagnostic manufacturers to support the biannual educational programmes
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Multiple myeloma is incurable so the aims of treatment are 1) to prolong survival (OS) 2) to prolong time until disease progression (Progression free survival - PFS) 3) to maintain / improve quality of life (i.e part of QALY)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in PFS and/or OS whilst maintaining quality of life.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes as the disease is incurable and life limiting, any treatment that prolongs time to disease progression and/or survival with acceptable side effects will help meet an unmet need

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	A combination of Pomalidomide and dexamethasone or Bortezomib/ Panobinostat and dexamethasone is used to treat patients after 3 prior therapies
9a. Are any clinical guidelines used in the	No current guidelines. Clinical guidelines for relapsed myeloma management led by BCSH in development

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes the pathway of care is well defined, and treatment options are defined by reimbursed treatment options
9c. What impact would the technology have on the current pathway of care?	Elranatamb will provide a new treatment modality for patients with difficult to treat disease. With a new mechanism of action and observed higher response rates in the licensing trial
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Elranatamab will be administered in escalating disease as an inpatient for the first 2 doses. Subsequent doses are administered as an outpatient. The current treatment options are fully outpatient based.
10a. How does healthcare resource use differ between the technology and current care?	Elranatamab use increases risk of infection in myeloma patients treated within MagnestisMM-3 trial. Patients were treated with on demand or prophylactic intravenous immunoglobulins to reduce risk/ severity of infection. This would become standard practice in the UK when Elranatamab is approved.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care Hospital setting
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new investment required

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Data from MagnetisMM-3 trial provides a clinically meaningful added benefit to relapsed myeloma patients over current care
11a. Do you expect the technology to increase length of life more than current care?	Myeloma Patients who are triple class refractory (CD38 Ab, PI, IMiD) have poor survival. Elranatamb in a phase 2 trial reports an overall survival of 56.7% at 15 months. This is a significant improvement over observed survival rates in myeloma patients at this stage of the illness.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Observed data from the MagnetisMM-3 trial show that patient do have a transient reduction in QoL (Global health score) in first 2 cycles , likely to inpatient admissions and treatment related toxicity. QoL improved across all measured scales and EQ5d following the initial drop and was maintained for the rest of the observed period.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are no subgroups to consider

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Need for inpatient facility use for the first 2 doses has be factored in for treatment elivery. This may be challenging in smaller hospitals who treat myeloma patients with no dedicated inpatient bed resource. Patients may need Tocilizumab if they develop Grade 2 cytokine release syndrome. Patients who develop severe infections despite antibiotic prophylaxis, would require immunoglobulin replacement therapy

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients reaching 4th line therapy would be eligible for this treatment. If patients progress on therapy based on blood or scan parameters, treatment will be discontinued
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	New technology in myeloma targeting BCMA using a bispecific antibody. The results in a single arm Phase 2 study is very encouraging
16a. Is the technology a 'step-change' in the management of the condition?	Yes, new target (BCMA) and a new technology bispecific antibody with significant uplift in response rates

16b. Does the use of the technology address any particular unmet need of the patient population?	The currently available drugs induce a response only in a third of patients. This new technology although not in a randomised study show up to 61% response. Therefore this provides a significant uplift in response rates which deals with the significant unmet need in this patient population.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Cytokine release syndrome – requires inpatient monitoring and/or Tocilizumab Recurrent severe infections – require intravenous immunoglobulin replacement therapy and closer monitoring of infections

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, except for subsequent therapies which may differ with what is available in the UK. Some patients received prophylactic IVIg which is not approved within current IVIg guidance
18a. If not, how could the results be extrapolated to the UK setting?	Corrected for available therapies in UK
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	PFS, DOR, OS
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS is a good surrogate for Overall survival

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None iam aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	NA
21. How do data on real-world experience compare with the trial data?	I have not seen any real world data with this technology

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Novel drug target - BCMA • New technology – bispecific antibody • High response rates, improved PFS and Overall survival • Qol is maintained on long term follow up • Patients need inpatient admission for first 2 doses which may restrict use to larger hospitals. Use of intravenous immunoglobulins is an additional health resource

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with multiple myeloma or caring for a patient with multiple myeloma. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **27 February 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with multiple myeloma

Table 1 About you, multiple myeloma, current treatments and equality

1. Your name	Jon Missin
2. Are you (please tick all that apply)	☒ A patient with multiple myeloma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with multiple myeloma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with multiple myeloma? **If you are a carer (for someone with multiple myeloma) please share your experience of caring for them**	I was diagnosed with Multiple Myeloma in 2015, at the age of 42. I have since undergone several operations, a stem cell transplant, several rounds of radiotherapy and am currently on my 4th line treatment which is a maintenance treatment. Whilst my current treatment is beginning to show signs that it is no longer working, I have been on my current treatment for some 25 months which, I am happy to say, is much longer than the median 12 months I was advised. My current treatment has kept my light chains down to normal levels and with the exception of my Stem Cell Transplant, no previous treatment has given me this length of remission. It is fair to say that the last 18 months have been an unexpected yet welcome bonus. As a Husband and father to a 10 year old son, it has enabled us to embrace our lives together and take the opportunity to create memories together as opposed to being limited by illness and the bleak thoughts of limited life. That said, my Wife and I now look at what the future holds for us and in particular, our son, now my current treatment is gradually becoming less effective.
7a. What do you think of the current treatments and care available for multiple myeloma on the NHS?	The treatment options for multiple refractory patients are inadequate. When you are diagnosed with a life limiting illness such as Myeloma, the impact of the disease and its treatments mean life as you know it, and your future plans change forever, which is traumatic to you as a patient and all those around you. Rather than dwelling on the negative, I have strived to remain positive by looking forward in the knowledge that there are a range of treatments still available and potentially new ones becoming available.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	However, the more my illness has progressed, the fewer options are available and therefore the harder it is to remain positive. In fact, life becomes very uncertain, particularly difficult to plan for, and day to day living is constantly surrounded by anxiety for me and my family. When my current treatment fails to work, I have only one option available to me which is Elranatamab. I feel fortunate to be able to understand the complexity of the disease I have, and where and how to seek the treatment options that are available. I know many patients who do not understand it and as such just accept what they are told and what they are given. I have asked many questions and have diplomatically challenged some suggestions along the way in order to fend for my best interests. Clinical trials and compassionate response schemes are a total lottery. I know of many patients who are late on in their treatment and they are all very anxious about future options, both availability and efficacy. We all desperately cling on to any positive findings from new research and development. This cohort of patients are understandably the most anxious and many, including myself, suffer from depression and mental health challenges as a result of their uncertain futures and increasing amount of disease symptoms.
8. If there are disadvantages for patients of current NHS treatments for multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Many treatments require multiple visits to hospital for treatment, despite the treatment varying in time given via an IV, the time taken in waiting for it to be requested from pharmacy, drawn up, administered, flushed etc can be considerable and as such this generally means the best part of a day being used up for treatment on a regular basis.

	These treatments also require the ongoing use of steroids and other accompanying drugs which can have a negative impact on physical and in the case of steroids, mental health. A common side effect of Dexamethasone for example, often talked about between patients, is that it keep you awake at night. I am not exaggerating that this is not just a few hours, but entire nights and as such this has a huge impact on being able to function in the days following and therefore in patients standard of living and wellbeing.
9a. If there are advantages of elranatamab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does elranatamab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Once the initial setup is complete, the administering of the treatment being done subcutaneously is a huge benefit in the time it take to receive the treatment and as such this will give patients an instant improvement to quality of life, work life and their general mental wellbeing. There is nothing worse as a patient with a life limiting illness, than sitting in a waiting room for hours waiting for your treatment and then sitting for hours receiving your treatment when you know these are valuable hours passing you by. These are often quite lonely times too, being away from your friends, family and "normality" outside of hospital. I understand more and more Trusts are looking at ways of delivering treatment in the community and as such, with Elranatamab being administered subcutaneously, this could potentially become a candidate for that, keeping patients out of hospital away from the risks associated with attending hospital as a immunosuppressed patient and receiving their treatment much quicker.
10. If there are disadvantages of elranatamab over current treatments on the NHS please describe these.	The risks of Elranatamab are no more than the risks associated with any other treatment option we are presented with from the point we are diagnosed.

For example, are there any risks with elranatamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from elranatamab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Without Elranatamab, there are quite simply no other lines of treatment available for those, like me, who are on their 4th line of treatment or more.
12. Are there any potential equality issues that should be taken into account when considering multiple myeloma and elranatamab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	n/a
13. Are there any other issues that you would like the committee to consider?	n/a

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- New treatments are desperately needed for those patients who have already exhausted multiple lines of treatment.
- The life expectancy of Myeloma patients has continued to increase in recent years, this trend needs to continue with the help of novel treatments such as Elranatamab.
- Myeloma patients need hope for the future and better ways of improving their lives and general wellbeing with different treatments, not just an acceptance that their lives will succumb to Myeloma and it will dictate the rest of their lives.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]

Produced by Aberdeen HTA Group

Authors Clare Robertson[1]
Charlotte Kennedy[2]
Thenmalar Vadiveloo[1]
Lorna Aucott[1]
Paul Manson[1]
Mary Kilonzo[2]
Miriam Brazzelli[1]
Gavin Preston[3]
Graham Scotland[2]

1 Health Services Research Unit, University of Aberdeen, UK
2 Health Economics Research Unit, University of Aberdeen, UK
3 NHS Grampian, Aberdeen, UK

Correspondence to Graham Scotland
Health Economics Research Unit, University of Aberdeen
Polwarth Building, Foresterhill
Aberdeen, AB25 2ZD
g.scotland@abdn.ac.uk

Date completed **Draft report**

Contains [redacted]

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number **NIHR136155.**

Declared competing interests of the authors

No competing interests to disclose.

Acknowledgements

Pfizer retain copyright for Figures 1-8, and 10-20, Tables 9, 10, 13 and 14, the quoted text in Table 4, and text quoted on pages 51-52.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Robertson C, Kennedy C, Vadiveloo T, Aucott L, Manson P, Kilonzo M, Brazzelli M, Preston G, Scotland G. Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]. NICE Single Technology Appraisal, Aberdeen HTA Group, 2023.

Contribution of authors

Clare Robertson reviewed and critiqued the clinical effectiveness evidence presented in the company submission and drafted the background section; Thenmalar Vadiveloo and Lorna Aucott checked and critiqued the statistical analyses presented in the company submission; Charlotte Kennedy, Mary Kilonzo and Graham Scotland reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission, and conducted further analysis; Paul Manson checked and critiqued the company's search strategies; Gavin Preston provided clinical guidance during the course of the appraisal; Miriam Brazzelli provided comments on the clinical effectiveness aspects of the appraisal; Graham Scotland coordinated all aspects of the appraisal and is the guarantor of this report. All authors contributed to the writing of this report and approved its final version.

Table of contents

List of Tables

List of Figures

List of abbreviations

BCMA	B-cell maturation antigen
BICR	Blinded independent central review
BORT	Bortezomib
CAR	Carfilzomib
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CRR	Complete response rate
CS	Company submission
DARA	Daratumumab
DEX	Dexamethasone
EAG	External Assessment Group
ECA	External control arm
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Multiple Myeloma Quality of Life Questionnaire
EQ-5D-3L	EuroQol 5 Dimensions questionnaire descriptive system 3 levels
EQ-5D-5L	EuroQol 5 Dimensions questionnaire descriptive system 5 levels
EQ-5D VAS	EuroQol 5 Dimensions questionnaire visual analogue scale
HR	Hazard ratio
HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
ISA	Isatuximab
IXA	Ixazomib

LSM	Least square mean
LEN	Lenalidomide
mAB	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MM	Multiple myeloma
NE	Not evaluable
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PANO	Panobinostat
PFS	Progression-free survival
PGI-C	Patient Global Impression of Change
PI	Proteasome inhibitor
POM	Pomalidomide
QALY	Quality adjusted life year
R-ISS	Revised International Staging System
RRMM	Relapsed or refractory multiple myeloma
SACT	Systemic anti-cancer therapy
SLR	Systematic literature review
TCR	Triple class refractory
THAL	Thalidomide

1. Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

The focus of the submission received from Pfizer is elranatamab (ELREXFIO®) for relapsed or refractory multiple myeloma (RRMM) in adults. The company's positioning of elranatamab is as a monotherapy for adults with RRMM who have received at least three prior treatments, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD) and an anti-CD38 monoclonal antibody (mAB) and have demonstrated disease progression on the last therapy.

In the CS, the main clinical effectiveness evidence for elranatamab is obtained from a cohort of B-cell maturation antigen (BCMA)-naïve patients (Cohort A, n=123) enrolled in the Phase II, open-label MagnetisMM-3 study. Supporting evidence for elranatamab is provided by the earlier Phase I, MagnetisMM-1 trial. The company also reports a matching-adjusted indirect comparison (MAIC) between MagnetisMM-3 and the POM+DEX arm of the MM-003 randomised controlled trial (n=302). The primary endpoint in MagnetisMM3 was the objective response rate (ORR). Progression-free survival (PFS) and overall survival (OS) data were not mature in Cohort A of MagnetisMM-3 and were considered in the MAIC.

Overall, the EAG agrees that the company have carried out sensible analyses and that there is evidence of benefit of elranatamab over the POM+DEX combination for PFS and OS.

However, there are differences in the patient populations (as patients from the POM-DEX arm did not have triple class refractory (TCR) MM) and the matching method significantly reduces the effective sample size. Therefore, the analysis estimates may be unstable and should be interpreted with caution.

Table 1. Summary of key issues

ID4026	Summary of issue	Report sections
1.	The company's proposed positioning cuts across lines of therapy and leads to heterogeneity in treatment history and degree of refractoriness in the cohort of patients who will be eligible for elranatamab.	2.3 and 4.2.3
2.	Immaturity of the survival data leads to substantial uncertainty in the extrapolated PFS and OS benefits.	4.2.6
3.	The extrapolation of PFS and OS lacks plausibility in that chosen curves converge early in the model time horizon. This effectively results in one curve being used to partition the elranatamab cohort between progression free or dead.	4.2.6
4.	Time to treatment discontinuation (TTD) with POM+DEX appears to have been overestimated, using a ratio that incorrectly infers treatment continues beyond progression.	4.2.6 and 4.2.8
5.	The EAG has some concern that elranatamab dose reductions, applied through the relative dose intensity (RDI) parameter in the model, may not all translate into real cost-savings in routine practice, and there is also some uncertainty regarding longer-term extrapolation of RDI.	4.2.8
6.	The proposed stopping rule for applied elranatamab is uncertain and lacks validation	4.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are that the EAG prefers to: 1) Give priority to a preferred and plausible extrapolations of OS to address the issue of curves crossing, rather than giving priority to the company's preferred extrapolation of PFS; 2) Select a PFS curve that remains below OS for most of the model time horizon, rather than selecting one that would cross OS; 3) Constrain the time to treatment discontinuation (TTD) curve for POM+DEX to remain below PFS, rather than allowing treatment to continue beyond progression. The EAG also prefers to

revise several costing assumptions in the company's model. These include the approximation of incident progression and capping of subsequent treatment durations, the cost of administering IVIG, and the application of higher end of life care costs and higher costs for treating grade 3-4 infections.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology (elranatamab) is modelled to affect QALYs by:

- Increasing overall survival compared to the comparator treatment;
- Prolonging time in the progression free health state compared to the comparator treatment; and
- Having a different adverse event profile compared to the comparator treatment.

Overall, the technology is modelled to affect costs by:

- Having different acquisition and administration costs compared to the comparator treatment.
- Accumulating, overall, greater health care resource use over a period of extended survival
- Having lower subsequent treatment costs due to effects of delayed/preventing progression
- Having higher adverse event costs

The modelling assumptions that have the greatest effect on the ICER are:

- The relative dose intensity applied to elranatamab and POM+DEX
- The combined extrapolation of OS and PFS for elranatamab and whether to give priority to PFS or OS when curves would otherwise cross.
- The assumed ratio between PFS and time to treatment discontinuation (TTD) applied to POM+DEX

- The calculations around incident progression and capping of subsequent treatment duration
- The stopping rule applied to elranatamab

1.3 The decision problem: summary of the EAG's key issues

The main issue related to the company's decision problem is the heterogeneity of the proposed patient population.

Issue 1. Heterogeneity within the proposed patient population

Report section	2.3 and 4.2.3
Description of issue and why the EAG has identified it as important	The company's proposed positioning cuts across lines of therapy, and whilst most patients meeting the positioning will be triple class refractory (TCR), as in MagnetisMM-3, some will not be. The wording for the indication will allow some patients to become eligible for elranatamab as early as third line (after second relapse), and some may only be refractory to one or two classes of therapy rather than three.
What alternative approach has the EAG suggested?	The EAG do not suggest an alternative approach but consider it important that the committee discuss the implications of adopting elranatamab according to the wording of the company's proposed positioning, in the context of the current care pathways and previous TA guidance.
What is the expected effect on the cost-effectiveness estimates?	The EAG has some concerns that the clinical effectiveness and economic case has not been made for a minority of elranatamab eligible patients who will become eligible at third line of treatment in the NHS, after two relapses. It is unclear exactly what proportion of the elranatamab eligible cohort this is likely to make up, or what proportion of patients at third line in the NHS it might apply to.
What additional evidence or analyses might help to resolve this key issue?	It would be useful to seek further insight from clinical experts on the percentage of patients at third line (second relapse) in the NHS who would be expected to meet the eligibility criteria for elranatamab, and what their alternative therapies would be in routine practice.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

A major limitation of the MagnetisMM-3 trial (14 March 2023 data cut) is the immaturity of the survival data, as both OS and PFS have yet to be met in Cohort A.

Issue 2. Immaturity of survival data

Report section	3.2.2 and 4.2.6
Description of issue and why the EAG has identified it as important	As of the 14 March 2023 MagnetisMM-3 data cut, median PFS and OS have not yet been reached. There is heavy censoring in the Kaplan-Meier curves around 15 months, making the shape of the distributions and longer-term extrapolations highly uncertain.
What alternative approach has the EAG suggested?	Not applicable.
What is the expected effect on the cost-effectiveness estimates?	The immature data leads to wide variation in the extrapolation of PFS and OS based on different fitted parametric curves. Several of curves produce implausible extrapolations without further adjustments, and the selection of more pessimistic curves produces reduced QALY gains and higher ICERs for elranatamab.
What additional evidence or analyses might help to resolve this key issue?	This issue cannot be resolved without extended follow-up of patients treated with elranatamab, including those in the MagnetisMM-3 study. The EAG notes that the company refer to a new data cut being available in November 2023, which would help to provide some further insight into the emerging shape of the PFS and OS distribution, but longer-term follow-up is likely to be required to substantially reduce the current uncertainties.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the cost-effectiveness evidence presented in the company's submission and identified the following key issues for consideration.

Issue 3 Extrapolation of PFS and OS lacks plausibility

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The PFS and OS Kaplan Meier curves for Cohort A (MagnetisMM-3) appear to converge towards the end of the currently observed follow-up period of the trial. As a result, the company's preferred independently fitted parametric curves cross early in the extrapolation phase. To avoid this, the company allow the modelled PFS and OS curves to converge, and allow OS to be dominated by PFS which is more mature. This effectively results in one single curve being used to partition the elranatamab cohort, between the progression free and dead states of the model. It further infers no progression risk, only pre-progression mortality, from early in the model time horizon. This is not in line with the EAG clinical expert's expectation and suggests underestimation of time spent with progressive disease, underestimation of subsequent treatment costs, and a corresponding over-estimation of QALYs gained with elranatamab compared to POM+DEX.
What alternative approach has the EAG suggested?	The EAG suggest that the company may be placing too much emphasis on selecting a parametric curve that captures the "plateau" in the tail of the PFS KM data, resulting in overly optimistic projections of PFS that are inconsistent with their preferred extrapolation of OS. The EAG suggest giving priority to a preferred OS extrapolation, based on statistical fit and plausibility of extrapolation, and choosing a PFS curve that remains below it for most of the model time horizon. The EAG also suggest that the company's preferred OS extrapolation is optimistic and suggest exploring alternative scenarios that use less optimistic extrapolations of OS and PFS combined.
What is the expected effect on the cost-effectiveness estimates?	Giving priority to the company's preferred extrapolation of OS over PFS in the model, reduces life years, QALYs and costs for elranatamab, and reduces the ICER when holding other company base case assumptions constant. Choosing a PFS curve (Weibull or gamma) that remains below their preferred OS exploration results in a substantial relative increase in the ICER as does applying both changes together.
What additional evidence or analyses might help to resolve this key issue?	The EAG believe that this issue stems from the immaturity of the PFS and OS data on which to base the extrapolations. An updated data cut could provide more data on PFS and OS, which may reduce some of the current uncertainty. It may not fully resolve the issue because at present it would only provide an additional three months or so of follow-up data.

Issue 4 Time to treatment discontinuation (TTD) with POM+DEX is overestimated.

Report section	4.2.6 and 4.2.8
Description of issue and why the EAG has identified it as important	Given a lack of published data on TTD for POM+DEX, the company approximate it by applying a ratio of median TTD to median PFS. This ratio, however, appears to have been derived using the outcome of median time to progression rather than time to treatment discontinuation. The resulting ratio infers that treatment with POM+DEX continues beyond progression, which goes against guidance and clinical expert opinion received by the EAG
What alternative approach has the EAG suggested?	The EAG suggest correcting this using the ratio between median time to treatment failure (TTF) and PFS. TTF was the outcome used in TA427 to model time on treatment for POM+DEX and was defined as the earliest of disease progression, treatment discontinuation, death or initiation of another anti-myeloma therapy. It gives a ratio of 0.725, resulting in the extrapolated time on treatment with POM+DEX falling below PFS as expected.
What is the expected effect on the cost-effectiveness estimates?	This change substantially reduces the acquisition and administration costs of POM+DEX in the model, increasing the ICER substantially.
What additional evidence or analyses might help to resolve this key issue?	The EAG do not believe further evidence is required on this issue, unless more granular data on TTD can be identified for POM+DEX which could be used to fit parametric curves independently.

Issue 5 The calculated relative dose intensity (RDI) for elranatamab may not be appropriate for estimating costs in the model.

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company apply a RDI to elranatamab in their cost calculations, reflecting overall RDI during time on treatment in MagnetisMM-3 trial. The EAG has some uncertainty as to whether average RDI observed over the follow-up period of MagnetisMM-3 is appropriate for extrapolation for the entire time horizon. It is also unclear to what extent dose reductions captured in the RDI would translate into drug acquisition cost savings in the context of fixed vial sizes and no vial sharing, and such reductions would be unlikely to affect administration costs (as they have been assumed to in the model).
What alternative approach has the EAG suggested?	The EAG have explored several scenarios that apply higher RDI and 100% RDI from different follow-up times to those who remain on treatment in the longer-term. They also explore the impact of removing RDI from administration costs.
What is the expected effect on the cost-effectiveness estimates?	The model is sensitive to the RDI and how it is applied, and increasing it substantially increases the incremental costs and the ICER.
What additional evidence or analyses might help to resolve this key issue?	The company have provided a more detailed breakdown of how the RDI was calculated and how it varied by cycle of treatment in MagnetisMM-3. This provides some reassurance that step down to Q2W dosing had no obvious impact on it, and so it may be reasonable to apply it in the extrapolation phase of the model. However, there is limited evidence to inform long-term RDI for those who remain on treatment beyond the median follow-up of the MagnetisMM-3 trial. Since it is an influential parameter, it would be useful for further discussion to focus on its extrapolation and also how observed dose reductions accounted for the in RDI are expected to translate into savings for the NHS if no vial sharing is permitted.

Issue 6 The proposed stopping rule for elranatamab is uncertain and lacks validation.

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company propose a stopping rule for elranatamab, to be applied to all those remaining on treatment at [redacted]. This is based on suggestion that elranatamab can induce a deep and durable response, which is maintained following discontinuation of treatment. Considering this against the risk of adverse events with long-term treatment, the company propose that a stopping rule would be appropriate for elranatamab. The EAG have reservations about this given the immaturity of the data for making inference about the durability of responses and the impact of stopping on disease progression.
What alternative approach has the EAG suggested?	Given the current uncertainties, the EAG have assessed the impact of removing the stopping rule.
What is the expected effect on the cost-effectiveness estimates?	Removing the stopping rule has a substantial upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	It would be useful to seek further clinical opinion on the proposed stopping rule, and a) whether it would be implemented in NHS practice, and b) whether there is confidence based on the current evidence that this would not have a detrimental effect on expected PFS and OS.

1.6 Other key issues: summary of the EAG's view

The EAG reviewed the cost-effectiveness evidence presented in the company's submission and agree that the case is made for the severity weighting for incremental QALYs. The proportional shortfall under POM+DEX lies between 0.85 and 0.95 for all scenarios explored, qualifying elranatamab for consideration of 1.2 weighting. The results presented reflect this weighting in the calculation of mean and incremental QALYs. The EAG also note the company's opinion that elranatamab would be a suitable candidate for cancer drugs fund.

1.7 Summary of EAG's preferred assumptions and resulting ICER

The EAGs preferred modelling assumptions are outlined in Table 2, individually, and then in combination, showing their impact on the company ICER.

Table 2. Summary of EAG's preferred assumptions and ICER

Preferred assumption	Incremental cost	Incremental QALYs	ICER £/QALY
Company base case	[redacted]	[redacted]	£1,926
EAG corrected company base-case (including correction of two minor bugs identified by the EAG (see section 5.3)	[redacted]	[redacted]	£1,905
Give priority to extrapolation of OS over PFS, rather than PFS over OS.	[redacted]	[redacted]	£1,577
Apply Gamma for PFS (Elranatamab), to ensure logical consistency with OS extrapolation	[redacted]	[redacted]	£3,889
Amend POM+DEX ratio of TTD:PFS = 0.725	[redacted]	[redacted]	£15,674
Apply EAG incident progression calculations	[redacted]	[redacted]	Dominant
Apply EAG subsequent treatment duration cap	[redacted]	[redacted]	£5,032
Apply increased costs of treating grade 3-4 infections (assume £2,512, as used for pneumonia (HRGs DZ11K, DZ11V)) included in the model	[redacted]	[redacted]	£1,844
Include administration cost of £207.59 for IVIG (based on SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance Outpatient NHS Reference costs 2021/22))	[redacted]	[redacted]	£2,048
Apply IVIG as a one-off cost in first cycle, to ensure consistency with the assumed usage rate and treatment duration.	[redacted]	[redacted]	£2,211
Apply higher cost (£5231.30) for end-of-life care	[redacted]	[redacted]	£1,706
Apply RDI for POM+DEX at agreed percentage from TA427 (95.94%)	[redacted]	[redacted]	Dominant
EAG's base case	[redacted]	[redacted]	£29,169

Modelling errors identified and corrected by the EAG are described in section 5.3 of the EAG report. For further details of the exploratory and sensitivity analyses done by the EAG, see sections 6.1 to 6.3.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Pfizer is relapsed or refractory multiple myeloma (RRMM) in adults. *The company's description of the health condition in terms of prevalence, symptoms and complications appears accurate and in line with the decision problem.* The relevant intervention for this submission is elranatamab (ELREXFIO®).

2.2 Background

The company submission (CS) describes multiple myeloma (MM) as a malignancy of plasma cells in the bone marrow and is characterised by abnormal cell growth and secretion of monoclonal paraprotein (M-protein) in the blood.[1] It accounts for 2% of all new cancer cases and is more common in men than women.[2] MM is more common in the elderly with a median age of diagnosis of 74.2 years.[2] The CS reports that the age-standardised incidence rate of MM in the UK is 9.7 cases per 100,000 population with approximately 6000 new cases diagnosed between 2016 and 2018. The 5-year UK age-standardised survival rate for newly diagnosed patients is 55.5%, although this reduces to 35.8% for patients aged ≥75 years.[3]

Complications associated with MM include anaemia due to reduced red blood cells and increased susceptibility to infections.[4] The build-up of monoclonal paraprotein can cause renal impairment and the accumulation of myeloma cells in the bone marrow can lead to bone marrow failure, bone degeneration resulting in bone fractures, and increased calcium in the blood (hypercalcaemia).[1] Myeloma cells can grow outside of the bone marrow and cause additional complications in other anatomical sites, such as in peripheral blood, soft tissues or organs.[5]

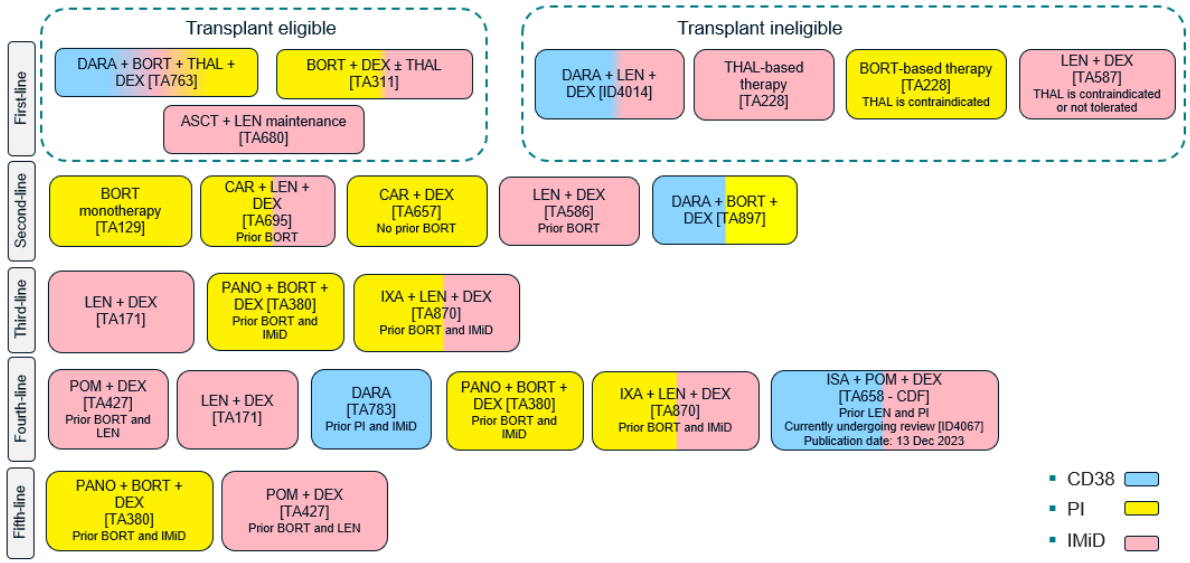
MM has a significant impact on patients' health-related quality of life (HRQOL) and both generic and disease-specific measures show declines in HRQOL with each additional line of treatment and increasing disease refractoriness due to increasing treatment toxicity and comorbidity, resulting in increased frailty.[6-8] Disease remission and a favourable treatment response are associated with improved HRQOL.[9-11] In a UK survey of MM patients, the symptoms most experienced by respondents included fatigue (87.6%), pain (71.5%) and

shortness of breath (60.8%).[12] Patients can also experience depression and anxiety.[13, 14] MM also has a significant physical, emotional, and financial impact on caregivers.[15-19]

MM is currently an incurable disease, and it is characterised by successively shorter periods of disease remission and relapse after each successive line of therapy and the chances of achieving treatment response and the duration of the response also diminishes with each successive relapse.[20] The main aims of therapy are to prolong survival and provide symptom relief. The company presents the current recommended clinical care pathway for MM in England in section B.1.3.3 and the EAG have reproduced Figure 2 of the CS below as Figure 1. The company's positioning of elranatamab is as a monotherapy for adults with RRMM who have received at least three prior treatments, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD) and an anti-CD38 monoclonal antibody (mAB) and have demonstrated disease progression on the last therapy. These patients are described as triple class refractory (TCR) and have either an inadequate response or disease progression while on therapy or within 60 days of their last line of treatment (LOT).[21] The company reports that clinical expert advice suggests that most patients will be TCR (and, consequently, eligible for elranatamab) from the fourth line of therapy onwards;[22] however, some patients will become TCR at the third line. The company also states that more patients are likely to become TCR earlier in the treatment pathway following the introduction of novel combination therapies earlier in their treatment. The company states that these patients currently lack effective treatment options and are likely to have poorer outcomes.

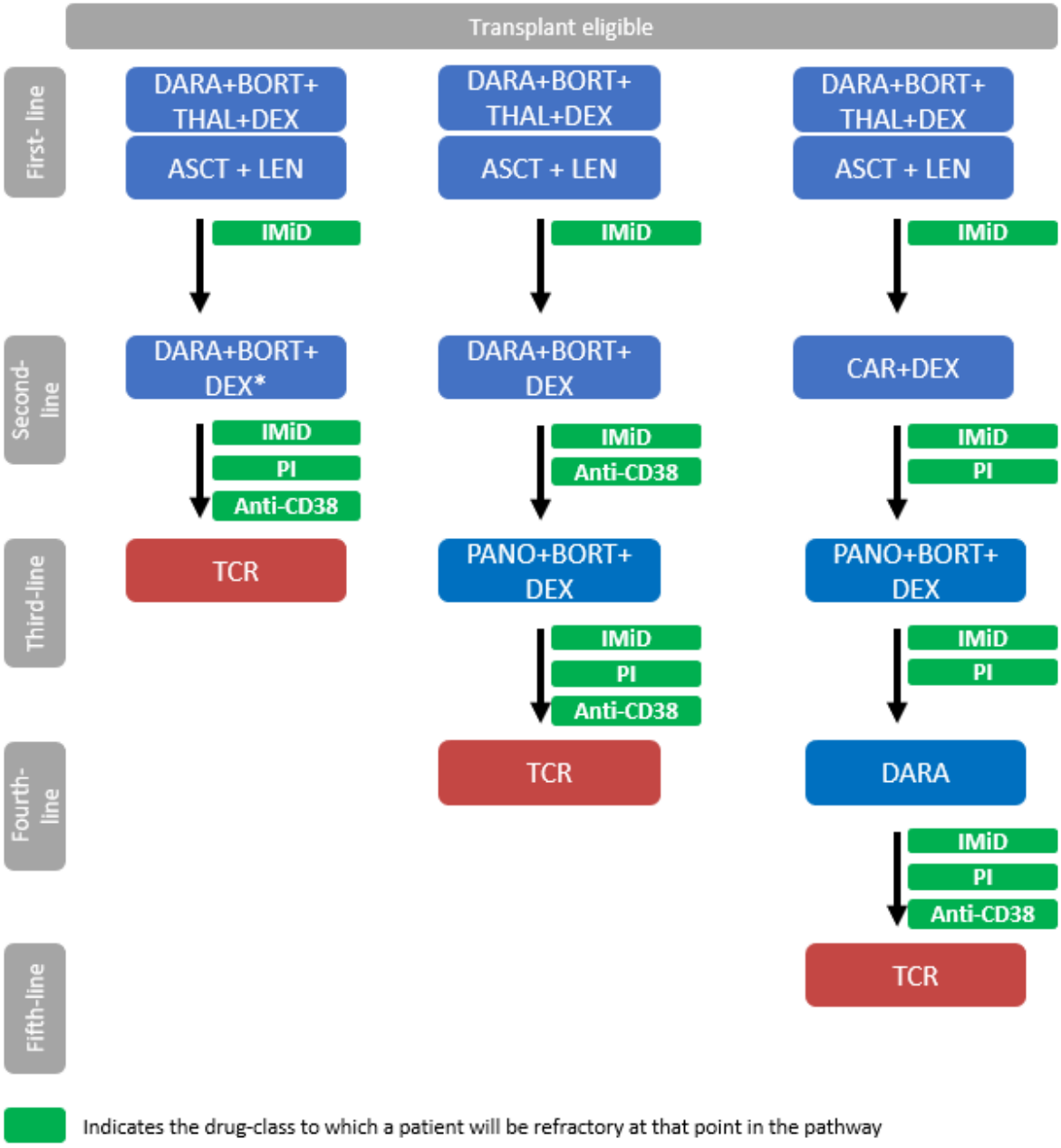
The company presents the potential routes to treatment eligibility for elranatamab for transplant eligible and ineligible patients in Figures 3 and 4 of the CS, and these are reproduced by EAG below as Figures 2 and 3. *The EAG clinical expert agrees with the company's positioning of elranatamab in the care pathway*.

Figure 1. NICE-approved therapies for the treatment of multiple myeloma



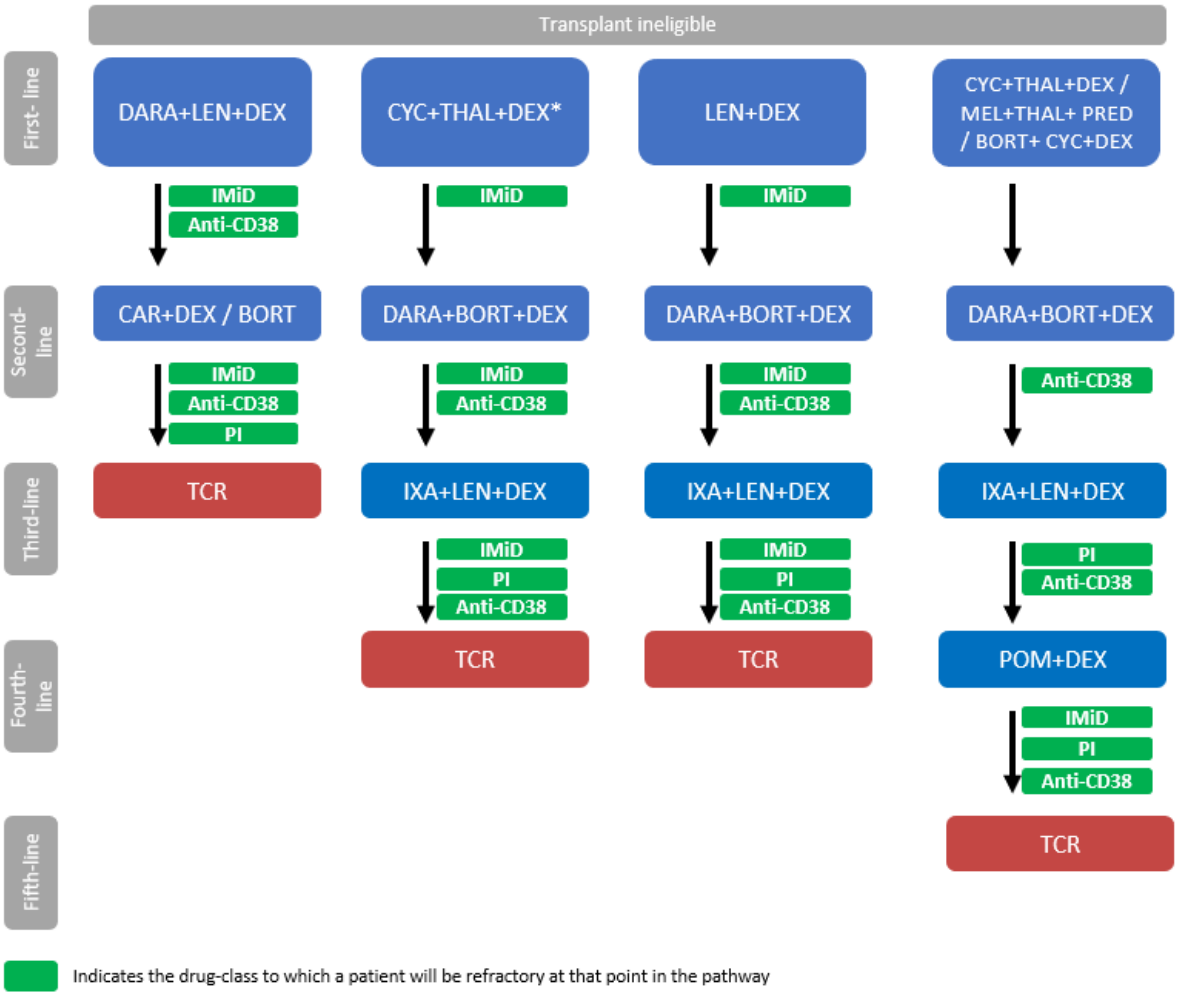
Key: ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, Carfilzomib; CDF, Cancer Drugs Fund; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PANO, panobinostat; PI, proteasome inhibitor; POM, pomalidomide; THAL, thalidomide.
Notes: Colours indicate the use of anti-CD38s, IMiDs, and PIs within the treatment pathway. Blue indicates the use of anti-CD38s, yellow indicates the use of PIs, and red indicates the use of IMiDs.
Source: Adapted from Pfizer, 2023;[22] NICE [NG35], 2018;[23] NICE [TA763], 2022;[24] NICE [TA311], 2014;[25] NICE [TA680], 2021;[26] NICE [ID4014], 2023;[27] NICE [TA228], 2011;[28] NICE [TA129], 2007;[29] NICE [TA587], 2019;[30] NICE [TA695], 2021;[31] NICE [TA657], 2020;[32] NICE [TA586], 2019;[33] NICE [TA897], 2023;[34] NICE [TA171], 2019;[35] NICE [TA380], 2016;[36] NICE [TA870], 2023;[37] NICE [TA427], 2017;[38] NICE [TA783], 2022;[39] NICE [TA658], 2020.[40]

Figure 2. Potential routes to eligibility in transplant eligible patients in the NICE pathway



Key: Anti-CD38, anti-CD38 monoclonal antibody; ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, carfilzomib; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; LEN, lenalidomide; NICE, National Institute for Health and Care Excellence; PANO, Panobinostat; PI, proteasome inhibitor; TCR, triple class refractory; THAL, thalidomide.
Notes: *Relapse within 10-months of DARA+BORT+THAL+DEX initiation.
This diagram illustrates potential routes through the NICE pathway to becoming TCR, it is not exhaustive. Owing to fixed-duration induction therapy, patients are typically only lenalidomide refractory after first line. Patients treated with daratumumab in combination with bortezomib and dexamethasone in second line are not typically bortezomib refractory, however they can be if they relapse early in treatment (within 10-months of starting).
Source: Pfizer data on file, 2023.[41]

Figure 3. Potential routes to eligibility in transplant ineligible patients in the NICE pathway



Key: Anti-CD38, anti-CD38 monoclonal antibody; BORT, bortezomib; CAR, carfilzomib; CYC cyclophosphamide; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; IXA, ixazomib; LEN, lenalidomide; MEL, melphalan; NICE, National Institute for Health and Care Excellence; PI, proteasome inhibitor; POM, pomalidomide; PRED, prednisolone; TCR, triple class refractory; THAL, thalidomide; TI, transplant ineligible.
Notes: *Early relapse on CYC+THAL+DEX.
This diagram illustrates potential routes through the NICE pathway to becoming TCR, it is not exhaustive. Note that not all patients relapsing after front-line therapy will be class-refractory owing to fixed-duration therapies. However, patients with aggressive disease may relapse early (as depicted with cyclophosphamide with thalidomide and dexamethasone) thus becoming refractory.
Source: Pfizer data on file, 2023.[41]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Patients with relapsed or refractory multiple myeloma after at least 3 prior therapies	Adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy	Aligns with anticipated marketing authorisation. While the anticipated indication is broader than the MagnetisMM-3 study population which was a TCR cohort (as per its eligibility criteria, see Section B.2.3.1), most UK patients will in fact be TCR, as per the anticipated label indication. This is due to the use of multi-drug combination therapies early in the pathway and fact patients are treated to progressive disease from second line of therapy onwards. In addition, UK clinicians have stated that the MagnetisMM-3 data is generalisable to the anticipated label population in the real world.[22]	The company's target population is more specific than that of the final scope and algins with the anticipated marketing authorisation of elranatamab. The company acknowledges that the MagnetisMM-3 trial cohort does not fully align with the anticipated treatment label indication in that some patients who are eligible to receive elranatamab in NHS clinical practice might be TCE without being TCR. At clarification, the company states that UK clinical advice indicates that 100% of MM patients will be TCE by their fourth line of treatment (LOT) and that 85% of these will also be TCR;[42] however, the company notes that there are challenges in quantifying the 'real world' numbers of patients who are TCE and TCR due to a paucity of

				available data and the heterogenous treatment routes that patients can take through their treatment pathway. The company states that the proportion of patients who are TCR is expected to be greater in later lines of therapy as patients are exposed to more treatments and argues that the data presented in the CS are generalisable to the clinical population who would be eligible for elranatamab therapy at fourth LOT given that 96.7% of the MagnetisMM-3 population were TCR compared with comparator populations in the MAIC (not TCE or TCR) and ECA (All TCE and [redacted]% TCR). The company outlines the potential routes to TCE and TCR in the NICE pathway in Figures 1 and 2 of their clarification letter. *The EAG clinical advisor agrees with the company that most patients who are eligible for elranatamab will be TCR*

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				and that, whilst there is some discrepancy between the treatment label indication and MagnetisMM-3 trial populations, the data presented in the CS are reasonably representative of MM patients who would be eligible for elranatamab therapy in NHS practice.
Intervention	Elranatamab	As per draft scope	Not applicable	The intervention described in the CS matches that described in the NICE final scope. Elranatamab is a bispecific B-cell maturation antigen (BCMA)-directed T-cell engaging antibody that binds CD3-epsilon on T-cells and B-cells and BCMA on plasma cells, plasma blasts and MM cells.[43] Elranatamab is indicated as monotherapy for the treatment of adult patients

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				with RRMM, 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. Elranatamab received PRIME designation on 26 March 2021 and is designated as an orphan medicine. Positive CHMP opinion was granted on 12 October 2023. EU marketing authority was granted on 07 December 2023. Great Britian (GB) marketing authority (MA) was granted on 04 January 2024.
Comparator(s)	• Lenalidomide plus dexamethasone	Pomalidomide plus low-dose dexamethasone	All proposed comparators have been carefully considered, with each justification for exclusion based on real world evidence studies using SACT and	The company have considered only one of the comparators outlined in the final scope: Pomalidomide

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Panobinostat plus bortezomib and dexamethasone • Pomalidomide plus low-dose dexamethasone • Daratumumab monotherapy • Ixazomib plus lenalidomide and dexamethasone • Belantamab mafodotin Cyclophosphamide plus dexamethasone		NHS centre data and extensive clinical guidance from practising NHS clinicians provided during: an advisory board meeting with nine clinicians, NICE Early Scientific Advice, HTA Access Forum meeting, NICE decision problem meeting, and individual clinician interviews. In addition, previous MM technology appraisals were reviewed, and the conclusions below reflect decisions on relevant comparators: • Pomalidomide plus low-dose dexamethasone (TA427) was included in the draft scope and is a relevant comparator for elranatamab in patients who have received 3 prior therapies, including a PI, an IMiD and an anti-CD38 mAb. Furthermore, pomalidomide plus low-dose dexamethasone has been accepted as a relevant comparator in prior NICE multiple myeloma appraisals (TA783, TA658).[39, 40] The appropriateness of this comparator was reiterated by practising clinicians at a Pfizer advisory board (May 2023),[22] the HTA Access Forum meeting (July 2023)[44] and individual clinician validation interview (August	plus low dose dexamethasone. *The EAG clinical expert generally agrees with the company's rationale for excluding lenalidomide plus dexamethasone, panobinostat plus bortezomib and dexamethasone, belantamab mafodotin, and cyclophosphamide plus dexamethasone and daratumumab monotherapy. There is less certainty around the justification for excluding ixazomib plus lenalidomide and dexamethasone (IXA+LEN+DEX) as a comparator for elranatamab because lenalidomide can be reused so is a potential third LOT option for patients who are eligible for elranatamab without being TCR; however, the EAG accepts that this is likely to apply to only a minority of patients. The EAG also notes the company's statement that*

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			2023).[42] It is also supported by real-world evidence generated from the national SACT database[45] • Lenalidomide plus dexamethasone (TA171) is not a relevant comparator for elranatamab in this setting, as clinical experts in TA505 stated that lenalidomide plus dexamethasone is mainly used after 2 prior therapies.[35] This is supported by the Pfizer BoD study where lenalidomide was most commonly given at second and third-line.[45] Furthermore, due to the recent approval of daratumumab in combination with lenalidomide and dexamethasone as first-line therapy in transplant ineligible patients (ID4014)[27] and lenalidomide maintenance following ASCT (TA680), nearly all patients will be lenalidomide refractory after first-line[26] • Panobinostat plus bortezomib and dexamethasone (TA380) is no longer a relevant comparator in this setting in the UK due to toxic adverse events and lack of efficacy, meaning it is typically used after 4 previous lines of treatment, as	*IXA+LEN+DEX was accessed through the cancer drug fund (CDF) until February 2023 and has only been available in routine practice for a relatively short period of time.*

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			confirmed through Committee conclusions in TA658 and TA783[39, 40] • While daratumumab monotherapy (TA783)[39] is recommended in patients with relapsed or refractory multiple myeloma after 3 prior therapies, patients eligible for elranatamab will, after three therapies, be refractory to an anti-CD38, having relapsed on either daratumumab in combination with lenalidomide and dexamethasone (ID4014), or daratumumab in combination with bortezomib and dexamethasone (TA897).[27, 34] UK clinicians confirmed that re-challenging patients with this drug class would be inappropriate in patients who had become refractory to daratumumab.[22, 40] Therefore, as the majority (96.7%) of patients in the MagnetisMM-3 trial were TCR, most would have received daratumumab before or in the line they become TCR. In addition, during TA783, the CDF clinical lead stated that the use of daratumumab monotherapy in the fourth-line setting had fallen following NICE's recommendation of isatuximab with pomalidomide and	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			dexamethasone.[39, 40] At the HTA Access Forum meeting (July 2023) the CDF clinical lead repeated that daratumumab would not be a suitable comparator for the reasons stated above.[44] This is further supported by the Pfizer BoD study where <5 patients received daratumumab monotherapy as their next treatment after becoming triple class exposed (TCE) (n = 848)[45] • Ixazomib plus lenalidomide and dexamethasone (TA870) is not a relevant comparator for elranatamab in the current context, based on expert clinical opinion and in line with the final scope for ID1635, which only lists comparators for patients who have had at least 1 (second line) or 2 (third line) therapies. This combination is predominantly used in the third line. Patients must be lenalidomide sensitive, which precludes any patients who have received lenalidomide maintenance following ASCT (TA680),[26] daratumumab in combination with lenalidomide and dexamethasone in first-line (ID4014),[27] lenalidomide in combination with dexamethasone or	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			carfilzomib in combination with lenalidomide and dexamethasone at second-line.[31, 33] According to clinician feedback, (given prior to the approval of daratumumab in combination with lenalidomide and dexamethasone) transplant ineligible patients will typically receive ixazomib in combination with lenalidomide and dexamethasone in the line in which they become TCR [22] • Belantamab mafodotin is not a relevant comparator. It is currently being evaluated by NICE in two separate appraisals: ID5108: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 2 therapies.[46] This appraisal was suspended on 16 November 2022. Therefore, this treatment option will not be part of UK clinical practice at the time of submission ID2701: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies.[47] As per NICE final draft guidance (July 2023), belantamab	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			mafodotin is not recommended in this indication and, therefore, should not be considered a relevant comparator for this appraisal[48] • Cyclophosphamide plus dexamethasone is not a relevant comparator for elranatamab in this setting, as confirmed by clinical experts during individual interviews.[42] When used, cyclophosphamide plus dexamethasone is given at third-line as a 'bridging therapy' to meet the unmet need (i.e. third-line gap) when lenalidomide has been given in prior lines.[42] It is, however, not considered as standard of care as part of the NICE care pathway	
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse events • Health-related quality of life	As per the NICE final scope	Not applicable.	The EAG is satisfied that the outcomes reported in the company's submission are clinically relevant and in line with the NICE final scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments			The company's economic analysis is broadly aligned with the NICE reference case. The results presented by the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to			company or in the main body of this report to do not reflect confidential prices available for comparator and subsequent treatment technologies. These will be taken into account in a separate confidential appendix to be complied by the EAG.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Subgroups	None specified	Several pre-specified subgroup analyses for ORR and CRR are presented as part of the clinical effectiveness evidence in the CS for Cohort A of MagnestisMM-3: • Baseline cytogenetics (high risk, standard risk) • Baseline extramedullary disease (yes, no) • Baseline bone marrow plasma cells (< 50%, > 50%) • Prior SCT (yes, no) • Disease stage (1–2, 3) • Number of prior lines (≤ 5, > 5) • Type of myeloma (immunoglobulin G	NA	The EAG notes that the primary outcome for MagnetisMM-3 was ORR. CRR was the secondary outcome. Consequently, the subgroup analyses have been applied to these outcomes and not PFS and OS, which are the focus of the company's submission. Considering MagnetisMM-3 is an open label, non-randomised study, it would have also been possible to conduct subgroup analyses for PFS and OS. This may have been helpful to further understand the population characteristic effects for these relevant outcomes for consideration with the indirect comparisons.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		[IgG], non-IgG, light chain only) • Age (< 65, ≥ 65, < 75, ≥ 75) • Sex (male, female) • Race (White, others) • Region (North America, Europe, Asia, other) • Renal function (creatinine clearance ≤ 60 mL/min, creatinine clearance > 60 mL/min) • Liver function (normal, impaired) • Refractory to last therapy (yes, no) • Penta-refractory (yes, no) • ECOG (0, 1-2)		
Special considerations	None specified			The company notes that currently reimbursement is

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
including issues related to equity or equality				made by line of treatment as opposed to receipt and/or refractory status to previous therapies. The company claims that this decision will create inequalities in treatment access for patients who become TCR at third-line or earlier and that clinicians would have to use treatments that lack robust efficacy data as "bridging therapies" to enable the patients to access elranatamab at the fourth line. *The EAG clinical expert agrees that patients who have received CD38 antibody, IMiD and PI in the first two lines of therapy do have limited options at third line and may be disadvantaged by delaying access to elranatamab.*

Abbreviations: ASCT, autologous stem cell transplant; BOD, Burden of Disease; CDF, Cancer Drugs Fund; CHMP, Committee for Medicinal Products for Human Use; CRR, complete response rate; ECA, external control arm; HTA, health technology assessment; IMiD, immunomodulatory drug; KOL, key opinion leader; mAb, monoclonal antibody; MAIC, matched adjusted indirect comparison; MM, multiple myeloma; NHS, National Health Service; NHSE,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
National Health Service England; ORR, objective response rate, PI, proteasome inhibitor; SACT, Systemic Anti-Cancer Therapy; TCE, triple class exposed; TCR, triple class refractory.				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The EAG's appraisal of the company's systematic literature review (SLR) methods is summarised in Table 4.

Table 4 EAG's appraisal of the literature review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research. Relevant conference proceedings and trial registers were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected.
Was study selection conducted by two or more reviewers independently?	YES	Appendix D, section D.1.2: "*Across each phase, all records were screened by two independent reviewers, with conflicts resolved (final judgement made) by a third, senior, independent reviewer*."

Was data extraction conducted by two or more reviewers independently?	PARTIAL	Appendix D, section D.1.2 "*Data were extracted into the data extraction table by one reviewer and a second reviewer assessed the entries to ensure consistency and accuracy against the source article as a validation step*."
Were appropriate criteria used to assess the risk of bias of identified studies?	YES	The Downs and Black checklist was used to assess the quality of the MagnetisMM-3 study and the external control arm (ECA) study.[49] The quality of the MM-003 study was assessed in accordance with the NICE user guide.[50]
Was the risk of bias assessment conducted by two or more reviewers independently?	PARTIALLY	One reviewer conducted the quality assessment for the MM-003 study using the NICE user guide. One reviewer conducted the quality assessment for the ECA study using the Downs and Black checklist.[49] One reviewer conducted the quality assessment of MagnetisMM-3 using the Downs and Black checklist and a second reviewer checked the assessment.[49]
Was identified evidence synthesised using appropriate methods?		While MAIC is a valid approach under the circumstances, the small effective sample size (ESS) could result in unstable estimates. The comparator too is probably the best (although there may be an option to consider lenalidomide plus dexamethasone at the 3rd line of treatment). The populations for the indirect comparison presented were somewhat different although these may have cancelled each other out in terms of benefits. The external control arm was small and this affected the precision of some of the direct comparisons

The EAG conducted a quality assessment of the methods used by the company for the SLR of clinical evidence based on the Centre for Reviews and Dissemination (CRD) criteria. The results are presented in Table 5.

Table 5 Quality assessment of the company's systematic literature review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Section B.2 of the CS. The main evidence for elranatamab is obtained from the MagnetisMM-3 study. MagnetisMM-3 is a Phase II, open-label, international, multicentre study of elranatamab monotherapy in RRMM patients who are refractory to at least one PI, one IMiD, and one anti-CD38 mAb, and who have relapsed or are refractory to their most recent treatment.[21, 51, 52] The study enrolled two parallel patient cohorts: Cohort A (BCMA-naïve, n=123) and Cohort B (BCMA-exposed, n=64). Because BCMA-targeted therapies are not currently reimbursed in the UK, the company presents only data from Cohort A in the main CS, with data from Cohort B presented in Appendices M.4 and M.5 for completeness. *The EAG agrees with the company that, for this submission, data from Cohort A are more relevant than data from Cohort B. The EAG critique of MagnetisMM-3, therefore, focuses only on data from Cohort A.* MagnetisMM-3 is currently ongoing in 76 sites from 10 countries, including one UK site. The CS also presents supportive evidence for elranatamab from the earlier Phase I trial, MagnetisMM-1, which evaluated the safety and tolerability of elranatamab at increasing dose

levels and provides more mature progression-free survival (PFS) and overall survival (OS) data in a sicker and more heavily pre-treated cohort of patients who received lower doses of elranatamab compared with the MagnestisMM-3 Cohort A patients.[53]

The company's SLR identified six eligible trials reporting relevant indirect evidence for the company's selected comparator of interest (POM+DEX). The company states that the six identified POM+DEX studies were likely to have enrolled patients that had disease that was less refractory and easier to treat than patients enrolled in the MagnetisMM-3 study. This is because the POM+DEX studies were either published before the introduction of anti-CD38 mAbs therapy, excluded patients who were refractory to anti-CD38 mAbs therapy, or began recruitment before the introduction of anti-CD38 mAbs therapy. The company therefore selected one of the six POM+DEX trials (the MM-003 trial),[54] that, in the company's opinion, includes the most comparable population to the MagnetisMM-3 study in terms of participant baseline characteristics and median lines of prior treatment. The company, therefore included MM-003 in the unanchored matching-adjusted indirect comparison (MAIC) presented in Section B.2.9.1 of the CS and this analysis has been used as the efficacy data for the POM+DEX arm in the company's base case economic analysis. *The EAG agrees with the company that the participants in the POM+DEX arm of MM-003 align more closely with the participants in MagnetisMM-3 participants in terms of their baseline characteristics than the populations in the other five POM+DEX trials identified in the company's SLR.* However, as patients in MM-003 were not TCR, the company claims that the efficacy outcomes from this trial will provide upper bound estimates of efficacy outcomes, given that true TCR patients will have worse outcomes.

The company also presents data from an external control arm (ECA) study ([redacted]) that was conducted by the company using real-world, patient-level data collected from the Arcturis UK dataset which includes over 5,500 MM patients from four National Health Service (NHS) centres in the UK.[55] The patients in this study had received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy (i.e. RRMM) treated with POM+DEX who had a median of [redacted] prior lines of treatment. Data from the ECA study have been used to inform an unadjusted direct comparison and have been used by the company as alternative efficacy scenario for the POM+DEX arm in the economic analysis. Summaries of the methodologies and the baseline participant characteristics of the MagnetisMM-3, MM-003, and ECA studies are presented in

Tables 6 and 7. *The baseline characteristics of participants are broadly similar across studies; however, the EAG notes that there are large amounts of missing data for ECOG status and ISS disease stage data for the ECA study, which makes it difficult to comment on the comparability of the ECA participants with those in the MagnetisMM-3 and MagnestisMM-1 studies for these two characteristics.*

The EAG clinical advisor is of the opinion that the participants in the MagnetisMM-1, MagnetisMM-3, MM-003, and ECA studies are broadly representative of MM patients seen in NHS clinical practice. However, the EAG notes that 81% of the MagnetisMM-3 patients had received prior pomalidomide therapy. The proportion of patients who receive prior pomalidomide therapy is higher than would be expected in NHS practice and suggests that the patients who were enrolled in MagnetisMM-3 were more heavily treated than those seen in routine clinical practice.

The EAG generally agrees with the company's quality assessment of the three studies and is of the opinion that the studies are of good methodological quality.

Table 6. A comparative summary of the methodologies of the MagnetisMM-1, MagnetisMM-3, MM-003 and ECA studies

	MagnetisMM-1	MagnetisMM-3	MM-003	ECA study
Study design	Phase I, open label, multi dose, multi centre, dose escalation, safety, pharmacokinetic and pharmacodynamic study	Phase II, open label, multicentre, non-randomised single arm study	Phase III randomised, open-label, multicentre study	Retrospective, real-world evidence study using IPD from EHRs extracted from four Arcturis UK dataset NHS centres
Population	Adult patients with RRMM who were refractory to at least one PI, one IMiD, and one anti-CD38 mAb	Adult patients with RRMM who were refractory to at least one PI, one IMiD, and one anti-CD38 mAb and who were relapsed or refractory to	Adult patients with RRMM patients who have received at least 2 lines of lenalidomide and bortezomib, alone or in	Adult patients with RRMM who had received at least one PI, one IMiD, and one anti-CD38 mAb and are refractory to the last therapy

	MagnetisMM-1	MagnetisMM-3	MM-003	ECA study
		their most recent regimen	combination	based on documented disease progression (according to the IMWG definition) within 60-days of the last dose, or during treatment with that drug class
Intervention	Elranatamab ≥215 μg/kg^{-1} (n = 55)	Elranatamab monotherapy (n = 123)	POM+DEX (n = 302)	POM+DEX (n = [redacted])
Comparator	N/A	N/A	DEX monotherapy (n = 153)	N/A
Primary endpoint	ORR and DOR	ORR	PFS	PFS
Median follow-up duration	12.0 months (range, 0.3–32.3)	14.7 months (range: 0.2–25.1)	10.0 months (IQR 7.2–13.2)	N/A
Definition of PFS		Time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause	Time from randomisation until documented disease progression, or death, whichever occurred earlier	Time (in days) from index date to the first recorded progression event, as defined by IMWG (with IgA being an acceptable substitute for quantified serum paraprotein if serum paraprotein values are unmeasurable), or death, within the approximately 25-month period following index

	MagnetisMM-1	MagnetisMM-3	MM-003	ECA study
				date
Definition of OS		Time from the date of first dose until death due to any cause	Time from randomisation to death	Time (in days) from index date to date of death, irrespective of cause, within the approximately 25-month period following index date

Key: DEX, Dexamethasone; EHR, electronic healthcare record; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IPD, individual patient data; mAb, monoclonal antibody; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed refractory multiple myeloma.
Source: Lesokhin et al. 2023; Miguel et al. 2013. Pfizer data on file, 2023.[54-56]

Table 7. Baseline characteristics of the participants included in the MagnetisMM-1, MagnetisMM-3, MM-003 and ECA studies

Characteristics		MagnetisMM-1 (n = 55)	MagnetisMM-3 Cohort A (n = 123)	MM-003 (n = 302)	ECA study (n = [redacted])
Age	Mean (SD)		67.07 (9.45)		[redacted]
	Median (range)	64.0 (42–80)	68.0 (36.0–89.0)	64	[redacted]
	> 75 years, n (%)		21 (17)	24 (8)	[redacted]
Male, n (%)		29 (52.7)	68 (55.28)	181 (60)	[redacted]
Time since diagnosis (year, median)		NR	6.1	5.3	[redacted]
Time since the first diagnosis[a], months (Mean (SD)		NR	[redacted]	NR	[redacted]

Time since onset of current relapse[b], months, mean (SD)		NR	[redacted]	NR	[redacted]
Extramedullary disease (EMD), n (%)					
Yes		17 (30.9)	39 (31.7)	NR	[redacted]
Target EMD		NR	37 (30.1)	NR	[redacted]
Non-target EMD only		NR	2 (1.6)	NR	[redacted]
No		NR	84 (68.3)	NR	[redacted]
Non-target bone lesions only		NR	43 (35.0)	NR	[redacted]
No lesion			41 (33.3)		
ECOG, n (%)	0	-	45 (36.59)	110 (36)	[redacted]
	1	-	71 (57.72)	138 (46)	[redacted]
	0-1	50 (90.9)	-	-	[redacted]
	2	-	7 (5.69)	52 (17)	[redacted]
	≥2	5 (9.1)	-	-	
	Missing/not reported	-	0	2 (0.7)	[redacted]
Median (range) number of prior lines		5.0 (2–14)	5 (4, 6)	5 (2-14)	[redacted]
Type of prior therapy - Contains PI, n (%)		55 (100.0)	54 (43.90)	302 (100%)	[redacted]
Type of prior therapy - Contains IMiD, n (%)		55 (100.0)	38 (30.89)	302 (100%)	[redacted]
Type of prior therapy – Contains anti-CD38 mAb, n (%)		54 (98.2)	47 (38.21)	NR	[redacted]
Type of prior therapy – Other, n (%)		13 (23.6)	22 (17.89)	295 (98%)	[redacted]
	I	14 (25.5)	35 (28.46)	-	[redacted]

ISS disease stage, n (%)	II	20 (36.4)	47 (38.21)	-	[redacted]
	I-II	-	-	197 (65)	[redacted]
	III	11 (20.0)	24 (19.51)	93 (31)	[redacted]
	Missing	10 (18.2)	17 (13.82)	-	[redacted]
Cytogenetic risk, n (%)	High-risk	16 (29.1)	83 (67.48)	-	[redacted]
	Standard-risk	35 (63.6)	31 (25.20)	-	[redacted]
	Missing	4 (7.3)	9 (7.32)	-	[redacted]

Key: BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; IgG, immunoglobulin G; IMWG, International Myeloma Working Group; ISS, The International Staging System.
Notes: [a] Duration since first diagnosis in MagnetisMM-3 is from Date of Initial Diagnosis to date of first dose. [b] Time since onset of current relapse in MagnetisMM-3 is defined as date of first dose of study intervention – date of onset of current episode.
Source: Lesokhin et al. 2023; Miguel et al. 2013. Pfizer data on file, 2023.[54-56]

3.2.2 Primary and secondary efficacy endpoints

The MagnestisMM-3 efficacy and safety analyses were based on the safety analysis set, which included all enrolled patients in who received one or more doses of elranatamab.[21]

Primary efficacy endpoint

Objective response rate (ORR)

The primary efficacy endpoint of MagnetisMM-3 is objective response rate (ORR) by blinded independent central review (BICR) as defined by the IMWG criteria.[52] The ORR data presented in the CS are based on the company's interim analysis of the initial [redacted] patients at the data cut-off of [redacted]. After a median follow-up of approximately 15 months, the primary endpoint was met, with a significant and high ORR of 61.0% (95% confidence interval [CI]: 51.8, 69.6; $p < 0.0001$) achieved in Cohort A as assessed by BICR per the IMWG criteria. A summary of the best overall responses by BCIR and investigator assessment are presented in Tables 6 and 7 of the CS. The median ORR of the MM-003 POM+DEX arm was 31.0%

Secondary efficacy endpoints

The secondary efficacy endpoints of MagnetisMM-3 are presented below with supporting data provided by MagnetisMM-1. Of these endpoints, progression free survival (PFS) and overall survival were considered for the MAIC.

- **Overall survival (OS)**. OS data were not mature in Cohort A of MagnetisMM-3; median OS was not reached (95% CI: 13.9, NE) and 44.7% of patients had died at the time of the 15-month data cut-off. Figure 9 of the CS presents the Kaplan–Meier curve for OS. The probability of patients surviving at 15 months was 56.7% when treated with elranatamab. Among those who achieved a CR, the probability of patients surviving at 15 months was 92.6%. Median OS was 21.2 months (95% CI: 10.9–NE) in MagnetisMM-1.
- **Progression free survival (PFS)**. Median PFS by BICR was not reached in MagnetisMM-3 (95% CI: 9.9 months, NE) at the 15-month data cut-off Figure 8 of the CS presents the Kaplan–Meier curve of PFS assessed by BICR. The probability of being progression-free at 15 months when treated with elranatamab was 50.9%. Among those who achieved a CR, 89.5% of patients treated with elranatamab were progression-free at 15 months. Median PFS in MagnetisMM-1 was 11.8 months (95% CI: 6.0–19.1).

A summary of the OS and PFS outcomes considered in for the MAIC and unadjusted direct comparisons is presented in Table 8.

Table 8. Summary of outcomes used for clinical studies considered for the MAIC and unadjusted direct comparison

	MagnetisMM-3 Cohort A (n = 123)	**MM-003 (n = 302)**	**ECA study (n = [redacted])**
OS	Median OS at 15-months: Not reached (95% CI: 13.9, NE)	Median OS: • POM+DEX: 11.9 months (95% CI: 10.4, 15.5) • DEX: 7.8 months (95% CI: 6.4–9.2)	Median OS: [redacted] months (95% CI: [redacted])
PFS	Median PFS at 15-months: Not reached (95% CI: 9.9, NE)	Median PFS: • POM+DEX: 4.0 months (95% CI: 3.6, 4.7) • DEX: 1.9 months (95% CI: 1.9–2.2)	Median PFS: [redacted] months (95% CI: [redacted])
Key: CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; ISA, isatuximab; NE, not evaluable;			

	MagnetisMM-3 Cohort A (n = 123)	MM-003 (n = 302)	ECA study (n = [redacted])
OS, overall survival; PFS, progression-free survival; POM, pomalidomide. **Source**: Lesokhin et al. 2023; Miguel et al. 2013 ; Pfizer data on file, 2023.[54-56]			

Other secondary endpoints considered in MagnetisMM-3 included:

- **ORR by BICR according to baseline extramedullary disease (EMD) status per the IMWG criteria**. Data were significant for patients in MagnetisMM-3 both without baseline EMD (71.4%; 95% CI: 60.5, 80.8; $p < 0.0001$) and with baseline EMD (38.5%; 95% CI: 23.4, 55.4; $p < 0.0001$).[56] In MagnetisMM-1, the overall ORR was 63.6% (35/55; 95% CI: 50.4, 75.1).
- **Confirmed ORR by investigator per IMWG criteria in MagnetisMM-3**. The confirmed ORR by the investigator was 59.3% (95% CI: 50.1, 68.1) in MagnetisMM-3.
- **Complete response rate (CRR) by BICR and investigator per IMWG criteria in MagnetisMM-3**. 7.3% of patients with a confirmed complete response (CR) by BICR were still receiving elranatamab monotherapy and without disease progression. Overall, 15.4% of patients achieved a stringent complete response (sCR) and 19.5% achieved a CR, leading to a CRR by BICR of 35.0% (95% CI: 26.6, 44.1). In MagnetisMM-1, 56.4% (31/55) of patients achieving a Very good partial response (VGPR) or better and 38.2% (21/55) of patients achieving CR or better, with 27.3% (15/55) of patients achieving confirmed sCRs; 10.9% (6/55) achieved confirmed CR; 18.2% (10/55) achieved confirmed VGPR; and 7.3% (4/55) achieved confirmed partial response (PR).
- **Duration of response by BICR and investigator per IMWG criteria**. In MagnetisMM-3, the median duration of response (DoR) by BICR was not yet reached (95% CI: not evaluable [NE], NE). Figure 7 of the CS presents the Kaplan–Meier curve of DoR assessed by BICR. Overall, 71.5% of patients treated with elranatamab had ongoing responses at 15 months and responses deepened over time. In MagnetisMM-1, median time to first confirmed response of PR or better was 36.0 days (range, 7–262), and median duration of response (DoR) was 17.1 months (95% CI: 11.1–NE). Of the eight responders who transitioned to less frequent (every 2 weeks [Q2W]) dosing after ≥6 months of once weekly therapy, 75.0% (6/8) remained on elranatamab therapy and maintained or deepened response with time. Figure 14, Appendix M.6.3.2 of the CS presents the Kaplan-Meier figure of the duration of

response in MagnetisMM-1. Median duration of response in the MM-003 POM+DEX arm was 7.0 months (95% CI 5.8, 9.0).

- **Duration of complete response (CR) by BICR and investigator per IMWG criteria in MagnetisMM-3**. Median duration of CR by BICR was not yet reached (95% CI: NE, NE) in Cohort A at the time of the 15-month data cut-off. Among those who achieved a CR, 89.2% of patients treated with elranatamab were still on treatment without an event at 15 months and responses deepened over time (data presented in Figure 6 and Appendix M.3 of the CS). The EAG agrees with the company that the results of the investigator assessment were consistent with the BICR assessment.
- **Time to response by BICR and investigator per IMWG in MagnetisMM-3**. Of those patients who achieved an objective response, response to elranatamab therapy occurred within the first 2 months of treatment. Of the 75 responders, the median time to response, as assessed by BICR, was 1.2 months This is comparable to the median time to response by investigator assessment reported in Appendix M.3.1.4.
- **Minimal residual disease (MRD) negativity rate**. MRD negativity was achieved by 21.1% of patients in MagnetisMM-3 at a sensitivity level of 10^{-5}.[89] MRD negativity in complete responders (sCR/CR) was achieved in most patients (89.7%). In MagnetisMM-1, 13 patients were MRD evaluable. Of these, all (100%) patients achieved MRD negativity at a sensitivity of 1×10^{-5}, and nine (69.2%) patients with confirmed CR or better achieved MRD negativity at the 1-month assessment. Eight (61.5%) patients had sustained MRD negativity lasting beyond six months, including two (15.4%) patients with ongoing sCR beyond two years.

Indirect and unadjusted direct treatment comparisons

The company presents the results of the naïve and unanchored MAICs for MagnetisMM-3 versus MM-003 in section B.2.9.1.2 of the CS and the EAG have reproduced the company's Table 15 and Figures 18 and 19 as Table 9 and Figures 4 and 5.

Elranatamab led to significant improvements in both PFS and OS compared to POM+DEX in the naïve comparisons. The company conducted a MAIC to map MagnetisMM-3 elranatamab cohort more closely to MM-003 POM-DEX treatment arm. This resulted in the effective sample size (ESS) with reduced numbers of individual patients (76/123 for PFS and 75/123 for OS) from the MagnetisMM-3 cohort. This is uplifted to 99 patients at risk for both PFS

and OS once MagnetisMM-3 is weighted to 'match' the MM-003 treatment arm sample, by the MAIC process. For PFS this has little impact on the hazard ratio, 95% CIs or p-value as seen in Table 9 and Figure 4. However, while elranatamab still appears beneficial compared to POM+DEX for OS, statistical significance was not reached for OS (p = [redacted]), Table 9 and the Figure 5.

Table 9. Unanchored MAIC: MagnetisMM-3 versus MM-003

Outcome and analysis	ESS	HR (95% CI) (Elranatamab vs POM+DEX)	p-value
PFS – Naïve comparison	123	[redacted]	[redacted]
PFS – Unanchored MAIC	76	[redacted]	[redacted]
OS – Naïve comparison	123	[redacted]	[redacted]
OS – Unanchored MAIC	75	[redacted]	[redacted]

Key: CI, confidence interval; DEX, dexamethasone; ESS, estimated sample size; HR, hazard ratio; PFS, progression-free survival; POM, pomalidomide.

Figure 4. Kaplan–Meier of PFS for the unanchored MAIC: MagnetisMM-3 versus MM-003

Key: DEX, dexamethasone; PFS, progression-free survival; POM, pomalidomide; blue line shows unweighted Kaplan-Meier data for cohort A; red line show MAIC weighted Kaplan-Meir data for cohort A.

Figure 5. Kaplan–Meier of OS for the unanchored MAIC: MagnetisMM-3 versus MM-003

Key: DEX, dexamethasone; OS, overall survival; POM, pomalidomide; blue line shows unweighted Kaplan-Meier data for cohort A; red line show MAIC weighted Kaplan-Meir data for cohort A.

The results of the unadjusted direct comparison of MagnetisMM-3 versus the ECA study are summaried by the company in section B.2.9.2.2. Table 19 and Figures 20-22 are reproduced by the EAG as Table 10 and Figures 6-8. The results indicate that compared to POM+DEX elranatamab led to greater improvements in PFS and OS.

Table 10. Unadjusted direct comparison: MagnetisMM-3 versus ECA

		Description	Effect Estimate	95% Confidence Intervals	
				Lower Bound	Upper Bound
PFS (INV)	Unadjusted Analysis	**Cox Regression (HR)**			
		ECA	REF	-	-
		MagnetisMM-3	[redacted]	[redacted]	[redacted]
		RMST (Months)			
		Difference	[redacted]	[redacted]	[redacted]
		Schoenfeld Residual Test	[redacted]		
PFS (BICR)	Unadjusted Analysis	**Cox Regression (HR)**			
		ECA	REF	-	-
		MagnetisMM-3	[redacted]	[redacted]	[redacted]
		RMST (Months)			
		Difference	[redacted]	[redacted]	[redacted]
		Schoenfeld Residual Test	[redacted]		
OS	Unadjusted Analysis	**Cox Regression (HR)**			
		ECA	REF	-	-
		MagnetisMM-3	[redacted]	[redacted]	[redacted]
		RMST (Months)			
		Difference	[redacted]	[redacted]	[redacted]
		Schoenfeld Residual Test	[redacted]		

Key: BICR, blind independent central review; ECA, external control arm; HR, hazard ratio; INV, investigator; OS, overall survival; PFS, progression free survival; REF, reference; RMST, Restricted Mean Survival Time.
Source: Pfizer data on file, 2023.[55]

Figure 6. Kaplan–Meier of PFS assessed by investigator for the unadjusted direct comparison: MagnetisMM-3 versus ECA

Key: ECA, external control arm; PFS, progression free survival.
Source: Pfizer data on file, 2023.[55]

Figure 7. Kaplan–Meier of PFS assessed by BICR for the unadjusted direct comparison: MagnetisMM-3 versus ECA

Key: BICR, blind independent central review; ECA, external control arm; PFS, progression free survival.
Source: Pfizer data on file, 2023.[55]

Figure 8. Kaplan–Meier of OS for the unadjusted direct comparison: MagnetisMM-3 versus ECA

Key: ECA, external control arm; OS, overall survival.
Source: Pfizer data on file, 2023.[55]

Subgroup analyses

The company presents the pre-specified subgroup analyses of the MagnetisMM-3 Cohort A in Section B.2.7 and Appendix E of the CS. The EAG notes that the primary outcomes assessed in the MagnetisMM-3 study were ORR and CRR. Consequently, the subgroup analyses have been applied to these and not PFS and OS, which are the focus of this submission.

A consistent ORR benefit was observed across all subgroups at a median follow-up of 15 months (data cut-off: 14 March 2023). The ORRs were lower in patients with poorer prognostic features (extra medullary disease, penta-refractory disease, and Revised International Staging System (R-ISS) stage III disease) than in the rest of the Cohort A population but response rates remained favourable for these patients. The probability of maintaining the response at 15 months was 77.9% (95% confidence interval [CI]: 45.9–92.3) versus 70.6% (95% CI: 56.4–81.0) in patients with and without extramedullary disease; 63.8% (95% CI: 37.5–81.3) versus 74.6% (95% CI: 59.5–84.7) in patients with and without penta-refractory disease, and 76.3% (95% CI: 63.1–85.3) versus 26.7% (95% CI: 1.0–68.6) in patients with R-ISS stages I–II and III disease, respectively.

As a non-randomised cohort study it would have been possible to conduct the subgroup analyses for MagnetisMM-3 on PFS and OS. This may have been helpful to further understand the population characteristic effects for these more relevant outcomes for consideration with the indirect comparisons.

3.2.3 Health-related quality of life (HRQOL)

The company presents HRQOL data in section B.2.6.1.3 of the CS. HRQOL analyses were based on the patient reported outcomes (PRO) analysis set, which includes all patients in the safety analysis set who completed a baseline PRO assessment and ≥1 post-baseline PRO assessment. Patients in MagnetisMM-3 demonstrated overall improvements in quality of life based on disease-specific (EORTC QLQ-C30 and QLQ-MY20) and generic (EQ-5D-3L) HRQOL measures.

Improvements in global health status (GHS) and pain from baseline, measured by the EORTC QLQ-C30, were observed from Cycle 3 Day 1 (following an initial significant worsening in GHS scores) and Cycle 4 Day 1 respectively. GHS continued to improve through cycle 15 Day 1 (least square mean [LSM] change from baseline: [redacted][95% CI[redacted]), except for a transient non-significant decrease at Cycle 13 Day 1. The improvement in pain scores (LSM change from baseline of [redacted] [95% CI:[redacted]]) was maintained through Cycle 15 Day 1, except for a transient and non-significant increase at Cycle 9 Day 1 and Cycle 18 Day 1. The company reports a summary of the observed EORTC QLQ-C30 scores for all domains in Appendix M.3.1.5. Scores for physical functioning, fatigue, nausea/vomiting and appetite loss showed similar initial worsening in domains scores to GHS, followed by a return to baseline levels or improvement above baseline levels. Patients showed significant reductions in MM symptoms from Cycle 5 Day 1 based on the EORTC QLQ-MY20 disease symptom domain (LSM change from baseline of [redacted] [95% CI:[redacted]]) and this was maintained through Cycle 12 Day 1 and beyond.

Generic HRQOL based on the EQ-5D-3L showed transient and early non-significant worsening, followed by an improvement in scores starting at Cycle 4 Day 1 and becoming significantly greater than baseline at Cycle 11 Day 1, (LSM change from baseline of [redacted] [95% CI: [redacted]]) and Cycle 12 Day 1 ([redacted] [95% CI:[redacted]]). A similar trend was observed for the EQ-5D VAS, which showed an improvement in general HRQOL, following

an initial worsening, from Cycle 6 Day 1, with an LSM change from baseline of [redacted] (95% CI: [redacted]) at Cycle 15 day 1.

Patients' belief in the efficacy of their treatment, measured by the Patient Global Impression of Change (PGI-C), showed that approximately [redacted]% of patients reported their clinical status as either 'a little better' or 'much better' compared with baseline as early as Cycle 1 Day 15 and this increased to more than [redacted]% by Cycle 7 Day 1.

3.2.4 Adverse events

The company reports adverse events (AE) data for elranatamab from MagnetisMM-3 and MagnetisMM-1 in section B.2.10 of the CS.

The most commonly observed treatment-emergent adverse events (TEAEs) included:

cytokine release syndrome: 71 (57.7%) and 48 (87.3%) of patients in MagnetisMM-3 and MagnetisMM-1;

anaemia: 60 (48.8%) and 37 (67.3%) of patients in MagnetisMM-3 and MagnetisMM-1;

neutropenia: 60 (48.8%) and 41 (74.5%) of patients in MagnetisMM-3 and MagnetisMM-1*;*

diarrhoea: 52 (42.3%) and 22 (40.0%) of patients in MagnetisMM-3 and MagnetisMM-1;

fatigue: 45 (36.6%) and 23 (41.8%) of patients in MagnetisMM-3 and MagnetisMM-1;

lymphopenia: 33 (26.8%) and 29 (52.7%) of patients in MagnetisMM-3 and MagnetisMM-1;

thrombocytopenia: 38 (30.9%) and 28 (50.9%) of patients in MagnetisMM-3 and MagnetisMM-1; and

decreased appetite: 41 (33.3%) and 19 (34.5%) of patients in MagnetisMM-3 and MagnetisMM-1.

Treatment discontinuation of elranatamab due to TEAEs occurred in [redacted]% of patients in MagnetisMM-3. The most observed (occurring in ≥1% of patients) TEAEs leading to discontinuation included: *neutropenia* ([redacted]%), *septic shock* ([redacted]%) and *sepsis* ([redacted]%).

Dose interruption of elranatamab due to TEAEs occurred in 77.2% of patients. The most observed (occurring in ≥1% of patients) TEAEs leading to dose interruption included: *neutropenia* (15.4%), *asthenia* ([redacted]%), *CRS* ([redacted]%), *thrombocytopenia* ([redacted]%), *fatigue* ([redacted]%), *leukopenia* ([redacted]%), and *peripheral sensory neuropathy* ([redacted]%).[56, 57]

The EAG presents a summary of the serious adverse events (SAEs), deaths and treatment-related adverse events (TRAEs) for elranatamab observed in MagnetisMM-3 and

MagnetisMM-1 compared with the POM+DEX treatment arm of the MM-003 study in Table 11. The number of deaths, any SAE and proportions of patients experiencing individual TRAEs were broadly similar between the two groups with fewer patients in MagnetisMM-3 experiencing events compared with patients in MM-003. Death occurred in 44.7% of patients in MagnetisMM-3 and 48% of patients in MM-003. The primary cause of death was due to progression of MM in both studies (30.1% of patients in MagnetisMM-3 and 68% of patients in MM-003). Deaths related to study treatment occurred in [redacted]% and 4% of patients in MagnetisMM-3 and MM-003 respectively.

Adverse events of special interest

The company highlight *cytokine release syndrome (CRS)*, *Immune-effector cell-associated neurotoxicity syndrome (ICANS)*, and *infections* as adverse events of special interest associated with elranatamab therapy in MagnetisMM-3. CRS occurred in 57.7% of patients and [redacted]% of patients developed ICANS. No patients experienced Grade 3 or higher CRS or ICANS events and no patients permanently discontinued elranatamab treatment due to CRS or ICANS. The company reports that most CRS events were limited to step-up doses with [redacted]% of CRS events occurring with the first three doses and [redacted]% occurring with the 12/32 mg step-up doses. The median (range) time to onset of ICANS following the most recent dose of elranatamab was 2.5 days (1.0, 4.0) for patients who received the 12/32 mg step-up regimen and all ICANS events resolved after a median (range) of 2.0 days (1.0, 6.0). Infections were reported in 69.9% of patients, of which 39.8% of patients experienced a Grade 3/4 infection and 8 (6.5%) patients experienced a Grade 5 infection. Grade 5 infections included: COVID-19 pneumonia (n = 2), septic shock (n = 3), adenoviral hepatitis (n = 1), adenovirus infection (n = 1), pneumonia adenoviral (n = 1), pneumonia pseudomonal (n = 1), and failure to thrive (n = 1). Treatment-related infections were reported in [redacted]% of patients and the company highlights the most commonly reported of these: pneumonia ([redacted]%), upper respiratory tract infection ([redacted]%), COVID-19 pneumonia ([redacted]%), and sinusitis ([redacted]%). Other reported infections included urinary tract infection (9.8%), sepsis (6.5%), bacteremia (5.7%) and cytomegalovirus infection reactivation (5.7%).[56]

Table 11. Summary of SAEs, deaths and TRAEs in MagnetisMM-3 and MM-003

Adverse event categories	MagnetisMM-3 Cohort A n (%) (n=123)	MagnetisMM-1 Elranatamab SC 215ug/kg to 1000 ug/kg Part 1.1 and Part 2A Total (n = 55)	MM-003 POM+DEX (n=300)
Serious adverse events (≥2% of patients)			
Any	[redacted]	[redacted]	183 (61)
COVID-19 pneumonia	[redacted]	[redacted]	NR
CRS	[redacted]	[redacted]	NR
Pneumonia	[redacted]	[redacted]	NR
Sepsis	[redacted]	[redacted]	NR
Anaemia	[redacted]	[redacted]	NR
COVID-19	[redacted]	[redacted]	NR
Pneumocystis jirovecii pneumonia	[redacted]	[redacted]	NR
Septic shock	[redacted]	[redacted]	NR
Acute kidney injury	[redacted]	[redacted]	NR
Febrile neutropenia	[redacted]	[redacted]	NR
Urinary tract infection	[redacted]	[redacted]	NR
Bacteraemia	[redacted]	[redacted]	NR
Pneumonia bacterial	[redacted]	[redacted]	NR
Pyrexia	[redacted]	[redacted]	NR
COVID-19	[redacted]	[redacted]	NR
Deaths			
Any	55 (44.7)	[redacted]	144 (48)
Deaths related to study treatment	[redacted]	[redacted]	11 (4)

Treatment-related adverse events (TEAEs) (≥5% of patients)	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	Grade 5
Any TRAE	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Cytokine release syndrome	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Neutropenia	[redacted]	[redacted]	[redacted]	NR	152 (51)	143 (48)	-
Injection site reaction	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Anaemia	[redacted]	[redacted]	[redacted]	NR	157 (52)	99 (33)	-
Lymphopenia	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Fatigue	[redacted]	[redacted]	[redacted]	NR	103 (34)	16 (5)	
Thrombocytopenia	[redacted]	[redacted]	[redacted]	NR	90 (30)	67 (22)	-
Decreased appetite	[redacted]	[redacted]	[redacted]	NR	36 (12)	2 (1)	-
Diarrhoea	[redacted]	[redacted]	[redacted]	NR	66 (22)	3 (1)	
Nausea	[redacted]	[redacted]	[redacted]	NR	45 (15)	2 (1)	-
Dry skin	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Asthenia	[redacted]	[redacted]	[redacted]	NR	48 (16)	11 (4)	-
Headache	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Leukopenia	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Epistaxis	[redacted]	[redacted]	[redacted]	NR	28 (9)	3 (1)	-
Hypercalcaemia	[redacted]	[redacted]	[redacted]	NR	21 (7)	13 (4)	-
Muscle weakness	[redacted]	[redacted]	[redacted]	NR	11 (4)	3 (1)	-

Source Lesokhin et al 2023;[56] Bahlis et al 2023;[53] Tables 9-11 in the company's clarification response letter; Miguel et al. 2013[54]

Intravenous immunoglobulin (IVIG) therapy

The company report that 53 (43.1%) of MagnetisMM-3 patients in Cohort A received IVIG therapy and that [redacted] ([redacted]%) of these patients received IVIG as prophylaxis but did not go on to develop a bacterial infection.[56] A further [redacted] patients received IVIG as treatment for COVID-19 but did not develop a bacterial infection. Overall, [redacted] ([redacted]%) patients received IVIG due to a bacterial infection or developed bacterial infection whilst on IVIG for a different indication. The median duration of IVIG use was [redacted] months and the mean was

[redacted]months. Given that UK NHS patients cannot currently receive prophylactic IVIG therapy,[42] the company have used the estimate of [redacted]% within their model as this is assumed to reflect the proportion of UK patients that would be eligible for IVIG usage in current practice if prophylactic treatment were available. This is discussed further by the EAG in chapter 4.

The EAG clinical advisor believes the adverse events observed in MagnetisMM-3 and MagnetisMM-1 are in line with the known toxicity profile of elranatamab. The EAG notes that NHS patients are likely to experience a higher rate of infections than that observed for patients in MagnetisMM-3 because prophylactic IVIG therapy is not currently routinely available in the NHS. The company states in the CS that the high infection rate observed in MagnetisMM-3 could be due to the timing of the trial coinciding with the COVID-19 pandemic and MM patients being at increased risk of COVID-19 infection and severe disease.[58] *Whilst this is possible and explains the number of COVID-19 and COVID-19 pneumonia events in the trial, the EAG clinical advisor notes that the other reported respiratory infections are associated with elranatamab use, independently of COVID-19.*

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The main comparison in the company's submission is between MagnetisMM-3 and MM-003. This needed to be an indirect comparison since while the company had access to patient level data for MagnetisMM-3 they only had aggregated data for MM-003. The EAG agrees with the company that the MM-003 POM-DEX treatment arm is the better cohort of the MM series to compare with the MagnetisMM-3 Cohort A. *However, the EAG clinical advisor noted that comparison with studies assessing lenalidomide plus dexamethasone (as suggested in the original scope) might have been an option at the 3rd line of treatment although they likely to have been exposed and not TCR.* The other treatments in the scope were otherwise agreed not to be useful for this submission.

The company also identified an external control arm (ECA). This was a small sample ([redacted]) of real-world, patient-level data extracted from the Arcturis UK dataset (5,500 MM patients from four National Health Service (NHS) centres in the UK).

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Had the ECA included a larger sample size this would have improved the precision of all treatment effect estimates especially as the data were available at individual level. As such the company correctly treat this comparison further only as a scenario within the economic analysis beyond the basic descriptions all of which are comparable to the main indirect comparison findings. During the factual correction process the company provided additional timelines regarding the MM-003 participants in the ECA used for the direct comparison suggesting they would not have overlapped with those in the indirect comparison that used summaries from the MM-003 study but later on.

Considering the main indirect comparisons, there are some population differences between the MagnetisMM-3 elranatamab cohort and the POM+DEX cohort in MM-003, as described earlier. These notably include differences in the ECOG categories proportions (although this may be more in favour for elranatamab having less severe patients) and that MMM-003 had less refractory and easier to treat patients than those enrolled in MagnetisMM-3. As such these two may have had the effect of cancelling each other out in terms of benefit to either of the treatments.

The unanchored MAIC is probably the best approach given that there is no control group in the MagnetisMM-3 cohort and that only MM-003 aggregated data were available. Although the unanchored MAIC is the best possible method to be used, the small effective sample size relative to the original sample size indicates the weights are highly variable and the estimates might be unstable.[59]

It was noted by the EAG that the definition of progression and overall survival is not the same in MagnetisMM-3 and MM-003 trials. In MagnetisMM-3, OS and PFS are calculated from the date of the first dose, while in MM-003 they are calculated from randomisation. Although the EAG's clinical advisor believes that this time difference is unlikely to impact findings, relevant data were not provided in the original submission to allow a proper comparison.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None.

3.6 Conclusions of the clinical effectiveness section

Overall, the EAG agree that the company have carried out sensible comparison analyses and that there is evidence of benefit of elranatamab over the POM+DEX combination for this patient population for PFS and OS; however, the magnitude of effect, and how sustained this is, is uncertain. There are some differences in the comparator populations. For the direct comparison the analyses were based on a very small sample of patients, and it is likely that these patients may also have been included in the indirect comparison analyses. For the indirect comparison, the comparator population of MM-003 differs in that there is not a targeted line of treatment, and the population is not restricted to the TCR MM group. Furthermore, the company's attempt to match the MagnetisMM-3 data to the MM-003 data reduced the effective sample considerably. Therefore, we should be cautious as the estimates of the analyses may be unstable. The other major limitation is the lack of maturity of the MagnetisMM-3 survival data (OS and PFS). The heavy censoring of the Kaplan-Meier data around 15 months, may have impacted the HRs and any longer-term efficacy will be uncertain.

The EAG has inspected the safety data for MagnetisMM-3 and MagnetisMM-1 and has no concerns about the rates of reported AEs or SAEs in the trials. Where comparable data were available, AE rates for elranatamab were broadly comparable to the rates observed for the POM+DEX arm of the MM-003 study.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

Systematic literature reviews (SLR) of economic evaluations, HSUV and cost and health care resource use were conducted by the company as detailed in section B.3.1 and appendices G, H and I of their submission. The search was undertaken on 7 November 2020, with six further updates repeated up until 30 May 2023. The original search was based on a broader, global purpose to identify published cost-effectiveness studies for elranatamab and relevant comparators in people with RRMM. After application of the final selection criteria to match decision problem addressed in the submission, there appears to have been 12 published studies identified for inclusion in the review (Company submission, Appendix G, Figure 6 and Table 17). However, the main submission document refers to only seven being seven unique published cost-effectiveness studies that met the inclusion criteria relevant to this submission. The company concluded that there were no cost-effectiveness analyses for patients with RRMM who have received at least three prior treatments (including a PI, an IMiD and an anti-CD38 mAb) and have demonstrated disease progression on the last therapy.

The EAG noted that the company have undertaken a thorough review of the published economic evidence of relevance to this appraisal. However, there appears to be a discrepancy in the number of studies reported in Appendix G and the number of relevant studies reported in the company's main submission document (Document B). The EAG suspect that the seven referred to in the company's summary are those identified from electronic database searches, but there are another five relevant studies presented in the appendix that were identified through other means, including searches of HTA agency websites (including NICE). The company pay close attention to the models from previous NICE submissions of relevance to the current appraisal, including two that were identified in their SLR (TA427 and TA783),[38, 39] and three additional appraisals in relapsed and refractory MM (TA658, TA870 and TA380)[36, 37, 40]. It seems generally appropriate that these studies have been selected by the company to help inform model development and assumptions for the current appraisal. Nevertheless, the validity of prior assumptions still needs to be considered in the context of the current submission and evidence.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with the reference case
Perspective on costs	NHS and PSS	Aligns with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with reference case
Synthesis of evidence on health effects	Based on systematic review	Aligns with reference case but limited evidence available to inform comparative efficacy and immature data for extrapolation.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Aligns with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with reference case but limited evidence on post progression quality of life.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with reference case. A severity weighting of 1.2 has been applied to QALYs gained.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Aligns with reference case with some uncertainty around certain values and assumptions.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with reference case
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company have submitted a partitioned survival model with four health states: Progression-free (PF) on treatment, PF off treatment, Progressed disease (PD), and Dead.

For the comparator, pomalidomide plus dexamethasone (POM+DEX), the PFS and OS curves from the MM-003 trial, and an assumption about the relationship between PFS and time to treatment discontinuation (TTD), are used to partition the cohort between the model health states.[54] For elranatamab, the company fit parametric curves to MM-003 adjusted Kaplan Meier data from cohort A of the MagnetisMM-3 trial (see figures 4 and 5 above). This is how the MAIC feeds into the economic model. Time on treatment with elranatamab is modelled by fitting parametric curves directly to the TTD data from the MagnetisMM-3 trial (i.e., without adjustment to the covariate distribution of MM-003). Given the immaturity of data, adjustments are made to selected curves to ensure extrapolated hazards to not fall below an excess all-cause mortality rate; determined by the application of time dependent standardised mortality ratios (SMRs), for multiple myeloma, to age and sex matched general population mortality.

The company acknowledge a complication resulting from the current shape of the OS and PFS Kaplan Meier curves for MagnetisMM-3, which appear to converge on one another in the tails of the distributions (Figure 9). The company put this down to "the greater number of events in the PFS curve which, unlike the OS Kaplan–Meier curve, has had time to plateau during trial follow-up." This results in the selected parametric curves crossing shortly into the extrapolation period. The company argue that the PFS data is currently more reliable due to the higher number of observed events, and therefore they give priority to the selected PFS extrapolation by not allowing OS to converge on it but not fall below it. They acknowledge that this goes against the more standard practice of giving priority to the extrapolation of OS, and ensuring PFS does not cross above it.

Figure 9 Elranatamab PFS and OS Kaplan–Meier curve and 95% CI from MagnetisMM-3 (Source: Figure 35 of the company submission, Document B).

The EAG are broadly satisfied with company's decision to use a PartSA model but have reservations about several structure assumptions and parameter selections used to determine the state occupancy:

- *The approach around elranatamab curve fitting results in an implausible base case whereby a negligible proportion of the cohort ([redacted]) resides in the progressive disease state beyond [redacted] years.*
- *The PartSA approach does not explicitly capture new transitions to the progressive disease state and the company's approximating approach will lead to underestimation of this, which in turn will lead to underestimation of subsequent treatment costs, particularly in the elranatamab arm; i.e. it suggests no new progression events beyond [redacted] in the model.*

These issues are discussed further in Section 4.2.6 below.

4.2.3 Population

Compared to the final scope, which defines the population as "*Patients with relapsed or refractory multiple myeloma after at least 3 prior therapies*", the company define a more specific target population as "*Adult patients with relapsed and refractory multiple myeloma,*

who have received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy" (Company submission, document B, Table 1). This aligns with the anticipated marketing authorisation and is more closely aligned with the MagnetisMM-3 study inclusion criteria which defined a triple class refractory (TCR) cohort. The company acknowledge that their target indication is still broader than the MagnetisMM-3 study population, in that it will include a proportion of patients who are considered triple class exposed (TCE) but not TCR as per the inclusion criteria for MagnetisMM-3. They argue, however, that most patients who meet their proposed positioning in the NHS will in fact be TCR. This, they say, is backed up by clinical experts and is due to the fact that multi-drug combination therapies are now used early in the treatment pathway for MM, and patients are treated to progression from second line of therapy onwards. They elaborate in section B.1.3.3.6 of their submission how patients (depending on whether they are transplant eligible or ineligible) can become TCR in the NHS treatment pathway by their third, fourth or fifth line of therapy. They do not, however, spell out how patients can become eligible for elranatamab according to the wording of their indication.

Following a clarification question from the EAG, the company confirmed that their proposed positioning will include some patients who are TCE but not yet TCR. The EAG also asked the company to comment on what percentage of patients they would expect to be TCR in the broader cohort of patients meeting their proposed positioning in routine NHS clinical practice. The company noted that this is difficult to determine based on the routine data but came up with an estimate based on clinical expert opinion, that 100% of patients are expected to be TCE by their fourth line of therapy, with up to 85% of these being TCR (Company response to clarification question A3).

The EAG have some concern regarding the wording of the proposed target population, and how it will result in a heterogenous group of patients at different lines of treatment being considered eligible for elranatamab (Company submission, Figure 2). Patients meeting the inclusion criteria for treatment may be refractory to one or two classes of treatment, rather than three, and we do not have an accurate assessment of the proportion(s) this might apply to, and/or what their alternative treatment options might be. The company argue that these proportions are likely to be small given the shift in treatment landscape towards the use of treat to progression combination therapies early in the pathway. The EAG accept the

company's assertion that most of the proposed target population will be TCR given the dominant treatment pathways. And the EAGs clinical advisor suggested that the those who are TCE would have similarly limited treatment options available to them as those who are TCR, as there would be reluctance to rechallenge with previously used treatments which may have been stopped due to toxicity. There remains and evidence gap, however, quantifying the proportion of potentially eligible patients in the NHS that will fall under different lines of treatment and different classes of refractoriness using UK routinely collected health data. The company described how they carried out analysis using the national Systemic Anti-Cancer Therapy (SACT) dataset to examine the characteristics of patients diagnosed with MM in England, their treatment patterns, and clinical outcomes (as reported in CS. Document B). They note that this was limited by the lack of definitions and data for refractoriness in SACT and the unavailability of data on CDF drugs and correspondingly, patients who received CDF drugs. Therefore, the company could only reliably undertake treatment and outcome analyses based on regimen and class exposure status and line of therapy (excluding CDF drugs). As a result, the company explored feedback from clinicians."

4.2.4 Interventions and comparators

The intervention is elranatamab, as per its anticipated marketing authorisation. It is to be delivered subcutaneously once per week after a two-dose step-up regimen in the first week as described in section B.3.2.3 of the company submission. Premedication is to be administered prior to the first three doses, and it is stated in the draft SmPC that patients should be monitored for signs and symptoms of ICANS and CRS and instructed to remain in the proximity of a healthcare facility for 48 hours after administration of the two step-up doses. The SmPC will also state that after at least 24 weeks, if patients have achieved a response, they should switch to Q2W dosing. The company note that this is slightly more permissive of dose switching compared to the MagnetisMM-3 protocol - which only allowed dose switching for patients who received at least 24 weeks of once weekly dosing if they had a partial response or better which persisted for at least 2 months. The company also describe a proposed stopping rule for elranatamab, which they have included in their base case. This is applied after [redacted]. It is not based on observed data and is not mentioned in the draft SmPC.

The EAG notes the discrepancy regarding the MHRA approved SMPC less stringent criteria for switching to the Q2W dosing, compared with the criteria in the MM-003 trial protocol. The company suggest that as a result their modelling assumptions, based on data from MagnetisMM-3, may overestimate acquisition costs compared to what can be expected in routine clinical practice, where they suggest more patients may step down treatment earlier. . There is some uncertainty about the appropriateness and acceptability of the proposed stopping rule given the lack of available long-term data for elranatamab. These issues are considered further in terms of their impact on costs (see section 4.2.8 below).

In terms of comparators, the company included only one: POM + DEX. The company have provided rationale for excluding several comparators identified in the final scope.

The EAGs clinical expert advisor was generally supportive of the rationale for excluding several of the comparators listed in the scope. He was less clear on the justification for excluding ixazomib plus lenalidomide and dexamethasone, as this could be a relevant treatment option for a minority of patients who become eligible for elranatamab without being TCR. The EAG's main concern with comparator choice, relates to the population and the unknown percentage of patients who meet the elranatamab indication but may be refractory to only one or two classes of treatment. These patients could then be potentially eligible for other comparators which have not been included in the analysis. Nevertheless, the EAG accept that such patients will be in a minority and even if not TCR, some will be intolerant to the classes they have been exposed to previously and so not likely to receive them again.

4.2.5 Perspective, time horizon and discounting

The perspective on costs is that of the NHS and personal social services. The perspective on benefits is health benefits (QALYs) accruing to patients. The chosen time horizon of the model is 25 years, which the company state is required to capture the costs and benefits accruing to a small fraction of patients projected to survive for that long, which they say is in line with clinical expert opinion. Shorter time horizons of 20 and 15 years were explored by the company in scenario analysis. The model uses a constant one-week cycle length, without half cycle-correction, and discounting is applied in line with the NICE reference case.

The EAG is generally satisfied that the company's modelling perspective. The time horizon is sufficiently long to capture all important differences in costs and benefits between the alternatives being compared. As the company point out, the 25 years is longer than the time horizon used in previous appraisals of multiple myeloma treatment in populations that have been exposed to three prior treatments. It also appears that clinical expert advice given to the company suggested that a 15-20 year time horizon would be more appropriate for this population, given the incurable nature of the disease. Related to this, the EAG has concerns that the chosen approach to extrapolation is overly optimistic, in that it results in a non-negligible proportion surviving beyond 20 years following treatment with elranatamab.

4.2.6 Treatment effectiveness and extrapolation

As discussed in section 3.2.2 and 3.4 above, the company performed an unanchored MAIC to compare PFS and OS between elranatamab and POM + DEX. In this analysis, the individual patient data (IPD) from MagnetisMM-3 were weighted to match aggregate baseline data from the MM-003 trial. This formed the basis of the comparative efficacy data feeding into the model base case. A further secondary analysis used real world PFS and OS data on [redacted] patients from the Arcturis UK dataset – covering four NHS centres (referred to as the external control arm (ECA) study).

For PFS and OS, the company have fitted independent parametric curves to the KM data from MM-003 (POM + DEX), and to the MAIC weighted KM data from MagnetisMM-3 (elranatamab). Their preference for independently fitted parametric curves, rather than the application of hazard ratios from the unanchored MAIC, is down to the company's rejection of the proportional hazards assumption based on consideration of log cumulative hazard plots and Schoenfeld residual plots (Company submission, appendix O). The company also outline their concerns with the MAIC relating to differences in the populations between the trials. This includes the fact that patients in MM-003 were not triple class refractory (no patients were anti-CD38 mAb exposed), and differences in the proportion with prior exposure to pomalidomide (81% in MagnetisMM-3 versus none in MM-003). There were also several other important prognostic values (PVs) and potential effect modifiers (EMs) that could not be controlled for due to these not being reported in MM-003.

The EAG acknowledges the limitations of the MAIC and agree with the company that known differences in the populations between MagnetisMM-3 and MM-003 are more likely to bias

comparative treatment effect estimates against elranatamab. However, the data for elranatamab are immature in the context of the model time horizon, and there is scope for independently fitted of curves to overestimate the magnitude of PFS and OS benefit for elranatamab versus POM+DEX. In this respect, it may be useful to consider the impact of a more conservative scenario that models PFS and OS for elranatamab by applying the hazard ratios from the MAIC to the reference curves for POM + DEX.

Progression free survival and overall survival

The company submission, sections B.3.3.2 to B.3.3.4, describes in detail the process of fitting and selecting parametric curves for PFS and OS using the Kalan Meier (KM) data from cohort A of the MagnetisMM-3 trial, and digitised KM data from the MM-003 trial. However, as indicated above, the company's base case in fact relies on parametric curves fitted to MM-003 weighted KM data from MagnetisMM-3 (elranatamab). These curves, their AiC and BiC statistics, and their projected survival landmarks are all provided in Appendix O of the company submission.

The company's approach is understandable, but emphasis was placed on choosing curves based on their fit to the unadjusted cohort A data, when in fact the base case relies on curves fitted to the MM-003 weighted KM data. The parametric curves fitted to the MM-003 weighted data are broadly similar to those fitted to the raw cohort A data, but in general provide slightly more pessimistic survival projections. The rankings of statistical fit for different parametric distributions also differ to an extent.

PFS

With respect to PFS, the company justify their choice of generalised gamma curve based on consideration of: Statistical fit (assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC); visual fit to the observed Kaplan–Meier data; and clinical plausibility of the long-term extrapolation beyond the extent of the Kaplan–Meier data. The latter criterion is assessed before and after an adjustment to ensure the extrapolated hazards for PFS (and OS) do not fall below an excess mortality rate informed by applying time varying SMRs to general population mortality (see section on adjustments made to elranatamab PFS and OS below).

The company point to the preferred statistical and visual fit of the generalised gamma curve to the observed cohort A PFS data. They acknowledge that the curve provides an implausibly optimistic extrapolation of PFS prior to adjustment for excess (SMR adjusted) all-cause mortality, but then claim that the curve's 5 and 10 year survival projections ([redacted]% and [redacted]%, respectively) are consistent with those suggested by clinical experts (10% to 20% at 5 years, and less than 15% at 10 years) after the SMR adjustment.

The EAG note that the generalised gamma curve does also provide the best statistical fit and a similar extrapolation when fitted to the MM-003 adjusted KM data from MagnetisMM-3 but note that the survival projections are very slightly lower at 5- and 10-years following adjustment for elevated all-cause mortality ([redacted] and [redacted], respectively). Figures 10 and 11 below show the alternative curves fitted to MM-003 weighted PFS data, with and without adjustment for excess mortality. In the EAG's opinion, it is problematic that a PFS curve has been selected that needs to be capped with projected hazards of all-cause mortality to produce plausible 5 and 10 year PFS projections for this indication. The PFS data from MagnetisMM-3 are immature, with heavy censoring evident in the tail of the KM curve. The number at risk drops from [redacted] between 14 and 18 months follow-up (from [redacted] when weighted), a period in which no further events were observed. The company appear to be interpreting this as evidence of a plateau emerging in the PFS curve. The EAG believe that too much emphasis is being placed on this when selecting a PFS curve. The data are immature, and the observed flattening of the curve may be a chance occurrence due to the heavy censoring and small numbers left at risk in the tail of the KM curve. Long-term follow-up is clearly required to confirm the shape of the PFS distribution in a population where treatment is not expected to be curative. The EAG, therefore, suggest that scenarios using the more pessimistic extrapolations of PFS based on the gamma or Weibull curves should be considered. These provide extrapolations that appear consistent with the 5 and 10 year survival landmark ranges suggested by clinical experts, without requiring a post-hoc adjustment for excess mortality.

Figure 10 Standard parametric fits of PFS, elranatamab (Elranatamab reweighted MAIC curve) – unadjusted for excess mortality (Source: Figure 20, company submission, Appendix O)

Figure 11 Standard parametric fits of PFS, elranatamab (Elranatamab reweighted MAIC curve) – adjusted for excess mortality (Source: Figure 21, company submission, Appendix O).

PFS for POM + DEX is based on parametric curves fitted to the digitised KM data from MM-003. Of the standard parametric curves considered, the company have selected the generalised gamma for their base case, based on consideration of statistical and visual fit to the observed KM data, consistency with the curve selected for elranatamab, and projections of 2 and 5 year PFS which they state are consistent with clinical expert opinion (see Company submission, document B, section B.3.3.3.1).

The EAG agree that the chosen generalized gamma curve provides a good statistical and visual fit to the observed KM data and that it provides a plausible extrapolation in line with clinical opinion. Note, however, that there appears to be an error in the company's reporting of the PFS curves for POM + DEX in the company submission document (Figures 41 and 42), whereby TTD (adjusted for excess mortality) rather than PFS is shown for some of the curves. The EAG has provided the correct unadjusted and adjusted PFS curves for POM + DEX below (Figure 12 and figure 12). The company are applying the generalised gamma adjusted for excess mortality (figure 12) in their base case. Note, the excess mortality adjustment has no bearing on the generalised gamma PFS curve for POM + DEX. The log-logistic curve, ranked first on statistical fit, also provides a plausible more optimistic extrapolation of PFS for POM + DEX. The gamma, ranked 4th on statistical fit, provides a more pessimistic extrapolation.

Figure 12 Standard parametric fits of PFS, POM+DEX (MM-003 parametric fits) – unadjusted for excess mortality (3 -year time horizon) – Source: Company's economic model

Figure 13 Standard parametric fits of PFS, POM+DEX (MM-003 parametric fits) – adjusted for excess mortality (3 -year time horizon)

Overall survival

For overall survival (base case), the company have fitted standard parametric curves to the MM-003 MAIC weighted OS data from MagnetisMM-3. The fitted curves can be found in Appendix O of the company submission. The preferred parametric functional form for OS, however, appears to have been chosen based on clinical plausibility and consideration of fit to the unadjusted cohort A KM data (Company submission, section B.3.3.2.2). Based on consideration of AiC and BiC, the company suggest that all the curves have similar statistical fit to the observed data; Although there is an almost 6 point difference between the curves with lowest and highest BiC (exponential and generalised gamma, respectively). The company suggest, however, that the generalised gamma curve provides the best visual fit to the observed KM data and hazards (Company submission, document B, Figure 33). Considering the extrapolations, the company rule out the exponential, Weibull and gamma distributions as providing implausibly low projections of OS at 10 years, but acknowledge the other curves provide unrealistically optimistic OS projections over the long-term. They refer to clinical opinion suggesting that 3% ten-year survival, based on the exponential fit, is overly harsh, but that 17% ten year OS, based on the generalised gamma, is not implausible. On this basis, the company choose the generalised gamma, but apply further adjustments to ensure consistency with SMR adjusted all-cause mortality and extrapolated PFS (discussed in section B.3.3.2.3 of their submission document).

The EAG agree that the differences in AiC are small between the alternative curves, but the generalised gamma is in fact ranked lowest on BiC (see company submission, Table 25), with a value that is nearly 6 points greater than the exponential (ranked 2nd on AiC/BiC combined) and approximately 5 points greater than the lognormal curve (ranked 1st on AiC/BiC combined). This same pattern is more pronounced when considering the curves fitted to the MM-003 reweighted data (Figure 14, Table 13 below). On these grounds, it could be argued that these alternative curves provide a better statistical fit to the observed data, which forms part of the justification for curve selection.

With respect to extrapolations, the EAG find it problematic that the chosen curve provides implausibly high OS in the long-run without further adjustment but acknowledges that this is a reflection of the immaturity of the MagnetisMM-3 data. It acknowledges that the exponential, Weibull and gamma provide pessimistic extrapolations of OS, but there are no other curves that provide a middle ground between the company preferred generalised

gamma and these more pessimistic options. It may also be noted that the generalised gamma curve does provide a less optimistic extrapolation of OS when fitted to the MM-003 weighted data from MagnetisMM-3, as per the company base case. The MM-003 weighted curves, with adjustment for excess mortality, as used in the company base case, are provided as Figure 15 below.

Figure 14 Standard parametric fits of OS, elranatamab (Elranatamab reweighted MAIC curve) – unadjusted for excess mortality (Source: Figure 22, Appendix O to company submission, document B).

Table 13: AIC and BIC statistics of the standard parametric fits of OS, elranatamab (Elranatamab reweighted MAIC curve) (Source: Table 61, Appendix O to Company submission, document B).

Parametric model	AIC	BIC	Average	Rank
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

[redacted]

Figure 15 Standard parametric fits of OS, elranatamab (Elranatamab reweighted MAIC curve) – adjusted for excess mortality (Source: Figure 23, Appendix O to company submission, document B).

Regarding OS for POM+DEX, the data are relatively mature compared to the elranatamab OS data, and standard parametric curves have been fitted (company submission, Document B, Figures 43 and 44). The company have argued that alternative curves have a similar statistical fit, based on small differences in AiC and BiC. They go on to select the generalised

gamma, citing consistency with the curve selected for elranatamab OS, and clinically plausible extrapolations as their reason.

The company's justification of the generalised gamma appears quite limited, but the selected curve does appear to provide a reasonable visual fit to the observed data and provides a middle ground in terms of extrapolated survival landmarks. The EAG could not find the clinical expert opinion on the expected survival of patients treated with POM + DEX in the validation report referred to by the company, but have consulted their own clinical expert on this.[42] He was of the opinion that it offered a reasonable extrapolation in line with expectations.

Adjustments made to elranatamab PFS and OS

As indicated in the sections above, given the immaturity of the KM data from which to extrapolate, the company have adjusted all their PFS and OS curves for excess mortality in multiple myeloma. This is done by ensuring extrapolated hazards do not fall below an elevated all-cause mortality rate, derived by applying standardised mortality ratios to UK age/sex matched general population all-cause mortality. The SMRs associated with RRMM were derived, following a targeted literature review, from a study by Giri et al.[60] This study reports SMRs for all-cause mortality for a cohort of 1,906 MM patients who had survived to two years following autologous peripheral blood stem cell transplantation (aPBSCT). SMRs were calculated against annual mortality rates for the age/sex matched US general population. The median follow-up period was 9.2 years for the cohort. Overall, the SMR over follow-up was 5.27 (95% CI 4.9-5.65), but the study found the SMR declined with follow-up time, and by 10 years had reached 1 (95% CI 0.85-1016). The company apply these time dependent SMRs to UK age/sex matched general population mortality in their model base case, to cap extrapolated OS and PFS. This ultimately allows extrapolated PFS and OS to fall equal to general population mortality for a fraction of the elranatamab cohort. – suggesting a cure.

The EAG have reservations about the application of these SMRs to the cohort of patients meeting the company's positioning for elranatamab. The population of the company's positioning are expected to have either progressed multiple times following a SCT or have not been eligible for SCT and progressed multiple times. The majority are expected to be triple class refractory. This population does not align with the cohort studied by Giri et al. and so the derived SMRs may not be applicable. Based on advice from its clinical expert, the

EAG believe it is questionable that a fraction of the TCR RRMM cohort will achieve a mortality hazard that is the same as the general population.

The further adjustment made to the elranatamab curves is to address the issue of fitted OS and PFS curves crossing. As seen in Figure 37 of the CS, this would occur early during the extrapolation period without adjustment. To overcome this, the company give priority to the excess mortality adjusted PFS curve, and don't allow the extrapolated hazard of mortality to exceed the extrapolated hazard of progression or death prior to progression. This happens from the point the curves would otherwise cross, which is at approximately [redacted] in the company base case. This allows the curves to quickly converge but never cross. It also generates a more optimistic extrapolation of OS than otherwise suggested by the fitted OS generalised gamma curve adjusted for excess mortality.

The EAG find it problematic that precedence if given to the PFS curve over the OS curve in extrapolation. The EAGs clinical expert advised that the company's extrapolated OS generalised gamma curve, adjusted for excess mortality, already provides an optimistic extrapolation of OS, projecting [redacted] survival at [redacted] years. This increases to [redacted] survival at [redacted] years and [redacted] survival at [redacted] years when fixed to PFS in the model cohort trace calculations (Figure 16).

It is also problematic that the hazards of PFS and OS should be the same and set equal to SMR adjusted all-cause mortality from so early in the model time horizon [redacted]). This is unrealistic, and essentially infers a single curve being used to model PFS and all-cause mortality, with a negligible proportion in the PD state from [redacted], no one progressing, and everyone dying prior to progression. The fraction that survives in the model to 10 years (~[redacted]), essentially faces the risk of age/sex matched general population mortality and are cured with respect to their survival outlook.

Figure 16 Model based extrapolation of PFS (blue) and OS (orange) compared to company's selected OS generalised gamma curve adjusted for excess mortality (black dashed) – adapted from the company model.

Time to treatment discontinuation

The company fitted parametric curves to the time to treatment discontinuation (TTD) data from Cohort A of MagnetisMM-3 and used this to partition the cohort between on and off-treatment in the progression free state. The Kaplan Meier data for TTD falls below the PFS data, reflecting the fact that patients are treated to progression but can stop treatment for other reasons such as adverse events or patient/physician choice. Figure 17 below shows the KM curves for PFS and TTD plotted on the same graph, together with the preferred generalised gamma curve for PFS (unadjusted and adjusted for excess mortality) and the alternative TTD curves. The company note that of [redacted] patients who had discontinued treatment by the 14 March 2023 data cut, [redacted] remained progression free. They state that these patients achieved an enduring treatment effect despite being off treatment. They suggest that this results in a gap between TTD and PFS that is greater than normally expected in MM trials (Figure 17).

The EAG acknowledge that this explanation is possible, but it is also uncertain with the current limited duration of follow-up. Further follow-up is required to determine how long this gap between TTD and PFS persist. It is possible that the impact of higher discontinuation rates will be seen in the form of increasing hazards of progression and convergence of the curves with longer follow-up of the cohort.

Figure 17 Standard parametric fits of TTD, elranatamab (MagnetisMM-3 15-month data-cut) – unadjusted for excess mortality (3-year time horizon). Also showing MM-003 weighted PFS KM data and preferred generalised gamma curve (unadjusted and adjusted for excess mortality) Adapted from Figure 49 of the company submission and the company's economic model

In terms of the curves fitted to the TTD data, the company have selected the log-normal as having the best statistical and visual fit to the observed data. The curve is further adjusted, to ensure the hazard of discontinuing treatment is never below the hazard of SMR adjusted all-cause mortality, but this doesn't start to have an impact until after [redacted] in the model, when [redacted] of the cohort remain on treatment. The company make a further argument to include a treatment stopping rule in the model at [redacted], which they justify on grounds of balancing the long-term risks of remaining on treatment with ongoing efficacy. This is

applied in the cost calculations of the model, whereby no further treatment costs are applied for elranatamab from [redacted].

The EAG have some concerns regarding the validity of the company's assumed stopping rule given the lack of longer-term experience with elranatamab. It is also uncertain what impact this might have on subsequent extrapolated PFS. This cannot be addressed without substantially longer follow-up of Cohort A.

The company state that there is a lack of published data on TTD for POM + DEX from the MM-003 trial, noting that only the median was reported in the trial publication.[61] Therefore, they model TTD for POM + DEX using the ratio between the median TTD and median PFS reported by San Miguel et al.[61] This gives them a multiplier of 1.18 (=4.7/4), which is applied as hazard ratio to the POM + DEX PFS curve, to approximate a TTD curve that lies above PFS.

The EAG believe it is implausible that treatment with POM + DEX continues systematically beyond disease progression. There appears to be a misinterpretation underpinning the company's calculated ratio of TTD to PFS. The publication by San Miguel et al. cited by the company does not report a median TTD of 4.7 months. Rather, it reports a median Time to Progression (TTP) of 4.7 months. Thus, the ratio of 1.18 is the ratio of TTP to PFS and is not appropriate for modelling TTD. The publication by San Miguel in fact states that treatment in MM-003 continued to progression or unacceptable toxicity. Given the adverse event profile of POM + DEX, it is more likely that the TTD curve lies below PFS. The EAG's clinical advisor agreed that this aligns with clinical expectation. Consultation of the paperwork for TA427 (Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib), reveals that time to treatment discontinuation was constrained to be lower than PFS for POM + DEX, based on a definition of time to treatment failure (TTF), the earliest of disease progression, treatment discontinuation, death or initiation of another anti-myeloma therapy. The data from MM-003 gives a median TTF of 2.9 months compared to a median of 4 months PFS (TA427, Company submission, Table 21). Following the company's approach, this gives a ratio of 0.725 (=2.9/4). The EAG propose to use this ratio to proxy TTD relative to the chosen PFS curve, since it is based on data from the MM-003 trial, the source of PFS data in the model for POM+DEX. The EAG acknowledges, however, that the extrapolation of time on treatment for POM+DEX remains uncertain. The EAG also acknowledge that the

company provided an alternative scenario of setting TTD equal to PFS, and believe that this may provide a reasonable upper bound for time on treatment with POM+DEX.

Adverse events

Adverse events have been included by the company, focussing on those of grade 3 severity or higher occurring in at least 5% of patients in the MagnetisMM-3 (Cohort A) or MM-003 (POM + DEX) trials. In addition to grade 3-4 events, the company have included CRS and neurotoxicity events of grade 1 and 2, as these have significant resource implications irrespective of severity. AEs are applied in the first cycle of the model as the percentage of patients experiencing each type of event (see Table 34 in the company submission, document B, for these percentages). One off costs and QALY decrements are then applied to these percentages.

The EAG acknowledge that the simplifying approach used by the company is consistent with that often adopted in economic models. However, it will tend to underestimate the cost and utility impact of adverse events. It excludes a substantial number of grade 3-4 AEs that occur in fewer than 5% of individuals, and it may underplay the impact of recurrent events such as infections that can happen more than once within individuals. Nevertheless, the same approach is used in both arms and the EAG do not expect that more complex modelling of the AEs would a substantial impact on cost effectiveness.

4.2.7 Health related quality of life

Quality of life was captured in the model by applying utility weights to the progression free and post progression health states with dis-utilities to adverse events. Quality of life data were based on EQ-5D-5L data generated from the MagnetisMM-3 trial 12 months data-cut. Utility weights were derived using the NICE recommended mapping method. The company describe how both univariate regression and multivariate repeated measures mixed effect regressions were conducted to estimate the utility values by health state. In line with the protocol, elranatamab was given until confirmed disease progression, unacceptable toxicity withdrawal of consent or study termination. The on/off treatment status was not selected as a variable in the analysis as it overlapped with the progression status. Results of the analysis showed that common AE, Grade 3-4, treatment emergent, and pre-progression or post progression status were significant predictors in univariate models. A backwards stepwise approach was used to remove non-significant predictors at each step, leaving the final utility

model with progression status and common adverse events (grade 3-4) (Table 14). The QALYs in the economic model are, therefore, driven only by the impact of different treatments on survival, progression status and adverse events.

Due to lack of comparative data, the company assumed that the utility inputs do not vary by treatment arm. The company argue that this may be considered conservative as they do not account for the differences in response across treatments. The limited number of EQ-5D assessments beyond documented progression ([redacted] observations) means that the PPS value is unlikely to reflect the full decline in the HRQL of RRMM patients. Therefore, an SLR was conducted to identify utility and HRQoL in RRMM and the model estimates were cross-checked against utility /disutility containing publications. Alternative HSUVs were applied in scenario analyses, exploring the impact of different PF and PD values, and treatment specific utilities to reflect the improved response rate for elranatamab versus POM + DEX in the PF health state.

The Company submission used the recommended method to estimate utilities. The EAG are satisfied that the PF utility is consistent with that used in prior appraisals (TA427, TA658), as reported in Table 37 of the company submission (Document B). The EAG agree that the lack of observed EQ-5D-5L data beyond progression in the MagnetisMM-3 trial is likely to be an area of uncertainty in the long-term extrapolation.

Table 14 Summary of utility values for cost effectiveness analysis (Source: Table 40 of the company submission, document B – incorporating corrections to the 95% CIs provided by the company in response to the clarification letter).

State		Utility value: mean	95% CI	Justification
PFS (on and off treatment)		0.71	[0.64,0.79]	Estimated directly from systematic analysis, mapping EQ-5D-5L to EQ-5D-3L data from patients informing effectiveness estimates, in line with the NICE reference case[62]
PPS		0.63	[0.59,0.67]	
AE disutility	Elranatamab	-0.0051*		
	POM+DEX	-0.0034*		
Key: AE, adverse events; CI, confidence interval; PFS, progression-free survival; POM+DEX, pomalidomide and dexamethasone; PPS, post-progression survival. **Note**: *Calculated in the cost effectiveness model				

Disutility of adverse events

In the base case, the utility decrement from the regression analysis was used to model the HRQoL impact of most AEs. Generally, only grade 3 or higher AEs with an incidence of 5% or more were considered – although CRS and neurotoxicity of any grade were included. Disutility for grade 3-4 AEs relevant to POM + DEX, that were not observed in MagnetisMM-3 trial, were based on data published in TA510.[63] Data on the duration of events were reportedly derived from the respective trials and combined with the utility decrements to determine the QALY losses attributable to each type of event. These were applied on a one of basis in the first cycle of the model to the percentage of patients reported to have experienced each type of included AE. Given limited observations of EQ-5D values for CRS and neurotoxicity, the disutility for these events was taken from the literature, with durations for grade 1 and 2 events sourced form MagnetisMM-3 and durations for grade 3-4 events taken from the literature (due to unavailability of data in MagnetisMM-3).

The company has undertaken a review of the literature to address the fact that limited observations of reported adverse events hampered the estimation of the disutility. The EAG agrees that the measures taken to generate the values and that they appear to be reasonable. As indicated above, there is some concern that the approach to incorporating AEs in the model fails to capture the impact of recurrent events. However, the EAG do not believe that the company approach to calculating adverse event QALY losses is likely to have a considerable impact on cost-effectiveness.

4.2.8 Resources and costs

The company conducted a systematic literature search to inform the relevant cost and health care resource use of patients in this indication. The review identified 27 reports of 23 unique studies. Of these, 26 were excluded as they were non-UK based. Just one study was identified which satisfied the inclusion/exclusion criteria of the review. This study did not inform any of the cost or resource use parameters used in the company base case.[64] However, the company did use several previous TAs of multiple myeloma to inform resource use estimates. Costs included in the model are broken down into several categories:

- Drug acquisition
- Drug administration
- Subsequent treatment
- Medical resource use

- Adverse events
- IVIG
- End of life care

The per patient cost by category within the company base case is provided in table 4 below.

Table 15 illustrates which states in the model these cost categories apply to in the company base case. In accordance with the NICE reference case, only direct medical costs incurred by the NHS and PSS are included.

Table 15 Costing category by model health state

	Drug acquisition/administration (Elranatamab)	Drug acquisition/administration (POM+DEX)	Subsequent treatment	Medical resource use	Adverse events	IVIG	End of life care
PFS	X	X		X	X	X	
PPS		X	X	X			
Death							X

Drug acquisition and administration

Elranatamab

The dosage schedule of Elranatamab within the model is described as:

- Two step-up priming doses of 12 mg on cycle 1 day 1 (C1D1) then 32 mg on cycle 1 day 4 (C1D4), followed by 76 mg per week (QW) starting on C1D8.
- In line with the SmPC, the company state that if a participant has received QW dosing for at least 6 cycles (24 weeks) and has achieved a partial response or better, the dose can be changed from QW to Q2W (beginning C7D1). This is applied to [redacted] of participants who are still on treatment at the start of cycle 25 in the model.

The drug acquisition cost of Elranatamab is [redacted] and [redacted] for the [redacted] respectively. A PAS discount of [redacted] has been submitted which brings the acquisition cost to [redacted] and [redacted].

Patients require premedication of 500mg paracetamol (oral), 20mg dexamethasone (IV or oral) and 25mg of diphenhydramine(oral) an hour before treatment. The cost of administration of premedication is £197.25, which is sourced from code SB11Z applicable to outpatient oral chemotherapy. This equates to a total premedication cost of £199.17. Elranatamab is administered by subcutaneous injection under the supervision of a healthcare professional with access to resources for managing adverse reactions. Following the step-up doses, Elranatamab is administered in the outpatient setting at a cost of £207.59 per dose.

There are two other factors which affect the cost of Elranatamab:

1. Drug acquisition and administration costs are multiplied by the RDI ([redacted]) – calculated based on observed data in the MagnetisMM-3 trial.
2. Application of a stopping rule at [redacted] months.

EAG comments

The company rationalize their decision to apply the RDI from the start of the model as the criteria for de-escalation in the SmPC is more permissive than that in the MagnetisMM-3 trial.[21] The MagnetisMM-3 protocol states that patients should receive "…QW dosing for at least 6 cycles…" and have "…achieved an IMWG response category of PR or better persisting for at least 2 months…" to change the dose interval to Q2W. Whereas the SmPC does not require response to be at least 2 months. The EAG identifies the following uncertainties around application of the [redacted] RDI figure to drug acquisition and administration cost in the base case:

- *There is some uncertainty as to whether average RDI observed over the follow-up period of MagnetisMM-3 is appropriate for extrapolation over the remaining time horizon, as it may be those who are more tolerant of elranatamab who remain on it the longest, leading to a higher RDI over time.*
- *The proportion of the RDI figure that is relevant to dose reductions or missed doses. The NICE reference case is to include wastage. The use of RDI is contingent on the assumption that patients would miss some doses all together*

and restart treatment. Elranatamab is available in fixed sizes, so lower doses between 44mg and 76mg would incur the same cost as the full 76mg dose, and any dose less than 44mg would incur the cost of 44mg vial. However, the company have drawn attention to treatment exposure data which suggests the RDI figure is driven more by dose interruptions than reductions, which alleviates this concern somewhat (Company response to Factual Accuracy Check).

- *Similarly, RDI is applied to administration costs in the model, which is a discrete unit of resource which we would not expect to decrease substantially when a patient receives dose reduction.*

Given the above uncertainties, the EAG proposes scenarios to explore the impact of applying 100% RDI from future time points and increasing it in increments to reflect potentially limited resource savings associated with dose reductions.

The stopping rule at [redacted] *is based on consideration of the observed relationship between TTD and PFS observed in MagnetisMM-3. The company propose that the greater than expected discrepancy between PFS and TTD can be explained by participants achieving deep and durable responses which are maintained after stopping treatment. And considering this emerging relationship, against the risk of adverse events with long-term treatment, the company propose that a* [redacted] *stopping rule would be appropriate for elranatamab (see Appendix N.2. to the company submission, Document B, for the company's detailed justification). Given the current uncertainties and immaturity of the PFS data, the EAG has provided a scenario where the stopping rule is removed from the model.*

POM+DEX

The drug acquisition and administration cost of POM+DEX constitutes the following model components:

- Drug acquisition cost of a pack of 21 4mg tablets of Pomalidomide
- Drug acquisition cost of a pack of 50 2mg tablets of Dexamethasone
- Patients under 75 receive 40mg Dexamethasone once a week and patients over 75 receive 20mg Dexamethasone once a week.
- RDI of 90% for Pomalidomide and Dexamethasone.
- Administration cost for the first cycle of the model

- A TTD:PFS ratio of 1.18

The dosage schedule of pomalidomide is 4mg on days 1-21 of a 28-day treatment cycle. The list price of pomalidomide is £8,884 per pack of 21 4mg tablets. A confidential PAS discount exists for Pomalidomide, which the EAG will account for in confidential appendix provided in addition to the EAG report. Patients receive 4 40mg doses of dexamethasone during each 28-day treatment cycle. When the patient reaches 75, this drops to 20mg per dose consistent with TA427. The list price of a packet of 50 2mg tablets is £2.46. Given both are oral preparations, an administration cost is only applied to the first treatment cycle of the model. A cost of £197.25 is applied which represents an outpatient appointment to deliver oral chemotherapy. All components are multiplied by an RDI of 90%. Taken together, the drug acquisition cost per weekly model cycle of POM+DEX is £1999.70 (without the PAS discount on pomalidomide).

The cost per model cycle is multiplied by the approximated TTD curve for POM+DEX to generate the per cycle cost of POM+DEX. Given limited data on TTD available from MM-003 the company applied a TTD:PFS ratio of 1.18 to generate the TTD curve (see 4.2.6 above).

EAG comments

Similar to the previous section, the EAG questions the use of RDI. Within TA427, following ERG comments from TA338, dose interruptions of less than 28-days were not considered. This is based on feedback that unused tablets within a pack cannot be reused by the NHS. Therefore, it was assumed that 4.06% of packs would not be distributed to patients due to interruptions greater than 28 days (based on MM-003 data).[65] The EAG proposes the following scenarios: setting RDI for POM+DEX at the level agreed in TA427 (95.94% (1-0.0406)), and removing of the application of RDI to administration cost.

As discussed in 4.2.6 above, the EAG believes that the TTD:PFS ratio has been incorrectly calculated based on time to progression rather than TTD from MM-003. The assumption that patients would continue to take POM+DEX after progression is not realistic. The EAG clinical expert, and consultants interviewed by the company stated that patients would not be treated with the same drug after progression.[42] The EAG have suggested a correction to the estimated ratio of TTD:PFS for POM + DEX, which constrains TTD to be lower than PFS.

4.2.8.2 Subsequent treatment

The total cost of subsequent treatment is informed by the following in the economic model:

- The distribution of subsequent therapies by treatment arm which is informed by clinical expert opinion in the company base case.
- An approximation of the proportion of patients progressing and the expected proportion of progressed patients who receive subsequent treatment upon progression.
- The expected duration of subsequent treatment, which is based on the median subsequent treatment duration observed in MagnetisMM-3. This has, however, been capped by mean post-progression life years projected by the model ([redacted] months in the Elranatamab arm under company base assumptions).
- RDI of 90% for POM+DEX as a subsequent treatment

The model calculates the total expected subsequent treatment cost for both arms based on the drug acquisition, administration and RDI (POM+DEX only) of a basket of treatments. This is multiplied by the approximated proportion of the cohort progressing in each cycle of the model (incident progression), and the proportion ([redacted]) of patients who received subsequent treatment in the MagnetisMM-03 study (CSR table 14.4.2.6.2).[57]

EAG comments

The EAG has confirmed with their clinical expert that the distribution of subsequent treatments is appropriate for this population of patients (Company submission, document B, Table 44). Of patients who receive subsequent treatment following progression on Elranatamab, [redacted] receive POM+DEX. However, it is worth noting that in MagnetisMM-3, 81% of patients were treated with pomalidomide previously (Page 75 of Document B). We, therefore, must assume that extrapolated survival outcomes of Cohort A are generalisable to the NHS positioning, despite the prior treatment history not being aligned.

The EAG clinical expert agrees with the company's assumption that not all patients would go onto receive subsequent treatment. However, the EAG clinical expert has advised that these patients would go onto receive palliative care. To address this, the EAG propose including greater end-of-life care costs which account for the longer use of palliative care of progressed patients (See end-of-life care costs below).

Very few patients progress in the Elranatamab arm in the model. This is an artefact of the extrapolated survival curves and the method used by the company to approximate incident progression in the PartSA model structure. The company do this by taking the difference in the proportion residing in the progressive disease state between the current and previous cycle of the model. This is not an accurate reflection of new incident disease. Further, since the PFS and OS curves converge quickly in the company's base case, this results in PD state occupancy falling from early in the model time horizon, suggesting no new incident progressions from cycle [redacted]*). This seems implausible and inconsistent with data from MagnetisMM-3. Furthermore, it is inappropriate to cap the expected duration of subsequent treatment by expected PD life years – as expected PD life years are averaged across the whole cohort and are not specific to proportion of patients who progress. These above assumptions lead to very low projections of subsequent treatment costs in the elranatamab arm of the company model. The EAG suggest an alternative approach, whereby a fixed proportion of PFS events are assumed to represent progression. This proportion* [redacted]*) is taken from the observed Cohort A PFS data from MagnetisMM-3 (MagnetisMM-3 CRS, Table 14.2.3.1).*[57] *Further, rather than cap subsequent treatment duration using expected PD life years, the EAG suggest capping it by PD life years conditioned on the proportion of patients assumed to progress.*

As per the discussion in the previous section, the application of 90% RDI to acquisition and administration costs for POM+DEX (as a subsequent treatment) is inconsistent with TA427. The EAG proposes a scenario where an RDI of 95.94% is applied to only the drug acquisition cost of POM+DEX based on TA427.

4.2.8.3 Medical resource use

All patients (PFS and PPS states) are modelled to incur the cost of an outpatient visit, complete blood count and biochemistry test each month. This is applied as a per cycle cost of £44.61. Within the first cycle of the model, a cost of 5 days in hospital (£517.29 per day) is applied to all Elranatamab patients. It is assumed that a complete blood count and hospitalisation for 48 hours after the first dose and 24 hours after the second dose is required to monitor for signs and symptoms of CRS and ICANS.

EAG comments

The EAG clinical expert finds the company's assumptions of monitoring and testing suitable and agrees that it would be similar for pre-progression and post-progression patients.

Upon commencement of Elranatamab treatment, the SMPC and CS (page 17 table 2 Document B) state that patients should remain in hospital for 48 hours after both loading doses of Elranatamab. The SmPC also states that patients should receive premedication for the first 3 doses of Elranatamab. Conversely, the economic model assumes that patients remain in hospital 24 hours after the second dose (page 152 document B) and applies premedication for just one of the doses. After accounting for premedication requirements, a hospital stay of 5 days is assumed. The company did run a scenario of 7 days which had a minor impact on the ICER.

4.2.8.4 Adverse events

Adverse events are applied as a one-off cost at the start of the model. The rate of grade 3+ events which occurred in ≥5% of patients are multiplied by a cost per episode. The cost per episode is stated to be a function of unit cost, incidence, recurrence, and duration of the event. Incidence, recurrence and duration figures are purportedly taken from MagnetisMM-3 for Elranatamab and MM-003 for POM+DEX (Section B.3.5.3, page 156 Document B of CS). Unit costs were sourced from relevant TAs (TA658, TA510, TA567)[40, 63, 66] and NHS reference costs 2021/22.[67] All grades of events of clinical interest are included in the model for Elranatamab, which include neurotoxicity and cytokine release syndrome (CRS).

<u>EAG comments</u>

The EAG did not find the company methodology transparent, as it was unclear how the costs were calculated and how recurrence and duration contributed to the management costs. Following further clarification, it was confirmed that the cost per episode was not based on recurrence and duration observed in MagnetisMM-3 and MM-003, but instead based on expected costs for different types of adverse event drawn from a variety of sources. The cost of specific types of event were assumed equal between the arms of the model. The company clarified that this was due to a lack granular data available from MM-003 trial. The EAG notes that several of the costs were sourced from TA658, where the company was criticised by the ERG for not accounting for the duration of AE in their calculation of cost (page 76 of ERG report for TA658).[40] The EAG would ideally prefer a method whereby rates of adverse events (inclusive of recurrent events) are calculated and applied on a cycle by cycle basis to

those on treatment, accounting for the duration of events specific to individual treatments. However, the EAG acknowledge that this is not possible given the data available.

Whilst the EAG was able to verify most of the percentages (of patients experiencing AEs) used in the model with percentages reported in the MagnetisMM-3 CSR[57] (Table 14.3.1.2.2) and the MM-003 publication,[54] the following uncertainties were identified:

- *The company has not included COVID-19 related pneumonia within the model. There were [redacted] patients who experienced treatment emergent events of grade 3+ COVID pneumonia during MagnetisMM-3.*
- *The definition of "Infections" in the model is not easily verifiable with the treatment emergent AEs reported in MagnetisMM-3 CSR. There were [redacted] patients who experienced grade 3+ events of system organ class infection and infestation observed in the study. The value used in the model is [redacted].[57] Similarly, there were 102(34%%) patients who experienced grade 3+ events under this system organ class for MM-003 whereas a rate of 16.0% was used in the model.*

Overall, the EAG find that the company's reporting of how adverse events have been included in the model lacks transparency. The approach appears to underestimate the percentage of patients that experience grade 3+ events in major categories such as infections and infestations, and it is unclear how durations have been accounted for in the costs. Furthermore, several of the event types are likely to have been recurrent within individuals, and it is not clear that the economic burden of this has been appropriately accounted for.

IVIG

IVIG could be used for prophylaxis or as a treatment for infection within the MagnetisMM-3 trial. In Cohort A, [redacted] ([redacted]) of patients received IVIG. Of the patients who received IVIG as prophylaxis, [redacted] did not develop a bacterial infection. There were [redacted] patients who received IVIG for treatment of COVID-19. Given that patients do not generally receive IVIG for prophylaxis in the UK, and to account for COVID-19 being a temporaneous risk, the company chose to assume a rate of [redacted] ([redacted] patients) for IVIG in the model (page 156, Appendix M.3.2.4 Document B of CS). A flow chart is provided in Figure 12, page 158 of the appendix which details patients who were included in the model.

The company combined the expected dosage for treatment of infection (0.5g/kg per month), mean weight of cohort A in MagnetisMM-3 of [redacted], list price (£42.50 per gram) and percentage who received IVIG for treatment of bacterial infection ([redacted]) to generate a cost per administration. This is then converted to a per cycle cost of [redacted] which assumes that there are 4 weeks in a month. The per cycle cost is multiplied by the occupancy of the PFS state up to the mean duration of IVIG treatment for patients with bacterial infections observed in MagnetisMM-3 ([redacted] months).

The EAG find that company's approach to incorporating IVIG cost in the model is inappropriate, as we have a flat expectation that [redacted] require IVIG for a mean of [redacted] months). It would therefore be preferable to calculate total expected costs of this and apply it as one-off cost in the first cycle of the model.

According to the CSR provided by the company (table 14.4.2.1.1), of the [redacted] patients who received IVIG, [redacted] patients received IVIG for prophylaxis and [redacted] received IVIG for treatment of infection. The EAG agrees that IVIG treatment would not be used as frequently in clinical practice as was observed in the MagnetisMM-3 trial. However, there may be a higher infection burden in clinical practice as a result. In response to clarification, the company provided analysis which showed lower monthly exposure adjusted infection rates (EAIR) for patients receiving immunoglobulin replacement (0.22 [95% CI, 0.18-0.27] vs 0.36 [95% CI, 0.33-0.40]). A similar trend was also observed for patients without versus with hypogammaglobulinemia (Company clarification response page 42). It may, therefore, be reasonable to consider a scenario whereby those who received prophylactic IVIG, or receive it for viral infection, are taken out of the denominator for calculating the percentage that are likely to require IVIG for bacterial infection in routine practice.

The company chose not to include administration cost as the use of IVIG is linked to the occurrence of other adverse events which are accounted for in the model (i.e., infection). However, grade 3-4 infection is assumed to occur in only [redacted] of patients in the Elranatamab arm at a cost of £431. This does not correspond to the [redacted] who received IVIG for treatment of infection in cohort A. The mean duration of IVIG treatment was 7.81 months (median 7.84 months) and it is typically administered as home therapy or as a day case in hospital. Therefore, the EAG does not find it plausible that the cost of administering IVIG is adequately captured within the model. Given this uncertainty, the EAG suggest a

scenario that adds the cost of delivering IVIG in outpatient setting using the NHS reference cost: SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance Outpatient. This is consistent with the approach used in TA894, TA677, and TA559.

End of life care

The company base case applies a cost of £961.67 to all new deaths in each cycle of the model, to account for the cost of terminal care for the last week of life. This is based on the company base case within TA338 which was then used as a scenario within TA427. The advisory board within TA338 stated terminal care usage as: hospital services (20%), hospice services (40%) and home services (40%). Costs sourced from The National Audit Office (2008)[68] were then used to calculate a weighted average of £867 per week and uplifted the cost to 2021/22 prices to £961.67.[69]

EAG comments

The cost utilised by the company is conservative given a median survival of 12.7 (95% CI: 10.4, 15.5) months was observed in MM-003 (Table 4, page 29, Appendix D.1.3.1.1. of CS). The EAG does not believe that it is reasonable to assume that patients would only require one week of terminal care. It is not clear why the company in TA338 made this assumption. It is also important to clarify that the cost used in the company base case of TA427, which replaced TA338, was £5,363 (2014/15 prices). This represents the cost of hospital care in the last 90 days of life for cancer patients.[70] The EAG will explore a scenario which utilises the terminal care usage from the TA338 advisory board with more up to date prices of the total cost of end-of-life care for cancer patients rather than assuming only one week of care.[69, 70] This equates to £5,231.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company present their base case results in section B.3.10 of their submission document (document B). The results presented by the company account for a proposed confidential PAS price for elranatamab, but do not include available PAS prices for pomalidomide or

panobinostat. The EAG will compile a separate confidential appendix of results which account for these confidential prices.

Compared to POM + DEX, elranatamab is projected to generate increased costs and QALYs, with an ICER of £1,926 per QALY gained (see CS, document B, Table 51). The breakdown of costs and QALYs in the model reveals that the QALY gains are driven by increased time spent in the PF health state compared to POM+DEX. Indeed, only a small fraction of the discounted life years are projected to accrue in the PD health state with elranatamab (compared to for POM + DEX). This is due to the convergence of the PFS and PS curves for elranatamab, resulting in a negligibly small proportion of patients residing in the PD health state for most of the model time horizon. Correspondingly, with PFS curves being used to approximate incident progression, and PD life years being used to cap expected time on subsequent treatment, the subsequent treatment costs are substantially lower for elranatamab compared to POM + DEX, partially offsetting the higher costs accruing in the PF health state.

The EAG believes that the company's extrapolation of PFS and OS are unrealistic for elranatamab, which may lead to overly optimistic cost-effectiveness findings.

5.2 Company's sensitivity analyses

The company's probabilistic results are provided in section B.3.11 of their submission document (Figures 53 and 54, and Table 53). The ICER for elranatamab is somewhat higher owing to a higher incremental cost and smaller incremental QALY. The probability of cost-effectiveness exceeds at threshold of £20,000 per QALY gain, without considering the PAS prices available for the comparator and subsequent treatments.

In addition to the PSA, the company have undertaken deterministic one-way sensitivity analysis (OWSA), showing the ICER to most sensitive to the relative dose intensity (RDI) for elranatamab, the RDI for POM + DEX, the percentage switching the Q2W dosing of elranatamab, the assumed duration of subsequent treatment, and the percentage receiving subsequent treatment following progression.

For the latter two inputs, lower values will lead to higher ICERs for elranatamab since subsequent treatment disproportionally affects the POM + DEX arm due to the company's extrapolation of PFS and OS for elranatamab.

Following their OWSA, the company present the results of scenario analysis. A key scenario is the comparison with POM + DEX using data from the ECA study. The company suggest that the MAIC with MM-003 will tend to underestimate the relative efficacy of elranatamab versus POM + DEX at its proposed positioning. This is primarily because patients in MM-003 (POM + DEX) were not TCR and had not previously been exposed to anti-CD38 therapy. They argue that the efficacy of POM+DEX would be poorer in patients meeting the proposed positioning for elranatamab in routine NHS practice. To address this, they conducted a scenario using POM + DEX efficacy data from their ECA study based on real-world data. The results of this analysis are presented in Table 54 of the company submission (Document B). The ICER for elranatamab in this analysis is higher than in the base case, owing to the shorter PFS and TTD for POM + DEX. This translates into a larger relative increase in the incremental cost of elranatamab compared to the corresponding increase in incremental QALYs. They further present OWSA around this alternative efficacy scenario, showing the ICER to be most sensitive to a similar set of parameters as those observed to affect the base case; an exception being that utilities for the PD state now feature in the top five most influential parameters whilst the percentage switching the Q2W dosing of elranatamab does not.

In addition to the ECA efficacy scenario, the company present a range of further scenario analyses around their base case ICER – using the MAIC adjusted curves for elranatamab and MM-003 data for POM + DEX. These scenarios are presented in Table 56 of the company submission (Document B). An alternative scenario of applying the stopping rule for elranatamab when [redacted] remain on treatment, as opposed to applying at [redacted], resulted in the greatest upwards shift in the ICER. Other scenarios which utilised more optimistic extrapolations of PFS for POM + DEX (log-normal and log-logistic) resulted in elranatamab generating cost savings. *This is likely due to the assumed link between PFS and TTD in the company model, which the EAG believes is inappropriate*.

5.3 Model validation and face validity check

The model's internal validity over the phase corresponding to observed MagnetisMM-3 and MM-003 data is generally good, with parametric curves providing a reasonable visual fit to Kaplan-Meier curves, and the POM+DEX data are mature. There are no long-term data by which to assess the external validity of elranatamab extrapolations. The company note that they have consulted five clinical experts regarding various aspect of model development and assumptions, including survival curve extrapolations. It is not clear, however, if clinical experts have been consulted on the inferred implications of the company's combined extrapolation of PFS and OS. Based on its own clinical expert advice, the EAG find it implausible that PFS and OS will converge on each other from so early in the model time horizon. This has been discussed in section 4.2.6.

In terms of internal consistency, the company describe their approach to quality assurance of the model in section B.3.14.1.2 of their submission. In addition, the EAG conducted its own internal consistency checks, using a combination of cell-by-cell formula tracing and testing, and several black box tests suggested by Tappenden and Chilcott (2014). The results of the black box checks are summarised in Table 16 below. No major issues were identified. The EAG did, however, identify three minor inconsistencies in the model code:

1. The QALY calculation for PFS on POM+DEX was found to incorrectly refer to the half-cycle corrected state occupancy when the half-cycle correction was switched off, and vice versa.
2. The adjustment for excess mortality in the extrapolated OS, PFS and TTD curves for elranatamab and POM+DEX was found to be misaligned by one row with the corresponding life table data by age of the cohort.
3. The PSA distribution for the mix of subsequent treatments following POM+DEX was incorrectly able to sum to less than or greater than one (Parameters sheet R157:R162). This was due to incorrect adjustment of the distribution to the parameters of the corresponding subsequent treatment distribution for elranatamab.

These bugs have been corrected by the EAG, with minimal impact on the company base case.

Table 16 Results of black-box verification checks carried out by the EAG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	No issues identified. Equalised survival curves which gave equal LYs/QALYs for both arms.
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	No issues identified
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	The QALY calculation for PFS on Tx is incorrect on the "Model Engine – POMDEX" sheet as it uses the half cycle corrected figure when half cycle correction is off.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No issues identified.

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No issues identified. Discounted QALYs are calculated through a sum product formula of the discount factor multiplied by cost for each cycle. Increasing the discount rate leads to substantially lower discounted QALYs.
Cost estimation	Set intervention costs to 0	ICER is reduced	No issues identified.
	Increase intervention cost	ICER is increased	No issues identified.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	No issues identified.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	No issues identified. Discounted costs are calculated through a sum product formula of the discount factor multiplied by cost for each cycle. Increasing the discount rate leads to substantially lower discounted cost.
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	The market share of subsequent treatment baskets do not sum to 100% of "Parameters" sheet N153:N162. IVIG parameters are not included in the PSA.

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	No issues identified. Equalised survival curves in the POM+DEX arm to Elranatamab led to equal QALY and LY between arms. Costs are a complex calculation of a significant basket of treatments dependent on time in the model between arms so it was not possible to equalise between arms without significantly altering the structure of the model.
	Amend value of each individual model parameter	ICER is changed	No issues identified. Explored a sample of parameters in the model, all changed the ICER. Changing the mean age does nothing, if you change it to 80 the Elranatamab arm becomes unhappy as general population mortality risk above 100 is not available in life tables. Cyclophosphamide and Bortizomib IV cannot be edited using the override function on the parameters sheet. These are hardcoded into the “Detailed calculations” sheet cells S28:S33. IV admin costs in the “Parameters” sheet have no bearing on the model.
	Switch all treatment-specific parameter values	QALYs and costs for each option should be switched	Not possible due to the complex structure of the model with regard to drug acquisition costs.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG undertook a number of scenario analyses to address issues and uncertainties identified in chapter 4. These scenarios are outlined in Table 17. Prior to running them, the EAG corrected the coding bugs identified in section 5.3 above. This had a slight impact on the company ICER, which is the reference point for the other scenarios presented in Table 17. Some of the scenarios in Table 17 replicate existing scenarios that have already been explored by the company.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Results of the EAG scenario analyses are presented in Table 17. A severity weight of 1.2 is applied to the mean and incremental QALYs in all these analyses, as the proportional QALY shortfall of 0.85-0.95 in the POM+DEX arm is met for all of them. It should be noted that these analyse include the proposed PAS price for elranatamab, but to not include the available PAS price for comparators and subsequent therapies.

Scenarios around the PFS and OS extrapolation have mixed effects (Table 17). For example, the more pessimistic extrapolation of PFS for elranatamab, using the HR from the MAIC versus POM+DEX, results in elranatamab being dominant (scenario1). This because the curve, as well as reducing QALYs, substantially reduces costs given the capping TTD by PFS. The more modestly pessimistic PFS gamma curve reduces the incremental QALYs and has a substantial upward impact on the ICER (scenario 3). Changes to the OS curve for elranatamab (scenarios 4-5) have only a modest impact on the ICER due to the company base case assumption that the chosen PFS extrapolation is given priority over OS. Thus, more pessimistic OS curves get overridden by the more optimistic PFS curve.

More optimistic extrapolation of POM+DEX PFS (scenario 6) also results in elranatamab becoming cost-saving, due to the link between PFS and time on treatment for POM+DEX in the model. On the other hand, changing the ratio of TTD to PFS for POM+DEX (scenario 8), which constrains TTD to be lower than PFS, has a large

upward impact on the ICER for elranatamab. This is due to the now substantially lower POM+DEX acquisition costs, resulting in a higher incremental cost for elranatamab. Changing the calculation to approximate incident progression as a fixed proportion of PFS events in each cycle, as discussed in section 4.2.8, results in higher subsequent treatment costs in both arms, but more so in the POM+DEX arm when keeping other assumptions in line with the company base case settings (scenario 9). Reworking the cap on subsequent treatment duration on the other hand, to equal PD life years conditioned on progression, substantially increases subsequent treatment costs in the elranatamab arm, increasing the ICER. All scenarios that increase the RDI for elranatamab (scenarios 12-13; 18-19) have a large upward impact on the ICER, whilst those that increase the RDI for POM+DEX result in elranatamab delivering cost savings (scenario 14 and 15).

Table 17 EAG scenario analysis around the company base case

	Element	Company base case	EAG scenario analysis	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
Company base case				[redacted]	[redacted]	£1,926	
a)	Adjustment for excess mortality in "Elranatamab" and "POMDEX" worksheets	Misalignment of lifetable look-up by one row	Alignment of life table look by age at start of cycle	[redacted]	[redacted]	£1,897	[redacted]
b)	Cell referencing of state occupancy in QALY calculations for POMDEX	Incorrect look-up of half-cycle corrected state occupancy when half-cycle switched off	Align state occupancy look-up with half-cycle correction switch	[redacted]	[redacted]	£1,935	[redacted]
EAG corrected company base case (incorporating corrections a and b)				[redacted]	[redacted]	£1,905	[redacted]
Clinical efficacy scenarios							
1	Progression free survival (elranatamab)	Generalised gamma fitted to MAIC weighted Cohort A KM data	HR from MAIC ([redacted]) applied to POM+DEX reference curve	[redacted]	[redacted]	Dominant	[redacted]
2			Weibull fitted to MAIC weighted cohort A KM data	[redacted]	[redacted]	£2,661	[redacted]
3			Gamma fitted to MAIC weighted cohort A KM data	[redacted]	[redacted]	£3,889	[redacted]
4	Overall survival (elranatamab)	Generalised gamma fitted to MAIC weighted Cohort A KM data	HR from MAIC ([redacted]) applied to POM+DEX reference curve	[redacted]	[redacted]	£2,388	[redacted]
5			Exponential fitted to MAIC weighted Cohort A KM data	[redacted]	[redacted]	£2,236	[redacted]

	Element	Company base case	EAG scenario analysis	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
6	Progression free survival (POM+DEX)	Generalised gamma fitted to MM-003 KM data	Log logistic fitted to MM-003 KM data	[redacted]	[redacted]	Dominant	[redacted]
7			Gamma fitted to MM-003 KM data	[redacted]	[redacted]	£5,130	[redacted]
8	POMDEX TTD:PFS ratio (from MM-003)	TTD:PFS ratio = 1.18 (based on median TTP of 4.7 months and median PFS of 4 months)	PFS:TTF ratio = 0.725 (based on median TTF of 2.9 months and median PFS of 4 months)	[redacted]	[redacted]	£15,674	[redacted]
9	Incident progression calculation	Difference in PD state occupancy between current and prior cycle	Difference in PF state occupancy between current and prior cycle (multiplied by [redacted])	[redacted]	[redacted]	Dominant	[redacted]
10	Adjustment of subs Tx duration	Capped by expected PD life years	Capped on expected conditional PD life years	[redacted]	[redacted]	£5,032	[redacted]
Cost scenarios							
11	End of life care cost	£961.67	£5,231.30	[redacted]	[redacted]	£1,706	[redacted]
12	RDI: Elranatamab	[redacted]	85%	[redacted]	[redacted]	£5,533	[redacted]
13	RDI: Elranatamab	[redacted]	90%	[redacted]	[redacted]	£8,125	[redacted]

	Element	Company base case	EAG scenario analysis	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
14	RDI: POM+DEX	90%	95.94% based on TA427	[redacted]	[redacted]	Dominant	[redacted]
15	RDI: POM+DEX	90%	100%	[redacted]	[redacted]	Dominant	[redacted]
16	RDI: Administration cost	RDI applied to administration cost	RDI not applied to administration cost	[redacted]	[redacted]	£3,206	[redacted]
17	Stopping rule	[redacted] months	Removal of stopping rule	[redacted]	[redacted]	£5,755	[redacted]
18	RDI: Timepoint when RDI switches to 100%	Never	25 weeks	[redacted]	[redacted]	£9,662	[redacted]
19	RDI: Timepoint when RDI switches to 100%	Never	65 weeks (15 months)	[redacted]	[redacted]	£7,754	[redacted]
20	IVIG: Administration cost for IVIG applied	None (Assumed to be included in AE costs to avoid double counting)	£207.59 (Based on SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance Outpatient NHS Reference costs (2021/22))	[redacted]	[redacted]	£2,048	[redacted]
21	IVIG: Proportion receiving IVIG	[redacted] (Based on [redacted] participants who received IVIG for treatment of bacterial	[redacted] (Based on [redacted] patients who received IVIG in MagnetisMM-3)	[redacted]	[redacted]	£3,035	[redacted]

	Element	Company base case	EAG scenario analysis	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
		infections in MagnetisMM-3)					
22	IVIG: IVIG applied as one-off cost to all at start of model	Applied to proportion of PFS patients for mean duration ([redacted]) in MagnetisMM-3	One-off cost at the start of the model of [redacted] of treatment for [redacted] of patients)	[redacted]	[redacted]	£2,211	[redacted]
23	AE: Cost of treating infection	£431 based on NICE TA567	£2,512 (Cost of treating pneumonia in the model (NICE TA658, NHS reference cost 2021/22 (DZ11K, DZ11V))	[redacted]	[redacted]	£1,844	[redacted]
24	AE: 25 + Include Covid-19 related pneumonia	No ([redacted] infection rate)	Increase infection rate to [redacted](COVID-19 related pneumonia (16 patients ([redacted]))	[redacted]	[redacted]	£2,020	[redacted]
25	AE: 25+ Include all infections of system organ class "Infections and Infestations"	No (10.6% infection rate for Elranatamab and 14.0% for POM+DEX)	Use % of patients who experienced any grade 3+ event of system organ class Infections and Infestations from MagnetisMM-3 minus “Pneumonia” and “Sepsis” for Elranatamab [redacted]) and MM-003 for POM+DEX ((102-42)/300)	[redacted]	[redacted]	£1,945	[redacted]

6.3 EAG's preferred assumptions

Table 18 outlines the EAGs preferred modelling assumptions, as discussed and justified in the noted sections of the EAG report. These are applied cumulatively to the company base case, following correction of minor bugs, as per the row order in Table 18. A severity weight of 1.2 is applied to the incremental QALYs in all these analyses, and the EAG base also meets the proportional QALY shortfall to qualify for this. The greatest impacts on the ICER come through amending POM+DEX TTD curve (to lie below PFS) and changing the calculation of incident progression to a fixed fraction of PFS events (when now combined with the more pessimistic gamma extrapolation of PFS).

Table 18 EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Incremental cost	Incrementa QALYs	Cumulative ICER £/QALY
EAG corrected company base-case (a and b)	*5.3*	[redacted]	[redacted]	£1,905
Let OS override PFS	*4.2.6*	[redacted]	[redacted]	£1,577
Apply Gamma for PFS (Elranatamab)	*4.2.6*	[redacted]	[redacted]	£3,889
Amend POM+DEX TTD:PFS ratio = 0.725	*4.2.6*	[redacted]	[redacted]	£23,653
Apply EAG incident progression calculations	*4.2.8*	[redacted]	[redacted]	£30,956
Apply EAG subsequent treatment duration cap	*4.2.8*	[redacted]	[redacted]	£30,956
Apply increased costs of treating grade 3-4 infections category (assume £2,512, as per pneumonia (HRGs DZ11K, DZ11V) included in the model))	*4.2.8*	[redacted]	[redacted]	£30,869
Include administration cost of IVIG (£207.59 (Based on SB12Z Deliver Simple Parenteral Chemotherapy at First Attendance Outpatient NHS Reference costs 2021/22))	*4.2.8*	[redacted]	[redacted]	£31,089
Apply IVIG as a one-off cost in first cycle	*4.2.8*	[redacted]	[redacted]	£31,467
Apply higher cost for end-of-life care	*4.2.8*	[redacted]	[redacted]	£31,275
RDI for POM+DEX at agreed percentage from TA427 (95.94%)	*4.2.8*	[redacted]	[redacted]	£29,169

The combined changes in Table 18 take the EAG's base case ICER to £29,169. A full incremental deterministic analysis of the EAG's base case is provided Table 19. The corresponding probabilistic analysis is provided Table 20. When run probabilistically, the EAG base case is substantially lower than the deterministic ICER. This is thought to be due to the proximity of the OS, PFS and TTD curves for elranatamab, and the assumption that TTD is capped by PFS, and PFS capped by OS. This may act as a ceiling effect on the uncertainty surrounding elranatamab TTD and may also limit PD life years and subsequent treatment costs. This pushes the expected costs downwards when averaged over the PSA iterations compared to the deterministic results. The overall effect is a reduced ICER. The scatter-plot and acceptability curve are provided in Figures 18 and 19 respectively.

The EAG has also provided further deterministic scenario analysis around its base case, to address further uncertainties around the extrapolation of OS and PFS based on the immaturity of the MagnetisMM-3 data, and the RDI that is applied to elranatamab. There is further upward uncertainty in the ICER associated with application of a higher RDI for extrapolation, the ICER increasing substantially when it is increased to 100% from 15 months.

Table 19 Mean deterministic EAG base case results

	Total costs	Total LYs	Total QALYs	Incremental Elranatamab versus POM+DEX			ICER
				Costs	LYs	QALYs	
Elranatamab	[redacted]	2.87	[redacted]				
POM+DEX	[redacted]	1.36	[redacted]	[redacted]	1.51	[redacted]	29,169
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; POM+DEX, pomalidomide and dexamethasone; QALYs, quality-adjusted life years.							

Table 20 Mean probabilistic EAG base case results

	Total costs	Total LYs	Total QALYs	Incremental Elranatamab versus POM+DEX			ICER
				Costs	LYs	QALYs	
Elranatamab	[redacted]	2.90	[redacted]				
POM+DEX	[redacted]	1.44	[redacted]	[redacted]	1.46	[redacted]	22,093
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; POM+DEX, pomalidomide and dexamethasone; QALYs, quality-adjusted life years.							

Figure 18 Cost-effectiveness scatter-plot (EAG base case)

Figure 19 Cost-effectiveness acceptability curve (EAG base case)

Table 21 Scenario analysis around the EAG base case

	Element	EAG base case	EAG scenario analysis	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
EAG base case				[redacted]	[redacted]	£29,169	
1	OS extrapolation	Generalised gamma caped on SMR adjusted general population mortality	Exponential capped on SMR adjusted general population mortality	[redacted]	[redacted]	£9,301	[redacted]
2			MAIC HR applied to POM+DEX reference curve	[redacted]	[redacted]	£12,049	[redacted]
3			Generalised gamma caped on SMR adjusted general population mortality – but with an SMR of 1.2 beyond 10 years	[redacted]	[redacted]	£29,276	[redacted]
4	PFS extrapolation	Gamma caped on SMR adjusted general population mortality	MAIC HR applied to POM+DEX reference curve	[redacted]	[redacted]	£12,910	[redacted]
5	OS and PFS extrapolation	Generalised gamma for OS, gamma for PFS	MAIC HRs applied to POM+DEX reference curves for PFS and OS	[redacted]	[redacted]	£28,880	[redacted]
6	Elranatamab RDI	RDI [redacted] for duration of model time horizon	RDI 100% from 15 months	[redacted]	[redacted]	£37,352	[redacted]

6.4 Conclusions of the cost effectiveness section

The economic case is an uncertain one due to the immaturity of the survival data from MagnetisMM-3, and the limitations of the MAIC. The immaturity of the MagnetisMM-3 data leads to highly uncertain and variable extrapolation of PFS and OS. The ICER is upwardly sensitive to the selection of more pessimistic PFS and OS curves for elranatamab, but the selection of plausible parametric curves is restricted by the logical inconsistency of curves crossing. This is caused by the proximity of the tails of the Kaplan Meier curves for OS and PFS based on the current follow-up of MagnetisMM-3. The EAG have attempted to provide an alternative analysis which it believe provides a more plausible combined extrapolation of OS and PFS. This still generates what the EAG believe to be a very optimistic extrapolation of OS, but alternative more pessimistic OS curves seem incompatible with all but the most pessimistic extrapolation of PFS, leading again to curves crossing.

The model is also highly sensitive to the RDI placed on elranatamab and the proposed stopping rule, both of which have been discussed in section 4.2.8 and raised as key issues for consideration.

8 References

1. Multiple Myeloma Research Foundation. Understanding Multiple Myeloma. Available from: https://themmrf.org/multiple-myeloma/#:~:text=Multiple%20myeloma%20is%20a%20blood,protect%20your%20body%20from%20infection (Accessed 7 November 2023).

2. Cancer Research UK. Myeloma incidence statistics. 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-One (Accessed 7 November 2023).

3. NHS Digital. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021/survival-by-cancer-group (Accessed 9 November 2023).

4. Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc. 2016;**91**(1):101-19.

5. Kumar SK, Rajkumar V, Kyle RA, et al. Multiple myeloma. Nat Rev Dis Primers. 2017;**3**:17046.

6. Lee HC, Ramasamy K, Weisel K, et al. Treatment Patterns, Survival, Quality of Life, and Healthcare Resource Use Among Patients With Triple-Class Refractory Multiple Myeloma in US Clinical Practice: Findings From the Connect MM Disease Registry. Clin Lymphoma Myeloma Leuk. 2023;**23**(2):112-22.

7. Tang D, Hari P, Ramasamy K, et al. Real-World Treatment Patterns and Clinical, Economic, and Humanistic Burden in Triple-Class Refractory Multiple Myeloma: Analysis of the Connect ® Multiple Myeloma (MM) Disease Registry. Blood. 2021;**138**:117.

8. Jordan K, Proskorovsky I, Lewis P, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. Support Care Cancer. 2014;**22**(2):417-26.

9. Pfizer. Multiple Myeloma Lifelines - TCR Cohort [data on file]. 2023.

10. Despiégel N, Touboul C, Flinois A, et al. Health-Related Quality of Life of Patients With Multiple Myeloma Treated in Routine Clinical Practice in France. Clin Lymphoma Myeloma Leuk. 2019;**19**(1):e13-e28.

11. Hu X, Katic B, Lowe M, Purnomo L, Gibson C, Rodriguez A, Health related quality of life in patients with multiple myeloma in relation to line of treatment and response. 21st Annual european Hematology Association Congress; 2016; Copenhagen.

12. Ramsenthaler C, Osborne TR, Gao W, et al. The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. BMC Cancer. 2016;**16**:427.

13. Richardson EM, Schüz N, Sanderson K, Scott JL, Schüz B. Illness representations, coping, and illness outcomes in people with cancer: a systematic review and meta-analysis. Psychooncology. 2017;**26**(6):724-37.

14. Molassiotis A, Wilson B, Blair S, Howe T, Cavet J. Unmet supportive care needs, psychological well-being and quality of life in patients living with multiple myeloma and their partners. Psychooncology. 2011;**20**(1):88-97.

15. Lyall M, Crawford R, Bell T, et al. Characterizing the Patient Journey in Multiple Myeloma: Qualitative Review. JMIR Cancer. 2022;**8**(3):e39068.

16. Molassiotis A, Wilson B, Blair S, Howe T, Cavet J. Living with multiple myeloma: experiences of patients and their informal caregivers. Support Care Cancer. 2011;**19**(1):101-11.

17. Goodwin JA, Coleman EA, Sullivan E, et al. Personal financial effects of multiple myeloma and its treatment. Cancer Nurs. 2013;**36**(4):301-8.

18. Kurtin S, Lilleby K, Spong J. Caregivers of multiple myeloma survivors. Clin J Oncol Nurs. 2013;**17 Suppl**:25-32.

19. Tang W, Thomas R, Parikh K, et al. PCN218 Burden of Illness on Patients And Caregivers and Quality of Life Outcomes of Triple-Class Exposed (TCE) Patients With Multiple Myeloma (MM) In The United States. Value Health. 2021;**24**:S60.

20. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;**28**(suppl_4):iv52-iv61.

21. Pfizer. 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 [data on file]. 2023.

22. Pfizer. HTA Advisory Board for Elranatamab for Treating Relapsed or Refractory Multiple Myeloma after Three Therapies. 2023.

23. National Institute for Health and Care Excellence. Myeloma: diagnosis and management [NG35]. 2018. Available from: https://www.nice.org.uk/guidance/ng35/chapter/Recommendations#managing-newly-diagnosed-myeloma (Accessed 13 November 2023).

24. National Institute for Health and Care Excellence. Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable [TA763]. 2022. Available from: https://www.nice.org.uk/guidance/ta763 (Accessed 13 November 2023).

25. National Institute for Health and Care Excellence. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation [TA311]. 2014. Available from: https://www.nice.org.uk/guidance/ta311 (Accessed 13 November 2023).

26. National Institute for Health and Care Excellence. Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma [TA680]. 2021. Available from: https://www.nice.org.uk/guidance/ta680 (Accessed 13 November 2023).

27. National Institute for Health and Care Excellence. Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable [ID4014]. London: NICE; 2023. Available from: https://www.nice.org.uk/guidance/gid-ta10914/documents/674. (Accessed 13 November 2023)

28. National Institute for Health and Care Excellence. Bortezomib and thalidomide for the first-line treatment of multiple myeloma [TA228]. 2011. Available from: https://www.nice.org.uk/guidance/ta228 (Accessed 13 November 2023).

29. National Institute for Health and Care Excellence. Bortezomib monotherapy for relapsed multiple myeloma [TA129]. 2007. Available from: https://www.nice.org.uk/guidance/ta129 (Accessed 13 November 2023).

30. National Institute for Health and Care Excellence. Lenalidomide plus dexamethasone for previously untreated multiple myeloma [TA587]. 2019. Available from: https://www.nice.org.uk/guidance/ta587 (Accessed 13 November 2023).

31. National Institute for Health and Care Excellence. Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma [TA695]. 2021. Available from: https://www.nice.org.uk/guidance/ta695 (Accessed 13 November 2023).

32. National Institute for Health and Care Excellence. Carfilzomib for previously treated multiple myeloma [TA657]. 2020. Available from: https://www.nice.org.uk/guidance/ta657 (Accessed 13 November 2023).

33. National Institute for Health and Care Excellence. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib Technology appraisal guidance [TA586]. 2109. Available from: https://www.nice.org.uk/guidance/ta586 (Accessed 13 November 2023).

34. National Institute for Health and Care Excellence. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma [TA897]. 2023. Available from: https://www.nice.org.uk/guidance/TA897 (Accessed 13 November 2023).

35. National Institute for Health and Care Excellence. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies [TA171].

2019. Available from: https://www.nice.org.uk/guidance/ta171 (Accessed 13 November 2023).

36. National Institute for Health and Care Excellence. Panobinostat for treating multiple myeloma after at least 2 previous treatments [TA380]. 2016. Available from: https://www.nice.org.uk/guidance/ta380/evidence (Accessed 13 November 2023).

37. National Institute for Health and Care Excellence. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [TA870]. 2023. Available from: https://www.nice.org.uk/guidance/ta870/evidence (Accessed 13 November 2023).

38. National Institute for Health and Care Excellence. Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib [TA427]. 2017. Available from: https://www.nice.org.uk/guidance/ta427/evidence (Accessed 13 November 2023).

39. National Institute for Health and Care Excellence. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [TA783]. 2022. Available from: https://www.nice.org.uk/guidance/ta783 (Accessed 13 November 2023).

40. National Institute for Health and Care Excellence. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [TA658]. 2020. Available from: https://www.nice.org.uk/guidance/ta658/evidence (Accessed 13 November 2023).

41. Pfizer. Routes to TCR in the NICE pathway [data on file]. 2023.

42. Pfizer. Clinical Validation Interview Report for the NICE Submission of Elranatamab for Treating Relapsed or Refractory Multiple Myeloma after Three Therapies [data on file]. 2023.

43. Pfizer. Elranatamab: draft summary of product characteristics [data on fle]. 2023.

44. Pfizer. ILAP HTA Access Forum engagement meeting with Pfizer (OMA-1125 – ILAP-111) [data on file]. 2023.

45. Pfizer. Burden of disease in patients diagnosed with multiple myeloma in England: A descriptive, retrospective population-based cohort study using national cancer registry data [data on file]. 2023.

46. National Institute for Health and Care Excellence. Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 2 therapies [ID5108]. 2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11018 (Accessed 6 November 2023).

47. National Institute for Health and Care Excellence (NICE). Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies

[ID2701]. 2023 updated 14.06.2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10568 (Accessed 18.07.2023
48. National Institute for Health and Care Excellence. Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]. 2023. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10918 (Accessed 6 November 2023).

49. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;**52**(6):377-84.

50. National Institute for Health and Care Excellence. Single technology appraisal and highly specialised technologies evaluation: user guide for company evidence submission template (PMG24). London/Manchester: NICE; 2015. Available from: https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333. (Accessed 13 November 2023)

51. Bahlis NJ, Tomasson MH, Mohty M, et al. Efficacy and Safety of Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma Naïve to B-Cell Maturation Antigen (BCMA)-Directed Therapies: Results from Cohort a of the Magnetismm-3 Study. Blood. 2022;**140**(Supplement 1):391-3.

52. Mohty M, Tomasson M, Arnulf B, et al., Elranatamab, a B-cell maturation antigen(BCMA)-CD3 bispecific antibody, for patients with relapsed/refractory multiple myeloma: Extended follow up and biweekly administration from MagnetisMM-3. ASCO; 2023 3rd August; Yokohama, Japan.

53. Bahlis NJ, Costello CL, Raje NS, et al. Elranatamab in relapsed or refractory multiple myeloma: the MagnetisMM-1 phase 1 trial. Nat Med. 2023;**29**(10):2570-6.

54. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;**14**(11):1055-66.

55. Pfizer. ECA in MM using RWE [data on file]. 2023.

56. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023.

57. Pfizer. MagnetisMM-3 15 Month Study Report Output [data on file]. 2023.

58. Pagano L, Salmanton-García J, Marchesi F, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA). J Hematol Oncol. 2021;**14**(1):168.

59. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect

comparisons in submissions to NICE. University of Sheffield: NICE Decision Support Unit; 2016. 82 p.

60. Giri S, Chen Y, Wu J, et al. Reduction in Late Mortality Among Patients With Multiple Myeloma Treated With Autologous Peripheral Blood Stem Cell Transplantation-A Blood or Marrow Transplant Survivor Study Report. Transplant Cell Ther. 2021;**27**(10):840 e1- e7.

61. San Miguel JF, Weisel KC, Song KW, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica. 2015;**100**(10):1334-9.

62. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013: The reference case. 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (Accessed
63. National Institute for Health and Care Excellence. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [TA510]. 2018. Available from: https://www.nice.org.uk/guidance/ta510 (Accessed 6 December 2023).

64. Gonzalez-McQuire S, Yong K, Leleu H, et al. Healthcare resource utilization among patients with relapsed multiple myeloma in the UK, France, and Italy. J Med Econ. 2018;**21**(5):450-67.

65. National Institute for Health and Care Excellence. Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985] Committee papers. London/Manchester: NICE; 2016. Available from: https://www.nice.org.uk/guidance/ta427/documents/committee-papers. (Accessed 6 December 2023)

66. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]. 2019. Available from: https://www.nice.org.uk/guidance/ta567 (Accessed 8 November 2023).

67. NHS England. 2021/22 National Cost Collection Data. 2023. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ (Accessed 8 November 2023).

68. National Audit Office. End of life care. London: TSO; 2008. Available from: https://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf. (Accessed 8 November 2023)

69. Personal Social Services Research U. Unit Costs of Health and Social Care. 2022. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/ (Accessed
70. Georghiou T, Bardsley M. Exploring the cost of care at the end of life. London: Nuffield Trust; 2014. Available from:

https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life. (Accessed 8 November 2023)

Single Technology Appraisal

Elranatamab for treating refractory multiple myeloma after 3 standard therapies [ID4026]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 10 January 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Company FAC related to EAG key issues

Issue 1 Heterogeneity within the proposed patient population reflects real world clinical practice and patient need

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.3 page 53 "It is somewhat unsatisfactory, however, that the proportion of potentially eligible patients in the NHS that will fall under different lines of treatment and different classes of refractoriness has not been explicitly quantified using data." Without context could be interpreted inaccurately	Please add context, suggested wording "*There remains an evidence gap quantifying the proportion of potentially eligible patients in the NHS that will fall under different lines of treatment and different classes of refractoriness using UK routinely collected health data. Analysis by the company using the national Systemic Anti-Cancer Therapy (SACT) dataset to examine the characteristics of patients diagnosed with MM in England, their treatment patterns and clinical outcomes (as reported in CS. Document B) were limited by the lack of definitions and data for refractoriness in SACT and the unavailability of data on CDF drugs and correspondingly, patients who received CDF drugs. Therefore, the company could only reliably undertake treatment and outcome analyses based on regimen and class exposure status and LOT (excluding CDF drugs). As a*	We have explored patient eligibility by lines of treatment and by class refractoriness as best as available UK routinely collected health data allows. In the External Control Arm (ECA) study (CS. Document B Section B.2.9.2 and Appendix D), we undertook internal analyses to determine how many drug classes patients were refractory to at study index. Given the ECA sample presented in the CS was relatively small ([redacted]), it is unsurprising that the results generated were affected by small numbers and subject to data suppression. We did however confirm in our response to Clarification	Proposed changes accepted with some minor rephrasing.

	result, the company explored feedback from clinicians."	Questions that 61.5% of eligible patients were TCR. Additionally, we undertook a national study using SACT to characterise the characteristics, treatment patterns and outcomes of patients with multiple myeloma (MM) (as reported in CS. Document B.1.3.3.6). As SACT does not have data fields specifically for refractoriness and there are no suitable proxies for refractoriness, this study was only able to report results based on treatment exposure and line of treatment (LOT). Furthermore, analyses by Cancer Drug Fund (CDF) drug and patients who received CDF drugs is prohibited using SACT and therefore the study results did not reflect the entire population of interest. Alongside these analyses, discussions with clinical	

		experts were undertaken to validate the study results. We acknowledge the limitations of data presented but ask that the report reflect that we have made every effort to provide this information. The word "unsatisfactory" in some sense suggests that our analyses could have been better. We don't believe this to be the case and we don't believe this is the point the EAG are making.	

Issue 2 Extrapolation of PFS and OS as described by EAG misinterprets the company approach.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Table, Page xvii: "To avoid this, the company give priority to their preferred PFS curve and let OS converge on it. This effectively results in one	*"To avoid this, **the company allow the modelled PFS and OS curves to converge, with OS being dominated by PFS which is more mature**.* *This effectively results in one single curve being used to*	The company acknowledges that given longer-term progression free survival (PFS) and overall survival (OS) data are not available for elranatamab, there is uncertainty	Partially accepted and report amended to acknowledge the company's justification that

single curve being used to partition the elranatamab cohort, between the progression free and dead states of the model. It further infers no progression risk, only pre-progression mortality, from early in the model time horizon.”	*partition the elranatamab cohort, between the progression free and dead states of the model,* ***which reflects the observed data from Cohort A****...”*	over long-term survival used in the analysis. However, the current text is misleading as it implies that PFS curve selection was prioritised over OS selection. PFS and OS extrapolations were validated, along with the plausibility of patients experiencing a deep and durable response, in clinician interviews. We suggest the strategy would more accurately be described as fitting the observed data but managing the 1 year, 2 years, 5 years and 10 years plus extrapolations to clinical opinion (which cannot be verified without longer term data). Both extrapolations were selected based on the same criteria and a constraint was imposed to prevent curves crossing, on the basis that observed PFS data are more mature.	PFS data are more mature than OS. But the EAG disagree that using one single curve to partition the cohort is reflective of the observed data from cohort A. The observed data is immature and a single curve lacks clinical plausibility based on the EAGs clinical expert advice.

EAG report: Page xx: *"It may not fully resolve the issue as at present it would only provide an additional **6 months** or so of follow-up data."*	Amend text to read: *"It may not fully resolve the issue as at present it would only provide an additional **3 months** or so of follow-up data."*	The analysis uses the 15-month data cut. November 2023 is the 18-month data cut (even though the months of the two respective data cuts becoming available seem to suggest an approximate 6-month period in between. This corresponds to 3 additional months of follow up data not 6 months as outlined in the EAG report	Accepted and report amended.
Section 4.2.6 page 56 *"They acknowledge that the curve provides an **impossibly** optimistic extrapolation of PFS".*	Amend to read: *"They acknowledge that the curve provides an **implausibly** optimistic extrapolation of PFS"*	Minor edit	Accepted
Section 4.2.6 page 56, *"The company's approach is understandable, but it is somewhat **counterintuitive** that so much emphasis was placed on choosing curves based on their fit to the unadjusted cohort A data, when in fact the base case relies on curves fitted to the MM-003 weighted KM data."*	Statement should be removed, or amended to: *"The company's approach is understandable, but emphasis was placed on choosing curves based on their fit to the unadjusted cohort A data, when in fact the base case*	"Counterintuitive" is a prejudicial statement. The approach used by the company was not counterintuitive as validation was sought for unadjusted Cohort A PFS and OS extrapolations using the available, observed unadjusted Cohort A Kaplan Meier (KM) data.	Text has been amended.

	relies on curves fitted to the MM-003 weighted KM data."		
Section 4.2.6, page 56 *"The EAG considers it* ***problematic*** *that, prior to further adjustments, a curve has been selected that overestimates what clinical experts believe to be plausible 5 and 10 year PFS for this indication".*	Statement should be removed or amended to: *"The EAG notes that adjustment was required to attain an estimation of PFS at 5 and 10 years in line with clinical opinion based on prior experience."*	In line with NICE guidance, the company has attempted to match the observed data as well as possible whilst continuing to reflect the opinion of clinical experts on future survival estimates. The company argue that the observed data is more certain and have therefore anchored to this and tried to capture clinical opinion on unknown future extrapolated survival outcomes by adjusting the curves downwards, to avoid unduly optimistic estimates (that are unknown). The company acknowledge that further data will help reduce the uncertainty in longer term extrapolation estimates.	This is not a factual inaccuracy but the stated opinion of the EAG based on clinical expert feedback. Text reworded slightly to make clear it represents EAG opinion.

Section 4.2.6, page 57 *"The EAG believe that too much emphasis is being placed on this when selecting a curve and giving it priority over OS in the extrapolation. The data are immature and the observed flattening of the curve may be a chance occurrence due to the heavy censoring and small numbers left at risk in the tail of the KM curve. Long-term follow-up is clearly required to confirm the shape of the PFS distribution in a population where treatment is not expected to be curative."*	Amend text to: *"The EAG believe that too much emphasis is being placed on this when selecting a curve and constraining OS by PFS in the extrapolation. Whilst this has been an accepted method in earlier, similar appraisals (TA693, TA872), the data are immature, though more events are observed for PFS than OS. Whilst the PFS KM data provided are the best available evidence, the observed flattening of the curve may be a chance occurrence due to heavy censoring and small numbers left at risk in the tail of the KM curve. Long-term follow-up is clearly required to confirm the shape of the PFS distribution in a population where treatment is not expected to be curative."*	Minor edit The company agree that there is uncertainty over long-term PFS and OS used in the model but note that PFS is more mature than OS and that the constraint by PFS has been accepted in earlier, similar appraisals (TA693, TA872). The company agree that longer-term KM data may provide reassurance over the shape of PFS and OS hazards.	Not a factual inaccuracy. The fact that PFS has been allowed to dominate OS in prior appraisals is irrelevant to the point being made here which is about selecting a PFS curve that is compatible with clinical opinion without the need to cap it with a projection of the all-cause mortality hazard. The statement "and giving it priority over OS" has been removed to make this clearer.
Section 4.2.6 page 61 *"appears to have been chosen based of*	Amend text to:	Minor edit accurately reflecting that clinical plausibility was considered	Accepted with slight rephrasing so as not to change the point being

consideration of the fit and plausibility of parametric distributions fitted to the unadjusted cohort A data."	*"appears to have been chosen based on **clinical plausibility** and consideration of fit to the observed KM data."*		made, that curves were selected based on clinical plausibility and fit to unadjusted cohort A KM data.
Section 4.2.6, page 61 *"On these grounds, it could be argued that these alternative curves provide a better statistical fit to the observed data."*	Amend text to: *"On these grounds, it could be argued that these alternative curves provide a better statistical fit to the observed data **which forms part of the justification for curve selection**."*	Minor edit to note that statistical fit only provides information on the fit of extrapolations to the observed data, and not to the likely longer-term survival.	Not a factual inaccuracy but accepted for completeness.
Section 4.2.6, page 61 *"The company suggest, however, that the generalised gamma curve provides the best visual fit to the observed data"*	Amend text to: *"The company suggest, however, that the generalised gamma curve provides the best visual fit to the observed **KM data and hazards**".*	Minor edit	Accepted.

Section 4.2.6 page 64 *"The EAG have also observed some inconsistencies in the company's presentation of the KM OS data for POM + DEX, noting that the observed follow-up time varies from Figure 43 in the CS, where it is over 1.5 years, to figure 44 in the CS where it terminates before 1.5 years (at approx. 40% survival). The KM data plots in the model appear to be truncated at an even earlier timepoint. Given the discrepancies, the EAG would like reassurance that the parametric curves have in fact been fitted to all the available OS data, and not the truncated data presented in Figure 44 of the CS or in the model."*	Please delete this statement	We acknowledge an incorrect copy of Figure 43 was supplied in CS; this was corrected in response to Clarification questions B5. We can confirm that all relevant KM data was utilised in the statistical analysis of the POM + DEX data.	This is not a factual inaccuracy. The observation refers to the revised company report, which still shows discrepancies between figures presenting the same KM data. This led to uncertainty when reading the report as to whether all the KM data had been used for fitting. With the further clarity now provided the text has been deleted as we are reassured it is only a minor presentational issue.
Section 4.2.6 page 65 "*It is questionable whether a fraction of the TCR RRMM*	Please rephrase and remove strikethrough text.	The company has applied a time-varying standardised mortality ratio as reported by Giri et al. in the	Not a factual accuracy, but opinion of the EAG based on its own clinical expert

cohort will achieve a mortality hazard that is same as the general population."	*"The company assumed, based on clinical opinion which is uncertain that ~~It is questionable whether~~ a fraction of the TCR RRMM cohort will achieve a mortality hazard that is same as the general population*	model. Accordingly, modelled patients, have a heightened mortality risk compared to the general population as reported by Giri et. therefore, do not reach a mortality hazard equal to the general population until model year 10. This assumption means that the modelled extrapolations provide survival estimates in line with clinician predictions. The company agrees that there is some uncertainty around long-term all-cause mortality in the modelled population but maintain that the time varying SMRs used reflect the best available evidence.	advice. Rephrased to make clear it is opinion based on EAG clinical expert advice. "*Based on advice from its clinical expert, the EAG believe it is questionable that a fraction of the TCR RRMM cohort will achieve a mortality hazard that is the same as the general population."*

Issue 3 Time to treatment discontinuation (TTD) with POM+DEX by EAG is overly pessimistic and doesn't reflect UK RWE.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6 page 68, TA427 assumption (2.9/4=0.725 vs 4.7/4 =	Please rephrase and acknowledge the limitations including age of the TA427	The company acknowledges the limited data to support the TTD extrapolations for POM + DEX and	Not a factual inaccuracy, but based on published data from the MM-003 trial showing that

1.18 company is overly pessimistic. "*The data from MM-003 gives a median TTF of 2.9 months compared to a median of 4 months PFS (TA427, Company submission, Table 21). Following the company's approach, this gives a ratio of 0.725 (=2.9/4).*"	submission, published in 2017 or Miguel 2015. Furthermore, please acknowledge that several options were explored by the company including assuming TTD is equal to PFS.	investigated several options in the company submission including: • Applying an exponential based on median outcomes. • Applying a TTD:PFS ratio based on reported median outcomes to the PFS curve. • Assuming TTD is equal to PFS The company based its assumption based on investigating both the MagnetisMM-3 study, to reflect the comparison to elranatamab and the ECA to reflect real world outcomes. With regard to the ECA study, when comparing the PFS and TTD curves indicates quite often that TTD is greater than PFS. Therefore, we assumed TTD would be greater than PFS in practice.	median time on treatment (as assessed by TTF) sits below PFS. This was in line with the EAGs clinical expert's expectation. However, the text has been augmented to acknowledge the uncertainty in the extrapolation of time on treatment with this approach. The report has also been amended to acknowledge the company's alternative scenario of setting TTD equal to PFS. The company's other approach of fitting an exponential through the median, fits to the median time to progression which does not reflect time on treatment. This remains an area of uncertainty which has an impact on the ICER and requires discussion by the

			committee and clinical experts present.

Issue 4 The calculated relative dose intensity (RDI) for elranatamab is appropriate for estimating costs in the model.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page xix, EAG interpretation of RDI is factually incorrect and requires amending	The company provided responses in CQs on how RDI was calculated. The company apologises if the CQ response was insufficient however we have provided further information on RDI. We propose an amendment to the EAG report.	Given the importance of RDI to the ICER and the circumstance around the CQs we have provided further supporting data as attachment to correct for inaccuracies. In response to EAG clarifying question (B18) on how RDI was calculated the company presented. Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] *100 There was ambiguity and some misinterpretation with the clarification questions and the subsequent information shared. However, we welcome the opportunity to rectify it. Please find specific comments and related responses below.	With the clarity now provided that permitted dose frequency reductions in MagnerisMM-3 are accounted for as reductions in he planned dose intensity in the RDI calculation, the EAG has revised its critique of the RDI parameter throughout the report. This was not clear to the EAG based on the company's response to the clarification letter, hence the wording in our original report.

Section 4.2.8 page 73 "*The EAG finds the source of the [redacted] RDI figure is not clear from document B, appendix M or the company response to clarification.*"	Proposed amendment is for the EAG to review the inclusion of RDI in the report and update accordingly.	The RDI of [redacted] is the median for cohort A presented in TLR table 14.4.1.2.1 taken from the 15-month data cut and referenced in the company submitted cost effectiveness model (Appendix A: Table 14.4.1.2.1 PF-06863135 Exposure to Treatment – Overall). The RDI in the cost effectiveness model reflects both dose reductions and interruptions as they were allowed in the trial protocol and Statistical Analysis Plan (SAP) (Appendix A: Statistical analysis plan (SAP) section 6.6.3 Study Intervention Exposure) As both reductions and interruptions were allowed in the trial it is difficult to estimate what the RDI would be with interruptions alone as if no reductions were allowed more patients may have had dose interruptions.	This statement has been edited out in response to the general issue.
Section 4.2.8 page 73, "It is unclear to EAG, but there is concern that the dose frequency reductions which were permitted within the	Proposed amendment is for the EAG to review the inclusion of RDI in the report and update accordingly.	RDI is not double counting the (Q2W. RDI is the overall dose intensity / planned dose intensity. When the patient switched to Q2W the planned dose intensity is adjusted in the calculation (Appendix A	This statement has been edited out in response to the general issue.

MangetisMM-3 trial are counted towards the RDI calculation, and such dose frequency reductions are being explicitly modelled for the 87.88% assumed to move to Q2W dosing after 24 weeks. The RDI of [redacted] is then further applied on top of this step down in dose frequency. If this is the case, there is double counting of permitted dose frequency reductions.		Statistical analysis plan (SAP) section 6.6.3 Study Intervention Exposure) The total planned dose for a given cycle is defined as: Cycle 1: • Planned dose (mg/cycle) = 12+32 + 76 × 3 After Cycle 1: If the participant is on QW dosing schedule for the cycle: • Planned dose (mg/cycle) = 76 × 4 If the participant is on Q2W dosing schedule for the cycle: • Planned dose (mg/cycle) = 76 × 2	
Section 4.2.8 page 74, "Furthermore, even if the RDI does not count permitted dose frequency reductions towards reductions in relative dose, it may not be appropriate to apply the same RDI following the dose frequency reduction at 24 weeks; Particularly	Proposed amendment is for the EAG to review the inclusion of RDI in the report and update accordingly.	The RDI by cycle is relatively similar pre & post QW to Q2W switch. This data has been updated following the latest data cut (15 months) which continues to show no noticeable increase in RDI after Q2W switch (Appendix A Table 14.4.1.3 Exposure to Treatment - by Cycle).	With notice drawn to the additional data showing RDI by treatment cycle, we are reassured that Q2W dosing has not had an obvious impact on RDI, and so have removed this from the critique. We note, however, that the by cycle RDI calculations provided used a 9 month data cut,

the more permissive reductions assumed for Elranatamab in the model. This is because the drug may be better tolerated when the dose frequency is reduced, resulting in higher RDI at the new planned Q2W doses.”			and the same analysis has not been shown for the more mature data. We have retained a general point regarding uncertainty around extrapolation of the RDI over the time horizon of the model. This relates to uncertainty over RDI in those who stay on elranatamab for a long time. In light of the clarification provided, we have edited our report to remove the application of 100% RDI (from 25 weeks) from the EAG base case and retained the company’s [redacted]. We have, however, retained scenarios that increase RDI to 100% in the long-term (from 15 months), or increase it to 80% or 90%, to explore potential impact of limited

			cost-savings materializing from dose reductions. We have also modified the key issues table and text in the Exec summary in line with our revised critique of the RDI.
Section 4.2.8 page 74, "*There is also uncertainty around the proportion of patients who will switch to Q2W dosing in practice, and the [redacted] applied in the base case is greater than the proportion who switched in the MagnetisMM-3 trial, on which treatment efficacy is based. There were 75 patients in cohort A of MagnetisMM-3 who achieved response and 50 switched to Q2W dosing after 6 cycles (24 weeks). Therefore, the EAG proposes a scenario where 66.7% (50/75) of*	Please amend with correct information, calculation, and scenario results.	In real world clinical practice, we would expect more patients to step down given the more permissive label recently approved by the MHRA (CS. Appendix C Summary of Product Characteristics). Therefore, the company believes the current company assumptions are conservative and would expect more patients to step down (and earlier) and this would actually have a consequential impact downwards on RDI not captured in the company model assumptions. Table 14.4.1.1.1 Duration by cycle. Included as additional supporting data in Appendix A. [redacted] patients started cycle 7 & [redacted] patients switched to Q2W after 6 cycles. [redacted] = [redacted]. The n=50 the EAG reference is	We acknowledge our original misunderstanding of this data, and now understand the derivation of the [redacted]% from MagnetisMM-3 data. We have removed this part of the critique and the associated scenarios from the report accordingly.

patients move to the Q2W dosing schedule after 24 weeks of 76mg QW dosing." The calculation in an inaccurate representation of the scenario.		among patients who switched to Q2W at least 6 months before the data cut-off. *"Among responders per BICR who switched to Q2W dosing at least 6 months before the data cutoff date (n = 50), 80.0% maintained or improved their response at least 6 months after the switch, with deepening of response observed in 40.0% of patients, including 38.0% who improved their response to ≥CR*" Lesokhin, A.M., Tomasson, M.H., Arnulf, B. et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med 29, 2259–2267 (2023). https://doi.org/10.1038/s41591-023-02528-9 18-month data supports the value used in the company base case ([redacted]%) as a conservative assumption (Appendix A: Table 14.4.1.1.1 PF-06863135 Duration of Treatment (18 month data).	

Company FAC related to any additional areas of accuracy

Issue 5 Updated Marketing authorisation dates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3, page 10, Please note for information the EU MA and GB MA has been granted	If possible, please update or note updated information. EU MA: 07 December 2023 GB MA: 04 January 2024	Updated marketing authorisation information. Correction required in EAG report: 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 antiCD38 antibody and have demonstrated disease progression on the last therapy. No other changes needed.	Amendment made

Issue 6 Incorrect primary outcome CRR.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3 page 19, Primary outcome was ORR only. CRR was a secondary outcome	Update report noting correct primary and secondary outcome	Inaccuracy	Amendment made

Issue 7 The external control arm study presented by the company is credible for reasons outlined below.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1 Table 4, Page 24, EAG states "*The external control arm was too small to be a truly credible direct comparator and included some of the indirect comparator patients".* Statement incorrect Section 3.4, page 46 "*many of the patients in the ECA would likely to have*	Please remove statements, referring to the inclusion of patients in the ECA who are also included in the indirect comparator analyses	The company believes this is incorrect. Indirect comparator patients came from MM-003 study. That study enrolled relapsed refractory multiple myeloma (RRMM) patients between 2011 and 2012 who had received two prior LOT and failed treatment with bortezomib and lenalidomide. Therefore, by the ECA study period (2015 to 2023), the indirect comparator patients from MM-003 were likely to have progressed beyond eligibility for the ECA. Furthermore, the MM-003	We thank the company for the additional information regarding the timelines that the direct control arm participants would not have overlapped with the indirect. The ECA is however a small data set and so have amended: Table 4: As requested below "The external control arm was small and this affected

been included in the summaries from the MM-003 study used for the indirect comparison". Statement incorrect Section 3.6, page 47 "*and it is likely that these patients may also have been included in the indirect comparison analyses". Statement incorrect*		study end date was August 2017 which pre-dates the index date of almost all patients in the POM+DEX ECA cohort. Also, there was no overlap between MM-003 UK study sites and the sites contributing data to the ECA. In the ECA dataset, we did not see any POM+DEX patients with a historical record for MM-003 trial participation.	the precision of some of the direct comparisons." Section 3.4 "...During the factual correction process the company provided additional timelines regarding the MM-003 participants in the ECA used for the direct comparison suggesting they would not have overlapped with those in the indirect comparison that used summaries from the MM-003 study but later on." Section 3.6-Removed as indicated
Section 3.4 Page 46, "Had the ECA been larger and more robust this would have been a credible comparator especially as the data were also at individual level"	"Had the ECA included a larger sample size this would have improved the precision of all treatment effect estimates especially as the data were available at individual level".	Paragraph to be updated to reflect EAG's intended message (as perceived by the company) that a larger sample size in the ECA could have improved the precision of treatment effect estimates.	Amended a requested

incorrect statement and contradicts an earlier statement from the EAG (Page 27) "*The EAG generally agrees with the company's quality assessment of the three studies and is of the opinion that the studies are of good methodological quality.*"		We believe the ECA was methodologically robust, and this statement contradicts the earlier statement (EAG report, page 27) that *"...The EAG generally agrees with the company's quality assessment of the three studies and is of the opinion that the studies are of good methodological quality."* Additionally, we have registered the study on a public RWE registry and to support responses to Clarification Questions we submitted the study protocol, SAP, DataSAT and Methods to Address Bias documents, as recommended good research practice and in line with the NICE RWE Framework. The RECORD-PE checklist is also available on request.	
Section 3.1 Table 4, Page 24, EAG states "*The external control arm was too small to be a truly credible direct comparator and included some of the indirect comparator patients".* Statement incorrect	"The external control arm was small and this affected the precision of some of the direct comparisons".	The EAG state that the size of the ECA was too small for meaningful inferences to be drawn. We believe that this characterisation is incorrect. Despite the small sample size in absolute terms, the confidence intervals/uncertainty around the direction of the estimated treatment effect for PFS are conclusive.	Amended a requested

Section 3.4 Page 46, “Had the ECA been larger and more robust this would have been a credible comparator especially as the data were also at individual level” Statement incorrect		Therefore, we ask that the wording for Section 3.1 Table 4 Page 24 be updated.	

Issue 8 Step down Q2W as outlined in the SMPC has been accepted by EMA and MHRA as part of elranatamab approved label.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4, page 53 “The EAG has some concern regarding the company’s relaxed criteria for switching to the Q2W dosing, which may underestimate treatment consumption (and associate acquisition costs) compared to that observed in MagnetisMM-	Suggested wording, “The EAG notes a discrepancy regarding the MHRA approved SMPC less stringent criteria for switching to the Q2W dosing, compared with the criteria in the MM-003 trial protocol, which may overestimate treatment consumption (and associate acquisition costs)	Note the response to the EAG incorrect interpretation of RDI above may provide additional assurance in addressing this accuracy issue. The Q2W step-down (SMPC CS. Appendix C), recently approved MHRA MA label. The criteria have also been accepted by the EMA and FDA through robust evaluation and are satisfied with the data	Accepted and amended with some slight rephrasing.

3”. Statement lacks appropriate context and doesn’t reflect robust evaluation by regulators.	compared to that observed in MagnetisMM-3 as more patients switch earlier.”	presented. We argue these “concerns” are not justified from a clinical or economic perspective. Clinical practice will be reflective of the approved SMPC therefore this statement is inaccurate and lacks generalisability to clinical practice. From an economic perspective, the current company base case assumption is conservative. In real world clinical practice, we would expect more patients to step down (and earlier) given the more permissive label recently approved by the MHRA (CS. Appendix C). Therefore, the company believes the current company assumptions on this are conservative. The overwhelming opinion of clinical experts is that the real world practice and expected use of bispecific monoclonal antibodies (BsAbs) is to step down earlier than 24 weeks.	

Issue 9 Adverse Events company methods

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.4 page 79 "*The EAG does not find the company methodology transparent, as it is unclear how the costs were calculated and how recurrence and duration contributed to the management costs."* *EAG suspects that the cost per episode is not based on recurrence and duration observed in MagnetisMM-3 and MM-003 as the management costs do not differ between arms. It is highly unlikely that the duration and recurrence of events observed in MagnetisMM-3 and MM-003 would have been equal.*	Please add statement to ensure correct interpretation reflecting the context of the available data. *"The EAG (and company) are unable to take this approach as this requires AE management cost by day for each specific AE and the duration for each specific AE as observed in both trials. For the AE durations in MagnetisMM-3, they can be calculated based on the trial individual patient data (that would be available to the company). For MM-003, the inputs are not available publicly. Therefore, this uncertainty is unresolvable without additional available data for POM-DEX."*	The company acknowledge some of the differences were not explained however all CSR tables were transparently referenced in the company submitted model. We acknowledge more information could have been presented in the company submitted model notes to allow for this information to be clearer. Some of the suggestions are unresolvable without further data being available for comparators which is out of the company's control. AE durations were not accounted in the AE cost calculation in the company model. The AE cost was calculated as the weighted product of the AE incidence and AE unit cost. The unit cost was sourced from the NHS reference cost (we used TA658/TA567/TA510 to identify the specific NHS reference cost code for the AEs).	For clarity the text has now been edited to confirm the actual approach used and the company's justification for this.

		EAG prefers to calculate the AE cost accounting for the different AE durations observed in MagnetisMM-3 and MM-003. This requires AE management cost by day for each specific AE and the duration for each specific AE as observed in both trials. For the AE durations in MagnetisMM-3, they can be calculated based on the trial IPD. For MM-003, the inputs are not available. There is no evidence to suggest durations of AE would be different between studies. Therefore, the current simplifying approach is correct given the lack of inputs and paucity of available data between the two studies.	

Issue 10 Adverse events – Incorporation of IVIG in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.4 page 80 IVIG *"According to the CSR provided by the*	Please remove the final part of this statement.	Table 14.4.2.1.1 shows that, in cohort B, [redacted] ([redacted]) of patients received IVIG for prophylaxis and [redacted] received IVIG	Amendment made

company (table 14.4.2.1.1), of the [redacted] patients who received IVIG, [redacted] patients received IVIG for prophylaxis and [redacted] received IVIG for treatment of infection. The EAG has struggled to tally these figures with those reported in the submission document B. "	"*The EAG has struggled to tally these figures with those reported in the submission document B."*	as treatment for an infection. These data represent IVIG indication as entered by the study clinician. These data represent the indication for IVIG as entered by the study clinician. As IVIG is only available in the UK for the treatment of bacterial infections, the company conducted a post-hoc analysis of IPD to produce figures for what IVIG use would be expected had MagnetisMM-3 had to comply with UK IVIG release criteria (as set out in Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021). Using the methodology outlined in company submission Appendix M.3.2.4, the company analysed individual patient data (IPD) from MagnetisMM-3 to assess whether a patient had a (plausibly) bacterial infection before or during IVIG supplementation. It was felt that this would result in a more conservative estimation of expected IVIG in the real	

		world. Therefore, the company included in its submission patients who had received IVIG for treatment of an infection of plausible bacterial aetiology, or who developed a (plausibly) bacterial infection whilst in receipt of IVIG prophylaxis/treatment for a non-bacterial infection. This is the reason for the discrepancy between the CSR (table 14.4.2.1.1) and Document B. In the post-hoc analysis of IVIG data, the company found the following: • [redacted] patients received IVIG during the study period. • [redacted] patients received IVIG as treatment for COVID and were excluded. • [redacted] patients received IVIG as prophylaxis and did not develop a bacterial infection whilst on IVIG. • [redacted] patients received IVIG as treatment for a bacterial infection, or developed a	

		bacterial infection whilst on IVIG for another reason (such as prophylaxis or treatment for a viral/fungal infection) In its submission, the company used [redacted] of patients receiving IVIG for a mean of [redacted] months (median was [redacted]). Had we used the CSR figure, we would have submitted [redacted] receiving IVIG for treatment.	
Section 4.2.8.4 page 80 IVIG *"It may, therefore, be reasonable to consider a scenario whereby those who received prophylactic IVIG, or receive it for viral infection, are taken out of the denominator for calculating the percentage that are likely to require IVIG for bacterial infection in routine practice. However, this is not possible with the provided IVIG use figures."*	Based on the correction of the error (tally of figures) above please remove the final part of this statement. *"It may, therefore, be reasonable to consider a scenario whereby those who received prophylactic IVIG, or receive it for viral infection, are taken out of the denominator for calculating the percentage that are likely to require IVIG for bacterial infection in routine practice.*	The company provided the appropriate data to correctly calculate the IVIG use data without those who received prophylactic IVIG or received it for viral or fungal infection. This is outlined in the paragraph above and in the company submission Appendix M.3.2.4. Therefore, we believe the statement to be inaccurate.	Amendment made

Typographical Errors

Location of Typographical Error	Amended	EAG response
Page xiii TRC MM	Should read TCR	Amendment made
Page xiii Table 1 row 1	Delete “to”	Replaced “to” with “and” (as originally intended)
Page 27 second paragraph	The proportion of patients not “patient”	Amendment made
Page 34 bullet 3 MRD	..” at a sensitivity level of 10-5.89” – 5 should be in superscript and 89 is the reference. ..”achieved MRD negativity at a sensitivity of 1 × 10−5” - -5 should be superscript	Amendments made
Page 36 paragraph 1	“summaries” should read summarised	Amendment made
Page 46 paragraph 2	..”sever” should read severe	Amendment made
Page 50 paragraph 2 Page 55 paragraph 2,4	“M-003 trial” should read MM-003	Amendments made
Page 59 paragraph 2	“figure 12” should read Figure 13	Amendment made

Page 60	“weighted OS data from MagnatisMM-3. The fitted curves can be found in Appendix O of the company submission. The preferred parametric functional from for OS” should read: “weighted OS data from MagnetisMM-3. The fitted curves can be found in Appendix O of the company submission. The preferred parametric functional form for OS”	Amendment made
Page 65 paragraph 4	“OS, projecting [redacted] survival at [redacted] years” should this read [redacted]% survival at 10 years? Note marking also	It was as intended. Noting the increase in long-term survival to 25 years when fixing to PFS. CiC marking updated on years.
Page 68 paragraph 1	“further arguments” should read “further argument”	Amendment made
Page 70 paragraph 2	“vary be treatment arm” should read “by treatment arm”	Amendment made
Page 77 paragraph 3	*“inappropriate to the cap” should read “inappropriate to cap”*	Amendment made
Page 96 paragraph 1	*“*The combined changes in Table 18 take the EAG’s base case ICER to £48,185” should this read £40,090	Amendment made to reflect revised EAG base case in response to further clarity on the RDI calculation.

Appendix A – Additional Supporting Data

Table 14.4.1.1.1 PF-06863135 Duration of Treatment (15 month data) (Cycle) (Safety Analysis Set) (Protocol C1071003)

Duration from switch to last dose (months) is calculated as (last non-zero Q2W dose date - first switch date +1)/30.4375 excluding QW dosing records.
*Excluding participants consented to version prior to Protocol Amendment 6
PFIZER CONFIDENTIAL SDTM Creation: 29MAR2023 (14:22) Source Data: adexsum Table Generation: 18APR2023 (21:30)
(Data cutoff date : 14MAR2023 Database snapshot date : 29MAR2023)

Table 14.4.1.1.1 PF-06863135 Duration of Treatment (18 month data) (Cycle) (Safety Analysis Set) (Protocol C1071003)

a. Duration from switch to last dose (months) is calculated as (last non-zero Q2W dose date - first switch date +1)/30.4375 excluding QW and Q4W dosing records.
b. Duration from switch to last dose (months) is calculated as (last non-zero Q4W dose date - first switch date +1)/30.4375 excluding QW and Q2W dosing records.
*Excluding participants consented to version prior to Protocol Amendment 6
PFIZER CONFIDENTIAL SDTM Creation: 02OCT2023 (13:12) Source Data: adexsum Table Generation: 12OCT2023 (02:19)
(Data cutoff date : 11Sep2023 Database snapshot date : 29Sep2023)

Table 14.4.1.2.1 PF-06863135 Exposure to Treatment - Overall (Safety Analysis Set) (Protocol C1071003) (15 month data)

[1] Cumulative dose = sum of actual dose levels (mg) of study drug.
[2] Relative Dose = total cumulative dose (mg)/total planned dose (mg)
[3] Overall DI (mg/week) = total cumulative dose (mg)/[sum of actual cycle duration (in weeks)]. Cycle DI (mg/week) = total cumulative dose for a given cycle (mg)/[actual cycle duration (in weeks)].
[4] Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] *100. Cycle RDI (%) = [Cycle DI (mg/week) / Cycle Planned DI (mg/week)] *100.
The descriptive summary statistics are calculated based on n, the number of Participants who have received at least one dose of study drug.
PFIZER CONFIDENTIAL SDTM Creation: 29MAR2023 (14:22) Source Data: adexsum Table Generation: 06APR2023 (03:26)
(Data cutoff date : 14MAR2023 Database snapshot date : 29MAR2023)

Table 14.4.1.2 PF-06863135 Exposure to Treatment - by Cycle (Safety Analysis Set) (Protocol C1071003) Cohort A (9 month data)

[1] Cumulative dose = sum of actual dose levels (mg) of study drug. [2] Relative Dose = total cumulative dose (mg)/total planned dose (mg).
[3] Overall DI (mg/week) = Total cumulative dose (mg)/(last zero/non-zero dose date - first dose date)/7 + (1 if on QW or 2 if on Q2W). Cycle DI (mg/week) = total cumulative dose for a given cycle (mg)/[actual cycle duration (in weeks)].
[4] Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] *100. Cycle RDI (%) = [Cycle DI (mg/week) / Cycle Planned DI (mg/week)] *100.
The descriptive summary statistics are calculated based on n, the number of Participants who have received at least one dose of study drug.
Cutoff date is 14OCT2022 for all participants.
PFIZER CONFIDENTIAL SDTM Creation: 27OCT2022 (15:37) Source Data: adexsum Table Generation: 28OCT2022 (09:39)
(Database snapshot date : 27Oct2022

Table 14.4.1.3 PF-06863135 Exposure to Treatment - Dose Reduction or Interruptions (Safety Analysis Set) (Protocol C1071003)

[1] A dose reduction is defined as a nonzero dose that is less than the planned dose and previous non-zero dose. Subsequent reductions after a dose re-escalation are counted as separate reductions.
[2] An interruption is defined as a 0 mg dose administered where reason for adjustment is provided on the dosing CRF.
The denominator of the row "Received Maximum 76 mg Dose after Initial Reduction" is number of participants with at least one dose reduction.
The denominator of the row "Received Maximum 76 mg Dose after Initial Reduction due to AE" is number of participants with any dose reduction due to AE.
The denominator of the row "Received Maximum 76 mg Dose after Initial Interruption" is number of participants with any dose interruptions.
The denominator of the row "Received Maximum 76 mg Dose after Initial Interruption due to AE" is number of participants with any dose interruption due to AE.
The denominator of all other rows is N, the number of participants in the Safety Analysis Set within each cohort.
PFIZER CONFIDENTIAL SDTM Creation: 29MAR2023 (14:22) Source Data: adexsum Table Generation: 06APR2023 (03:29)
(Data cutoff date : 14MAR2023 Database snapshot date : 29MAR2023)

Statistical Analysis Plan (SAP) section 6.6.3. Study Intervention Exposure (Full SAP available on request)

Exposure will be summarized based on the Safety Analysis Set.

Elranatamab is administered as a subcutaneous injection at 76 mg once every week on Days 1, 8, 15 and 21 of each 28-day cycle. Elranatamab is also administered on C1D4. A minimum of 2 days should be maintained between the 2 step-up priming doses (C1D1 and C1D4) and a minimum of 3 days between C1D4 dose and the first full dose (C1D8); a minimum of 6 days should be maintained between doses thereafter. The dose of elranatamab should be increased to 76 mg on C1D8 as long as the participant meets the criteria listed in Protocol Section 6.6.1. If a participant does not meet these criteria on C1D8, initiation of dosing with 76 mg should be deferred until the criteria are met. In addition, if a participant has received QW dosing for at least 6 cycles and has achieved an IMWG response category of PR or better persisting for at least 2 months, the dose interval will be changed from QW to Q2W. If the participant subsequently begins to have an increase of disease burden not yet qualifying as PD according to IMWG criteria, dose intervals should return to weekly dosing. If the dose interval is changed, cycles should remain the same length (ie, 4-week cycles).

The summary of treatment exposure elranatamab will include the following information:

- Treatment duration (months);
- Number of cycles started per participant (mean, median, min, max);
- Number and percent of participants starting a cycle (any cycle, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, ≥12-<18, ≥18-<24, ≥24 cycles);

- Total cumulative dose (mg);
- Overall dose intensity (mg/week);
- Overall relative dose (%);
- Overall relative dose intensity (%);
- Number and percent of participants who received 44 mg on the C1D1 visit;
- Number and percent of participants who received 32 mg on the C1D4 visit;
- Number and percent of participants who received 76 mg on the C1D8 visit;
- Number and percent of participants after 6 cycles who switched from QW to Q2W;
- Number and percent of participants, among those switching from QW to Q2W, who switched back to QW.

The treatment duration of elranatamab (in weeks) during the study for a participant is defined as:

Treatment duration (months) = (last dose date – first dose date + 1)/30.4375

The total cumulative dose (mg) of elranatamab is the sum of the actual doses that the participant received during the study; the cumulative dose (mg) of elranatamab per cycle is the sum of the actual doses that the participant received within that cycle (ie, total dose administered [mg]). Planned treatment duration is needed to calculate dose intensity (DI) and relative dose intensity (RDI). It is defined as follows:

- Planned treatment duration (weeks) = (number of cycles started x 4) - (number of weeks in the last cycle after permanent treatment discontinuation or data cutoff for those on-treatment).

The DI, relative dose (RD), and the RDI will be calculated for each participant overall across all cycles and also for each individual cycle as follows:

- Overall DI (mg/week) = Total cumulative dose (mg)/(last zero/non-zero dose date – first dose date)/7 + (1 if on QW or 2 if on Q2W). If C1D4 is the last visit, duration is 1 week if C1D4 occurred by then;
- Overall Planned DI (mg/week) = Total planned dose (mg)/ Planned treatment duration (weeks);
- Cycle DI (mg/week) = Total cumulative dose for a given cycle (mg)/Actual cycle duration (weeks);
- Cycle Planned DI (mg/week) = Total planned dose for a given cycle (mg)/4 weeks.

The total planned dose for a given cycle is defined as;

- Cycle 1: Planned dose (mg/cycle) = 12+32 + 76 × 3
- After Cycle 1:
- If the participant is on QW dosing schedule for the cycle:
- Planned dose (mg/cycle) = 76 × 4
- If the participant is on Q2W dosing schedule for the cycle:

- Planned dose (mg/cycle) = 76 × 2

  For last cycle, subtract planned doses after a participant permanently discontinues treatment or data cutoff for those on-treatment.

The total planned dose is the sum of the total planned dose across all cycles.
The RD and RDI are defined as follows:

- Cycle RD (%) = [Total given dose for a given cycle (mg) / Total planned dose for a given cycle (mg)] × 100;
- Overall RD (%) = [Total cumulative dose (mg) / Total planned dose (mg)] × 100;
- Cycle RDI (%) = [Cycle DI (mg/week) / Cycle Planned DI (mg/week)] × 100;
- Overall RDI (%) = [Overall DI (mg/week) / Overall Planned DI (mg/week)] × 100.
- Cycle DI and Cycle RDI will be summarized and plotted vs time (weeks).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]

Addendum to EAG Report

March 2024

File name:	Version	Contains [redacted]	Date
ID4026_Elranatamab _Addendum_v1	1	information	04/03/2024

Figure 1: Standard parametric fits of PFS, elranatamab weighted MAIC curve, adjusted for excess mortality (to replace Figure 1 in slide 16)

Figure 2 Final Company OS (generalized gamma) and PFS (generalized gamma) extrapolations applied in the model, adjusted for excess mortality. PFS extrapolation takes priority over OS extrapolation

(To replace Figure 1 in Slide 21)

Figure 3 EAG base case extrapolation of elranatamab MAIC weighted PFS (gamma) and OS (generalized gamma) data

Figure 4 EAG Scenario with elranatamab PFS and OS extrapolation curves derived by applying the hazard ratios from the MAIC to POM + DEX references curves (OS takes priority over PFS)