Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

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 GlaxoSmithKline:**
   a. Full submission
   b. Summary of Information for Patients (SIP)
   c. Submission addendum

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Myeloma UK

4. **External Assessment Report** prepared by Warwick

5. **External Assessment Report – factual accuracy check:**

6. **Technical engagement response from company:**
   a. Main response
   b. Updated severity modifier calculations
   c. Company factual accuracy check post-technical engagement

7. **Technical engagement responses and statements from experts:**
   a. Karthik Ramasamy, Consultant Haematologist & clinical expert nominated by GSK
   b. Rakesh Popat, Consultant Haematologist, clinical expert nominated by GSK

8. **Technical engagement responses from stakeholders**:
   a. Myeloma UK

9. **External Assessment Group critique of company response to technical engagement** prepared by insert EAG name:
   a. Main critique
   b. Critique on updated severity modifier calculations

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more prior therapies [ID2701]

Document B

Company evidence submission

October 2022

File name	Version	Contains confidential information	Date
ID2701 Belantamab mafodotin Company Evidence Submission Doc B v1.0 06Oct2022 AIC_CIC.docx	**v1.0**	**Yes**	**6th October, 2022**

Contents

List of figures

List of tables

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

B.1.1 Decision problem

This submission demonstrates the clinical and cost-effectiveness of Belamaf within its full marketing authorisation for this indication.

The decision problem addressed within this submission is broadly consistent with the NICE final scope for this appraisal as outlined in Table 1. The principal difference relates to the comparators considered relevant to this appraisal as detailed in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory multiple myeloma who have had at least 4 prior therapies, and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody, and whose disease has progressed on the last therapy.	As per scope	N/A
Intervention	Belantamab mafodotin (Belamaf, Blenrep®)	As per scope	N/A
Comparator(s)	Established clinical management without belantamab mafodotin including: Pomalidomide plus dexamethasone Panobinostat with bortezomib and dexamethasone Chemotherapy with or without a steroid and with or without thalidomide	Pomalidomide in combination with dexamethasone (PomDex) Panobinostat in combination with bortezomib and dexamethasone (PanoBorDex) – this is presented for completeness in Appendix M	PomDex is the most relevant comparator, representing current practice in the NHS. There is some use of PanoBorDex as observed in the NCRAS study however, clinical expert feedback suggests that the behaviour driving this usage is one of desperation. To acknowledge the usage observed in the NCRAS study, an analysis versus PanoBorDex is presented in Appendix M.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			The Company does not consider combinations of chemotherapy and a steroid (with or without thalidomide) to be relevant comparators for the reasons detailed in Section B.1.3.3.1.
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Time to next treatment Adverse effects of treatment Health-related quality of life	As per scope with the exception of time to next treatment (TTNT).	TTNT was not an endpoint in the DREAMM-2 trial. Time to discontinuation (TTD) was used to estimate the treatment duration, and therefore the treatment costs of Belamaf and PomDex in the economic analysis. Time to start of next therapy (TSNT), from discontinuation was used in combination with TTD to calculate TTNT for Belamaf.
Economic analysis	As per Reference Case	As per scope	N/A

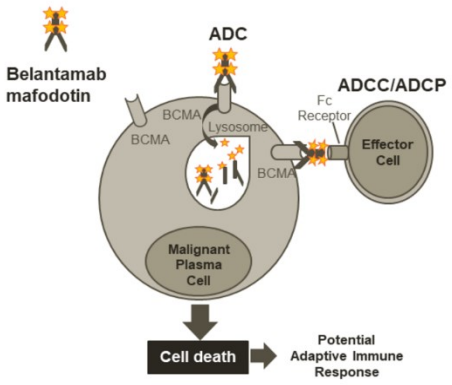
Abbreviations: AE, adverse event; CDF, cancer drugs fund; HRQoL, health-related quality of life; IMiD, immunomodulatory drug; MM, multiple myeloma; N/A, not applicable; NCRAS, National Cancer Registration and Analysis Service; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PanoBorDex, panobinostat with bortezomib and dexamethasone; PFS, progression-free survival; PomDex, pomalidomide with dexamethasone; TCR, triple class refractory; TTD, time to discontinuation; RRMM, relapsed/refractory multiple myeloma; 4L, fourth line; 5L, fifth line; 5L+, fifth line and beyond

B.1.2 Description of the technology being appraised

Table 2 presents a brief description of belantamab mafodotin (Belamaf) at a dose of 2.5 mg/kg for the treatment of 5L+ TCR MM.

The Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Belantamab mafodotin (Belamaf, brand name: Blenrep®)
Mechanism of action	Belamaf is a humanised IgG1κ monoclonal antibody conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF), targeting BCMA.[1] BCMA is expressed at high levels on MM cells, but is rarely expressed on most other cells aside from plasmablasts and differentiated plasma cells.[2–5] It is not expressed on memory B cells, naïve B cells, CD34+ haematopoietic stem cells, and other normal tissue cells.[6–8] BCMA works alongside two B cell activation receptors (BAFF-R) and transmembrane activator calcium modulator and cyclophilin ligand interactor (TACI) to regulate B cell proliferation and long-term survival, and maturation into plasma cells.[3] It does not maintain homeostasis of normal B cells, but is required for long-lived plasma cell survival.[9] Belamaf binds to cell surface BCMA and is rapidly internalised. Once inside the tumour cell, the cytotoxic agent is released disrupting the microtubule network, leading to cell cycle arrest and apoptosis. The antibody enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis induced by Belamaf is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells (Figure 1).[1] Due to the selective expression of BCMA, Belamaf is an effective therapeutic option for the treatment of relapsed/refractory multiple myeloma (RRMM).[9] **Figure 1. Belamaf mechanism of action**  Abbreviations: ADC=antibody-drug conjugate; ADCC/ADCP=antibody-dependent cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis; BCMA=B-cell maturation antigen.

Marketing authorisation/CE mark status	The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for Belamaf on 23rd July 2020.[10] The European Medicines Agency (EMA) and Medicines and Healthcare Regulatory Agency (MHRA) granted a conditional marketing authorisation for Belamaf on 25th August 2020 and 1st January 2021 respectively.[11,1]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Belamaf is indicated as a monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.[1]
Method of administration and dosage	Belamaf is for intravenous use. It is supplied as one vial of 100mg powder for concentrate for solution for infusion and therefore, must be reconstituted and diluted by a healthcare professional prior to administration. Belamaf should be infused over a minimum of 30 minutes.[1] The recommended dose is 2.5 mg/kg of Belamaf administered as an intravenous infusion once every 3 weeks. It is recommended that treatment should be continued until disease progression or unacceptable toxicity.[1] Recommended dose modifications in response to corneal adverse events and other adverse events can be found in the summary of product characteristics.[1]
Additional tests or investigations	Ophthalmic examinations (including visual acuity and slit lamp examination) should be performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and during treatment as clinically indicated.[1] Physicians should advise patients to administer preservative free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment as this may reduce corneal symptoms.[1] For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.
List price and average cost of a course of treatment	The list price of Belamaf is £5,707.83 for 1 vial of 100 mg powder for concentrate for solution for infusion.[12] The average cost of a course of treatment is £11,183.07 based on an average patient weight of 78.37kg in the DREAMM-2 trial. 2.5 mg x 78.37kg = 195.93 mg per patient 195.93 mg / 100 mg = 1.96 vials required 1.96 x £5,707.83 = £11,183.07
Patient access scheme (if applicable)	A confidential simple Patient Access Scheme (PAS) discount of [redacted]% has been proposed to NHS England/Patient Access Schemes Liaison Unit (PASLU). This results in a PAS price of £[redacted] for 1 vial of 100 mg powder for concentrate for solution.

Abbreviations: BAFF-R, B cell activation receptor; BCMA, B cell maturation antigen; CHMP, Committee for Medicinal Products for Human Use; mcMMAF, maleimidocaproyl monomethyl auristatin F; MM, multiple myeloma; NHS, National Health Service; PAS, Patient Access Scheme; PASLU, Patient Access Scheme Liaison Unit; RRMM, relapsed refractory multiple myeloma; TACI, transmembrane activator calcium modulator and cyclophilin ligand interactor

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

Overview of MM, epidemiology, humanistic and economic burden

- MM is an orphan, incurable, progressive, malignant plasma cell disorder, characterised by the abnormal proliferation of clonal B cells in the bone marrow.[13] It accounts for approximately 2% of all new cancer cases, with an estimated 5,951 new cases of MM in the UK each year, and accounting for an estimated 3,098 deaths every year.[14,15,16]
- The course of the disease typically involves periods of treatment and remission separated by relapses, known as RRMM.[17,18]
- The broad range of symptoms experienced by patients with MM pose a significant clinical burden, and at diagnosis are defined using the term "CRAB": hypercalcemia, Renal insufficiency, Anaemia and Bone lesions.
- The high symptom burden impacts HRQoL substantially, with a higher degree of symptom severity correlating with impact on HRQoL. Caregiver HRQoL is also affected, with MM patient carers reporting a lower QoL compared with those for patients with other cancers.
- Both health care resource utilisation and costs have increased over the last decades due to increased treatment options for patients with MM. This manifests itself as patient stays in hospital, of which the yearly hospitalisation cost for these patients was shown to be at least three times that of an average NHS patient.[19]

Current clinical pathway of care & unmet needs

- By the time patients reach 5L+, most will have been exposed to and be refractory to a PI, an IMiD and an anti-CD38 mAb, known as TCR, and the proportion of TCR patients is expected to increase as anti-CD38-based therapies become more widely available earlier on within the NICE pathway.[20]
- While there are treatment options recommended in broader populations capturing the 5L+ setting, there are no clear guidelines or established clinical practice specific to the management of 5L+ TCR MM.
- Patients in this setting are left with very limited and sometimes inadequate treatment options, which typically consist of PomDex, PanoBorDex, the inclusion in RCTs and/or compassionate use/early access programs and palliative care with chemotherapies.
- Survival outcomes in 5L+ TCR patients as observed in the England-based NCRAS study, where median overall survival ranged between [redacted] months with PanoBorDex and [redacted] months with PomDex.
- The limited effective treatment options in this setting may have a detrimental psychological impact on patients, leaving them with a feeling of hopelessness.[21]
- The urgent unmet need for this population and the high clinical demand for a treatment with a novel mechanism of action to extend survival and bring hope to patients is further evidenced

[redacted] and input from UK haematologists.

- There is therefore a need to rapidly broaden access to Belamaf in the NHS to help prolong disease control and overall survival for a group of patients that have a poor prognosis and limited treatment options.

Belantamab mafodotin

- Belamaf is a first-in-class anti-BCMA therapy, anticipated to be offered to patients in line with its licensed indication, *'as a monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy'* (5L+ TCR patients).[1]

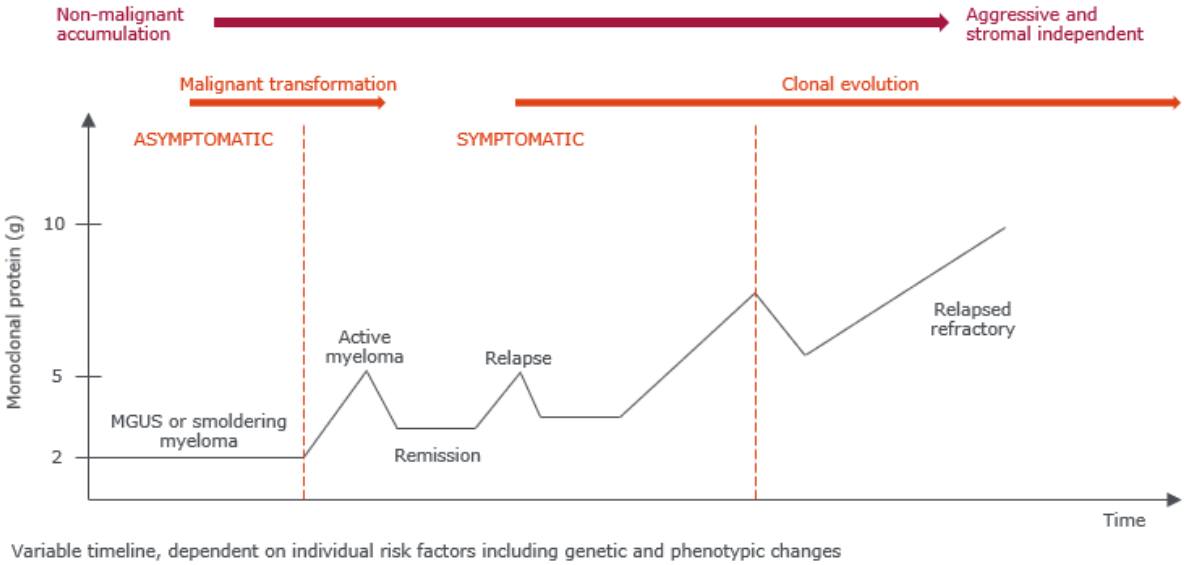
B.1.3.1 Disease overview

B.1.3.1.1 Overview of multiple myeloma

Multiple myeloma (MM) is an orphan, incurable, progressive, malignant plasma cell disorder, characterised by the abnormal proliferation of clonal B cells in the bone marrow.[13] These abnormal plasma cells produce and secrete large quantities of dysfunctional monoclonal immunoglobulins known as the M-protein, the hallmark of MM, at the expense of normal, infection-fighting antibodies. Cytogenetic abnormalities are detected in approximately 90% of the plasma cells with further genomic evolution occurring over the natural course of the disease.[22]

The clinical course of the disease, although variable, typically includes periods of treatment and remission separated by inevitable relapses, with the duration of response to treatment decreasing with subsequent treatments as shown in Figure 2.[23,24] Relapsed refractory multiple myeloma (RRMM) is defined as disease that becomes non-responsive while on therapy or that is progressive within 60 days of the last treatment in patients that previously achieved minimal response (MR) or better on prior therapy.[17,18] One of the major problems in MM is the evolution of the cancer and the build-up of resistance to different classes of therapies as the disease progresses.[25]

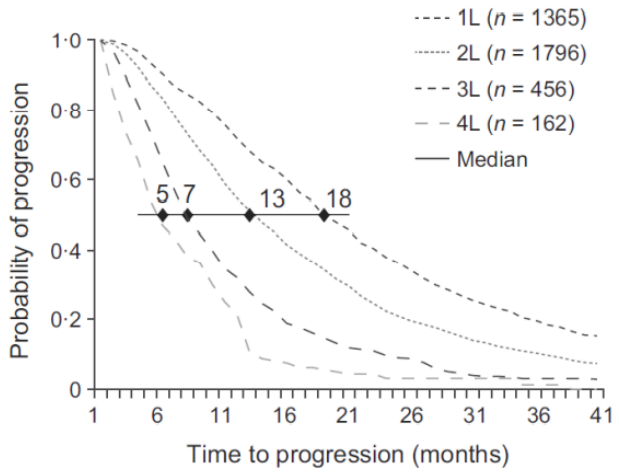
Figure 2. Clinical course of multiple myeloma



Adapted from Kurtin et al. 2013[24].
Abbreviations: MGUS, monoclonal gammopathy of undetermined insignificance

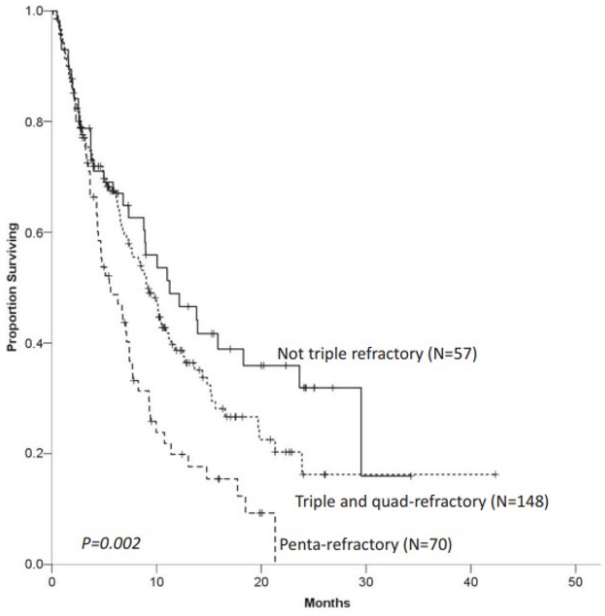
Time to disease progression of MM has been reported to decrease from 18 months, at first line (1L), to five months at (fourth line) 4L treatment by Yong et al. 2016[26] (Figure 3), in line with progression-free survival (PFS) being reported to decrease from 11 months, at 1L treatment, to seven months at 4L treatment by Jagannath et al. 2016[27]. Overall survival (OS) significantly decreases as patients progress to subsequent lines of therapy.[28] Refractory status has a considerable impact on OS based on real-world data (Figure 4).

Figure 3. Time to progression by line of treatment



From Yong et al. 2016
Abbreviations: 1L, first line; 2L, second line; 3L, third line; 4L, fourth line

Figure 4. OS of MM patients refractory to anti-CD38 MAb according to their refractoriness status to PIs and IMiDs



From Gandhi et al. 2019
Abbreviations: OS, overall survival; MM, multiple myeloma; mAb, monoclonal antibody; PI, proteasome inhibitor; IMiD, immunomodulatory drug

This submission focusses on 5L+ TCR MM, the population included in the decision problem. TCR MM, defined as being refractory to an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody (mAb), is a relatively recent population that has emerged following regulatory approval and reimbursement of the anti-CD38 agents Daratumumab and isatuximab.[29] In the UK, the anti-CD38 mAb Daratumumab was made available through the Cancer Drug Fund (CDF) from 2018 and was recommended through routine commissioning as monotherapy for patients who have received three prior lines of therapy including a PI and an IMiD in April 2022.[30]

B.1.3.1.2 Epidemiology

MM is a rare disease, accounting for approximately 2% of all new cancer cases (2016-2018) and 10.1% of haematological malignancies.[14,15] There are an estimated 5,951 new cases of MM in the UK each year, with an annual incidence of 12.05 cases per 100,000 people.[31] Each year, 43% of all new UK myeloma cases are diagnosed in patients aged 75 and over, with a median age at presentation of 72.6 years.[14,32] Older patients are more likely to have comorbidities, such as cardiovascular disease and renal insufficiency, which can eliminate more potentially efficacious therapies from being used due to increased risk of toxic side effects.[33] There is a greater incidence in males, accounting for 58% of cases in the UK, with females accounting for 42%.[31]

MM contributes to an estimated 3,098 deaths every year in the UK, which equates to more than eight deaths each day.[16]

B.1.3.1.3 Clinical burden

Patients with MM typically present with nonspecific symptoms including anaemia, bone pain, fatigue, weight loss, and renal dysfunction.[34] At diagnosis, the clinical manifestations of symptomatic MM are present in approximately 70% of patients and are commonly defined using the term “CRAB”: hypercalcemia, Renal insufficiency, Anaemia, and Bone lesions.[35,36] Hypercalcemia is often associated with nausea, vomiting, confusion, constipation, and lethargy and is present in 9% to 13% of patients at diagnosis.[13,35] Renal insufficiency is common, with close to 20% of patients presenting with renal impairment or renal failure.[13,35] Hypercalcemia can also contribute to renal dysfunction.[37] Anaemia is observed in about 70% of newly diagnosed MM patients; patients with anaemia may experience dyspnoea, fatigue, and/or dizziness.[13,35] Bone lesions and associated bone pain are present in up to 80% of newly diagnosed MM (NDMM) patients.[13] Symptomatic bone lesions commonly occur in the spine, pelvis, skull, humeri, and femurs.

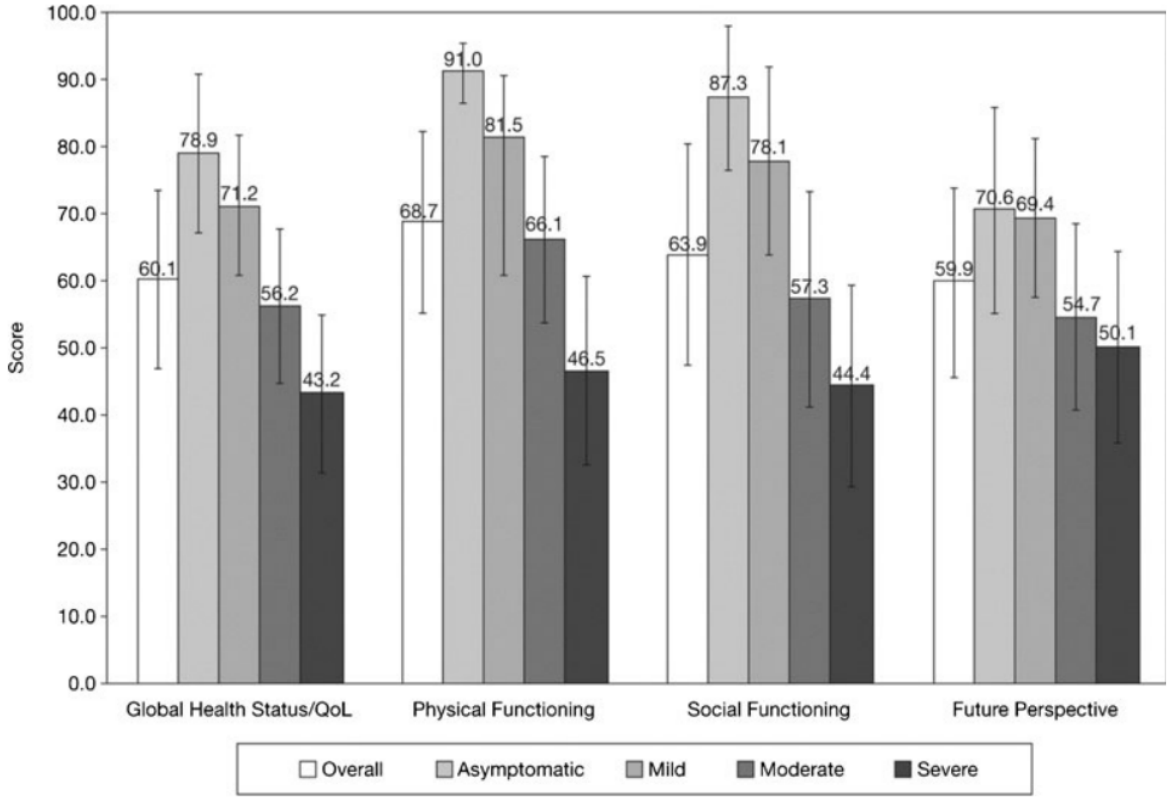
Other clinical manifestations of MM include neuropathy, hyperviscosity syndrome, haemorrhage/coagulopathy, and infections.[35] Approximately 1% to 2% of patients have extramedullary disease (myeloma cells forming tumours outside of the bone marrow) at the time of diagnosis, and 8% develop extramedullary disease later in the disease course.[36] In a meta-analysis of 34 clinical studies in MM patients (N=3,023), including 12 studies of patients with advanced stages of MM, the most prevalent symptoms were fatigue (98.8%), pain (73%), constipation (65.2%), and tingling in the hands and feet (53.4%).[38]

As the disease progresses, symptoms and complications from previous treatments may persist. In advanced stages of MM, the focus of this submission, patients continue to have a high symptom burden, including fatigue, bone pain, anaemia, and depression, which may significantly impair health-related quality of life (HRQoL).[38,39]

B.1.3.1.4 Humanistic Burden

The high symptom burden experienced by patients often results in a detrimental impact on HRQoL, with the impairment found to be greater with a higher degree of symptoms severity, disease or treatment related, as shown in Figure 5.[21]

Figure 5. Health-related quality of life score by symptom level in multiple myeloma[21]



From Jordan et al. 2014.[21]
Higher scores represent a better quality of life. Error bars represent standard deviation. Abbreviations: QoL, quality of life

A study comparing a cohort of RRMM patients to an age-matched general population control highlighted significant impairment in several quality of life dimensions, including physical ($p<0.0001$) and social function ($p<0.0001$).[40] Another study reported the decline in the European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (EORTC-QLQ-C30) global health status scores as treatment line progressed, beginning at a mean score of 63.0 at 1L to 53.6 at 4L or later ($p=0.0005$), highlighting the need for treatments that maintain or improve HRQoL.[41] Scores for all five of the functional scales were lower again as treatment line progressed, with physical and role functioning showing statistically significant reductions from 1L to 4L or later ($p=0.001$, $p=0.002$ respectively). The same pattern was reported with the EORTC MM module Quality of Life Questionnaire (QLQ-MY20) scores, demonstrating a worse HRQoL with more relapse cycles.[41]

The symptoms also affect patients' ability to work. Neuropathy can result in the inability to stand for extended periods of time, bone fragility and fractures occur more frequently, and fatigue is also a challenge that impacts patients being able to work.[42] However it is not only the physical symptoms that pose challenges; mental difficulty in accepting their diagnosis and/or relapse can lead patients to have low mood and a lack of motivation.[42,43] Furthermore, the limited effective treatment options available in the 5L+ TCR setting may have a detrimental psychological impact on patients, leaving them feeling underserved, abandoned and hopeless.

In addition to patients themselves, their caregivers' HRQoL is also negatively affected. Caregivers are often family members, adding to the psychological impact around fears of death and suffering.[44–46] The burden of caring for someone with MM may restrict the caregiver's daily activities, leading to isolation and a lack of social support.[47] Specifically, caregivers for patients with MM reported a lower quality of life compared with those for patients with other cancers.[48] A study on HRQoL of MM patient caregivers noted a lower quality of life was associated with financial and emotional unmet needs, and psychological morbidity.[49] Social support was shown to improve quality of life ($p<0.001$), as was better coping methods ($p<0.001$).

B.1.3.1.5 Economic burden

With the increased number of treatment options for MM over the last decades, patients are living longer and receiving more lines of therapy, including combination therapy, resulting in a substantial economic burden of MM. Health care resource utilisation and costs have increased, particularly for patients whose disease has repeatedly progressed on multiple lines of therapy.[50,51]

This economic burden manifests itself in terms of patient stays in hospital. It has been reported that the proportion of patients requiring at least one hospitalisation increased with successive treatment lines in the UK, with percentages rising from 10% for second line (2L) to 22% for 5L+.[50] Additionally, length of hospital stay increased with each therapy line, from an average of 7.2 days with 2L therapies, to an average of 8.1 days with 5L+ therapies.[50]

A retrospective study reported that UK hospitalisation rates in patients with three prior lines of therapy (at 4L treatment) were higher during active treatment (67%) than during off-treatment periods of remission/stable disease (29%) or post-progression periods (21%). This trend was also observed in patients with at least four prior lines of therapy (at 5L+ treatment).[50]

Between 1 April 2014 and 31 March 2018, an average of 188,586 NHS hospital admissions per year were accounted for by patients with MM. The mean annual core cost of these admissions was £45,847,286 for elective and £56,912,522 for unplanned. The yearly hospitalisation cost for patients with MM was shown to be at least three times that of an average NHS patient, and was higher than that of patients with a more prevalent cancer, such as colon cancer.[19]

B.1.3.2 Life expectancy

The survival of MM patients is influenced by both clinical and laboratory factors, such as prior lines of therapy, refractory status, and extramedullary disease.[52,53] While novel therapies have improved survival of MM patients over time, five-year survival rates remain below 50% in the UK,[54,55] with outcomes worsening over the course of the disease, and as patients develop treatment resistance.

Poor OS outcomes have been observed in heavily pre-treated triple class exposed/refractory patients. In the recent, Company-initiated, RWE study conducted in [redacted] 5L+ TCR patients using the England-based National Cancer Registration and Analysis Service (NCRAS) dataset, median OS reported for the 5L+ TCR MM cohort was [redacted] months (95% CI [redacted]).

Full details of the methods and results of the NCRAS study are presented in Section B.2.3.2 and B.2.5.2.

In the international LocoMMotion study and the three US-based studies (namely the MAMMOTH, Mayo Clinic and Connect® MM Disease Registry), poor survival outcomes were reported for TCR MM patients.[56–59] The prospective LocoMMotion study, was conducted in triple class exposed patients, of which approximately 75% were TCR patients. The total cohort reported a median of four prior lines of therapy, with a median OS of 12.4 months. Among those who were TCR, median OS was reduced to 11 months.[57] In the retrospective MAMMOTH study, a median OS of 10.3 months was reported for TCR patients who received a median of five prior lines of therapy.[56] In the Mayo Clinic study, conducted in heavily pre-treated TCR patients (the median number of lines of therapy for the entire cohort was eight (range 1–17), patients were exposed to a median of five (range 1–12) lines of therapy prior to TCR status, and median OS was one year.[58] Finally, in the recent study using the US Connect® MM Disease Registry, TCR patients experienced a median OS of 8.9 months. Median OS was higher (10 months) for those who had received less than four prior line of treatments than for those who had received four or more prior line of treatments (8.0 months).[59]

Although the TCR patients enrolled in the international and three US-based studies received some therapies not yet available in the UK, the survival estimates are broadly similar to the survival estimates observed in England in the NCRAS dataset.[60]

B.1.3.3 Clinical management of RRMM and place of Belamaf in the treatment pathway

The main goals of MM treatment are to maximise the depth and duration of response to improve overall survival and quality of life, as well as to alleviate symptoms and further organ damage, while minimising toxicity.[61]

B.1.3.3.1 Treatment pathway in 5L+ TCR MM

Although MM remains incurable, there has been a significant improvement in PFS and OS in the last 5-10 years with the introduction of new agents and combinations of agents to the MM therapeutic landscape.[62]

In the UK, after four prior lines of therapy, patients with RRMM usually have received and are refractory to a PI, an IMiD and an anti-CD38 mAb (so called TCR MM), limiting the options available to treat them upon progression. The proportion of TCR patients is expected to increase in this setting as anti-CD38-based therapies become more widely available earlier on within the NICE pathway.

Although NICE recommends PomDex and PanoBorDex as treatment options for 5L+ RRMM patients (TA427 and TA380 respectively), there is no established standard of care (SoC) for 5L+ patients who are also TCR.[63–65]

To better understand the MM treatment patterns and outcomes of patients in England who are 5L+ TCR, the Company conducted a RWE study using the NCRAS dataset.

PomDex

In this study, PomDex use was reported in [redacted] and [redacted] of the patients in the 5L+ TCR cohort and 5L only TCR cohort, respectively. These observations are consistent with the findings from the [redacted], showing that approximately [redacted] of patients received PomDex at 5L. This confirms that PomDex is the most relevant comparator for this appraisal.

PanoBorDex

Whilst some use of PanoBorDex in the 5L+ TCR cohort ([redacted]) was observed in the NCRAS study, feedback from external experts suggest this usage is the result of desperation in the absence of any alternative treatment options: *"…when clinicians are up against a patient who is multiply relapsed and refractory and there are no reasonable therapies, clinicians are wondering what would I be allowed to use?…it [the use of PanoBorDex] is a behaviour born out of desperation…"*.

Efficacy outcomes for PanoBorDex are likely to be poor in this setting based on UK RWE studies for 5L+ patients who are refractory to a PI,[66] double refractory to a PI and IMiD,[67] or TCR as demonstrated by the NCRAS study (median TTNT [redacted] months [95% CI [redacted]] and median OS [redacted] months [95% CI [redacted]]).

RWE studies also demonstrated that PanoBorDex is associated with significant levels of haematological toxicity as well as important neurological and gastrointestinal side effects which need to be carefully monitored and actively managed in the outpatient setting, and are dose limiting in many patients.[66]

The behaviour driving the usage of PanoBorDex and its expected efficacy and safety profile demonstrates the high unmet need for this group of patients. Furthermore, the limited use of PanoBorDex in a 5L+ TCR population results in a small sample size in the NCRAS study (N=[redacted] patients) which limits the interpretability of Kaplan-Meier (KM) curves for key efficacy endpoints. Thus, estimating the relative efficacy and cost-effectiveness of Belamaf versus PanoBorDex is challenging and associated with a high level of uncertainty.

For the reasons described above, the main and most clinically relevant comparator considered for this appraisal is PomDex. However, to acknowledge the usage observed in the NCRAS study an analysis versus PanoBorDex is presented in Appendix M.

Chemotherapy combinations

The NCRAS study captures some use of chemotherapies such as the treatment combination of dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide (DT-PACE), and cyclophosphamide in combination with thalidomide in a 5L+ TCR setting however, usage is limited ([redacted]) compared to PomDex ([redacted]) and is aligned with the level of usage seen within [redacted]. UK clinical experts indicated that this use of chemotherapies likely reflects a palliative usage rather than an active treatment approach.

A small use of bendamustine has also been observed within the NCRAS study and in the [redacted]. However, bendamustine is not commissioned by NHS England for the treatment of RRMM[68]; therefore, it is not an appropriate comparator.

For the reasons described above, combinations of chemotherapy and a steroid (with or without thalidomide) are not relevant comparators in this appraisal.

Other treatments

Finally, novel investigational agents may also be offered to 5L+ TCR MM patients however, this was not recorded in the NCRAS dataset and thus it would not be possible to generate evidence for key efficacy outcomes and subsequently derive any indirect comparison data.

B.1.3.3.2 Unmet need

By the time MM patients reach 5L within the NICE treatment pathway, most will be TCR as they will have been exposed to and become refractory to a PI, an IMiD and an anti-CD38 mAb,[20] and consequently will have extremely limited treatment options.

Due to the disease pathophysiology, recycling of existing therapies in RRMM has limited efficacy as patients are re-exposed to treatments or classes of agents that they have previously developed resistance to.[28]

Survival outcomes are very poor in 5L+ TCR patients, with a median OS ranging between [redacted] months with PanoBorDex and [redacted] months with PomDex, based on the NCRAS study.

This emphasises the high and urgent unmet medical need for therapies that have a novel mechanism of action which can extend survival, bring hope to patients and offer clinicians an increased flexibility in earlier treatment decisions by adding a new treatment option in the 5L+ TCR MM treatment pathway.[20]

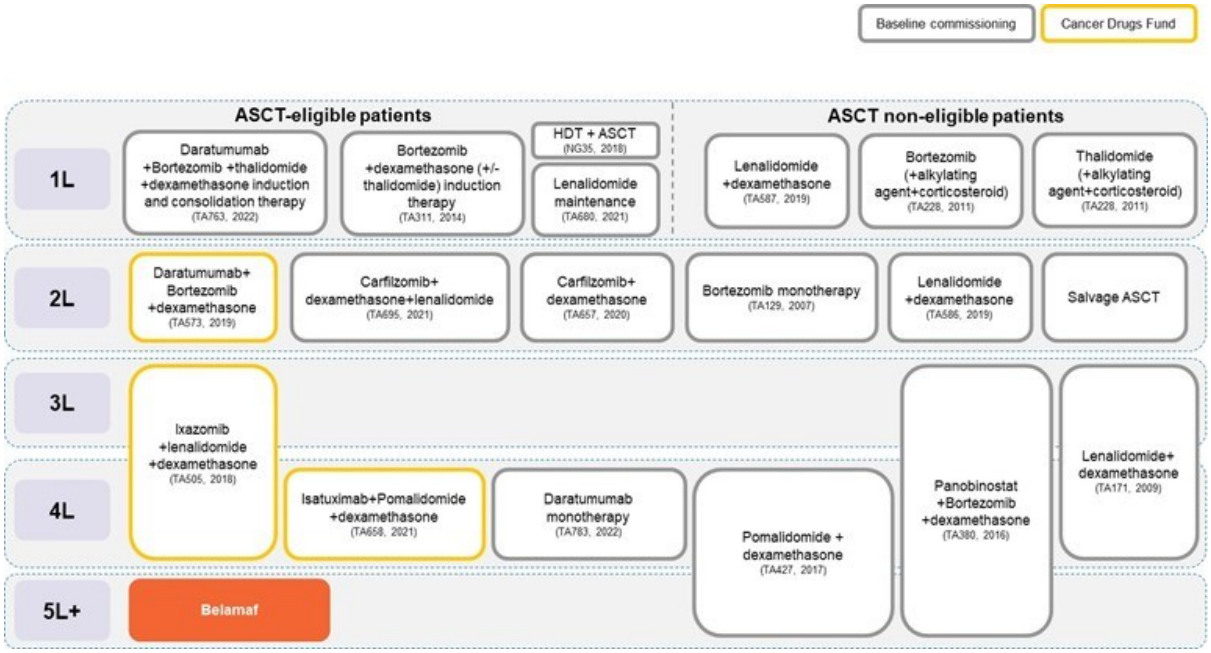
The extent of the unmet need is further evidenced by the observed increase in the uptake of [redacted].

The unmet need for 5L+ TCR patients is also acknowledged in comments from the UK Myeloma Forum (UKMF) during the consultation on the draft scope: *"This [appraisal] is urgent – there is a need to rapidly introduce effective therapies to help prolong disease control and overall survival. Importantly this [is] for a group of patients that have limited treatment options. This is evidenced* [redacted]".
There is therefore a need to broaden access to Belamaf in the NHS to help improve outcomes for a group of patients that have limited treatment options.

B.1.3.3.3 Anticipated positioning of Belamaf in the treatment pathway

In line with its licensed indication (adult MM patients, who have received at least four prior therapies and whose disease is refractory to at least one PI, one IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy[69]), Belamaf is anticipated to be offered to patients who are 5L+ and are TCR as depicted in Figure 6.

Figure 6. NICE treatment pathway in multiple myeloma and anticipated positioning of Belamaf



Abbreviations: ASCT, autologous stem cell transplant; HDT, high dose therapy; TA, technology appraisal; 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; 5L+, fifth line and beyond

Belamaf is already recommended for treating heavily pre-treated RRMM patients outside of the UK. It is recommended for TCR patients in the EHA-ESMO 2021 clinical guidelines for MM as well as for patients in 5L+ in the National Comprehensive Cancer Network (NCCN) 2022 guidelines.[70,71]

B.1.4 Equality considerations

There are no known equality issues relating to the use of Belamaf in patients with 5L+ TCR MM.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- The DREAMM-2 trial, an open-label, randomised, two-arm (without a comparator arm) multi-centre Phase II study investigates the efficacy and safety of Belamaf 2.5 mg/kg and 3.4 mg/kg in patients with MM who had disease progression on or after receiving three or more previous lines of anti-myeloma treatments. All the patients in the 2.5mg/kg arm were refractory to a PI, an IMiD and an anti-CD38 mAb.

- DREAMM-2 included 97 patients in the 2.5 mg/kg cohort (the licensed dose and focus for this submission). The primary endpoint of the trial was ORR based on IRC assessment of response, and the secondary endpoints were ORR based on IA, CBR, DoR, TTR, PFS, TTP, OS and HRQoL.

    - At the point of the final analysis, [redacted]% of responders achieved deep responses of VGPR or better, with a median TTR of [redacted] months. Median OS was [redacted] months, and [redacted]% of patients had died. Median PFS was [redacted] months, and [redacted]% of patients had progressed or died. Both median OS and PFS were longer in responders. TTD was [redacted] months, and [redacted]% of patients had discontinued treatment.

    - No new safety signals were identified in the final analysis of the DREAMM-2 study. The rates of grade ≥3 haematologic AEs were low (thrombocytopenia, [redacted]; anaemia, [redacted]; and neutropenia, [redacted]) as were IRRs of any grade [redacted]). There is recovery and resolution of keratopathy and best corrected visual acuity (BCVA) for the majority of patients in DREAMM-2 and there have been no reports of permanent loss of vision.

- There is currently no head-to-head data for Belamaf monotherapy versus PomDex in a 5L+ TCR MM population; a clinical SLR was conducted to identify clinical evidence for PomDex however, no relevant studies were identified.

- The RWE study conducted by the Company using the NCRAS dataset informed the efficacy of PomDex in a cohort of 5L+ TCR patients. The following efficacy outcomes were reported for PomDex: median OS = [redacted] months, median TTD = [redacted] months and median TTNT = [redacted] months.

- An unanchored MAIC was conducted to estimate the relative efficacy of Belamaf versus PomDex for OS, TTD, and TTNT. Overall, the MAIC suggested greater efficacy benefits for Belamaf for all outcomes. However, the interpretability of the results was limited due to the low effective sample size resulting from a partial adjustment. The MAIC outcomes were therefore considered plausible but not sufficiently reliable to inform the base-case economic analysis.

- A naïve comparison showed a longer OS in patients treated with Belamaf than in those treated with PomDex ([redacted] months versus [redacted] months), despite the notable differences in patients' characteristics suggesting that the Belamaf cohort may include more severe patients.

- The efficacy and safety data from DREAMM-2 and the NCRAS study demonstrate that Belamaf has the potential to shift the treatment paradigm in this heavily pre-treated, TCR MM patient population with a poor prognosis, where there are few alternative treatment options and an exquisitely high unmet medical need.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in May 2019 to identify clinical evidence for RRMM patients who received at least three prior lines of therapy. This clinical SLR has since been updated to August 2022, while restricting the population to patients in the 5L+ setting. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Belamaf

DREAMM-2 was the only identified trial to evaluate the clinical efficacy and safety of Belamaf for the treatment of 5L+ TCR MM patients. The clinical data and cost-effectiveness analyses presented in this submission are therefore based on this trial.

The DREAMM-2 trial evaluated the efficacy and safety of two doses of Belamaf: 3.4 mg/kg and 2.5 mg/kg. This submission focusses on the licensed 2.5 mg/kg dose of Belamaf therefore only the results for this treatment arm are reported (Sections B.2.3 to B.2.9). The clinical effectiveness evidence summary for DREAMM-2 is presented in Table 3.

Table 3. DREAMM-2 - Clinical effectiveness evidence for Belamaf

Study	DREAMM-2 study protocol[72], 13-months follow-up clinical study report[73], and unpublished final analysis, Lonial et al. 2020[69], Lonial et al. 2021[74]				
Study design	Phase 2, open-label, randomised, two-arm (without a comparator arm) multi-centre study				
Population	MM patients who had disease progression on or after receiving three or more previous lines of anti-myeloma treatments**, and** are refractory to a PI, an IMiD and an anti-CD38 mAb 97 patients received Belamaf 2.5 mg/kg				
Intervention(s)	Belamaf 2.5 mg/kg Belamaf 3.4 mg/kg (unlicensed and not reported in the rest of the submission)				
Comparator(s)	N/A				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	
Rationale for use/non-use in the model	This trial investigated Belamaf 2.5 mg/kg in the population included in the decision problem, and includes key outcomes used in the economic model				

Study	DREAMM-2 study protocol[72], 13-months follow-up clinical study report[73], and unpublished final analysis, Lonial et al. 2020[69], Lonial et al. 2021[74]
Reported outcomes specified in the decision problem	Overall survival Progression-free survival Response rates Time to treatment discontinuation Time to next treatment* Adverse effects of treatment Health-related quality of life
All other reported outcomes	Overall survival by response Progression-free survival by response Duration of response Time to progression Duration of response by response Time to response Minimum residual disease

Abbreviations: mAb, monoclonal antibody; MM, multiple myeloma; *endpoint reconstructed by combining time to discontinuation with time to start of next therapy from discontinuation

B.2.2.2 Comparators

The SLR did not retrieve any relevant clinical evidence for the comparator PomDex in 5L+ TCR MM patients. Therefore, to generate efficacy evidence for PomDex in the population considered in this appraisal, a RWE study was conducted by the Company using the England-based NCRAS dataset.[75] This study is described in Section B.2.3.2 and results are presented in Section B.2.5.2.

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

B.2.3.1 Belamaf (DREAMM-2)

B.2.3.1.1 Summary of trial methodology

DREAMM-2 is a phase II, open-label, randomised, two-arm study (without a comparator arm) to investigate the efficacy and safety of two doses of the antibody drug conjugate Belamaf in patients with MM, who had received 3 or more prior lines of treatment, are refractory to a PI, an IMiD and who had failed an anti-CD38 mAb. All patients in the 2.5 mg/kg arm of the trial were also refractory to an anti-CD38 mAb.

It was conducted in 58 MM specialty centres in 8 countries (Australia, Canada, France, Germany, Italy, Spain, the United Kingdom, and the United States), including 7 centres in the UK.

Patients were randomly assigned in a 1:1 ratio to Belamaf 2.5 mg/kg IV Q3W or Belamaf 3.4 mg/kg IV Q3W, through central assignment of a randomisation number, generated by the Company's Clinical Statistics Department. Stratification factors included the number of prior

lines of therapy (≤4 vs >4) and cytogenetic risk categories (high risk defined as t(4;14), t(14;16), and 17p13del vs non-high risk - all others).[76]

After the first treatment cycle, patients may have had their dose reduced for toxicities, as displayed in Table 4. If the patient could not tolerate the drug after the allowed dose reduction, they were withdrawn from the study for lack of tolerability; only one dose reduction to 1.92 mg/kg was permitted for the lower starting dose of 2.5 mg/kg.

Table 4. Permitted dose reductions in DREAMM-2

Starting dose	1st reduction
2.5 mg/kg	1.92 mg/kg

Source: DREAMM-2 trial protocol[72]

As this trial was open-label, the trial coordinators had access to the patient-level data throughout the study.

The primary efficacy endpoint was overall response rate (ORR) based on Independent Review Committee (IRC) assessment of response, defined as the percentage of patients with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]), according to the International Myeloma Working Group (IMWG) response criteria. It was assessed in patients with a confirmed response.

Other outcomes included:

- Secondary outcomes: ORR based on investigator assessment, clinical benefit rate (CBR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), and health-related quality of life (HRQoL)
- Exploratory outcome: minimum residual disease (MRD)

A summary of the study design and methodology is reported in Table 5, and efficacy outcome measures in Table 5.

Table 5. DREAMM-2 methodology

Study	DREAMM-2 study protocol[72], 13-months follow-up clinical study report[73], Lonial et al. 2020[69],Lonial et al. 2021[74] and unpublished final analysis
Trial design	Phase 2, open-label, randomised, two-arm (without a comparator arm) multi-centre study
Eligibility criteria	**Inclusion criteria:** • Age 18 or older • ECOG performance status of 0-2 • Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG criteria[77], and • Has undergone a SCT or is considered transplant ineligible • Has failed at least 3 prior lines of anti-myeloma treatments, • Is refractory to a PI, an IMiD and an anti-CD38 mAb for the 2.5 mg/kg arm • Has measurable disease with at least one of the following:

	a. Serum M-protein ≥0.5 g/dL (≥5 g/L) b. Urine M-protein ≥200 mg/24h c. Serum free light chain (FLC) assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65) • Patients with a history of autologous stem cell transplant were eligible for study participation provided the following eligibility criteria were met: a. Transplant was >100 days prior to study enrolment b. No active infection(s) c. Patient met the remainder of the eligibility criteria outlined in the protocol • Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies • Adequate organ system functions (including sufficient renal function as measured by estimated glomerular filtration rate ≥30 mL/min per 1·73 m²) • All prior treatment related toxicities (defined by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, must be ≤Grade 1 at the time of enrolment except for alopecia and Grade 2 peripheral neuropathy **Exclusion criteria:** The main exclusion criteria were: • Systemic anti-myeloma therapy within ≤14 days or five half-lives, whichever is shorter, or plasmapheresis within seven days prior to the first dose of study drug • Systemic treatment with high dose steroids (equivalent to ≥60 mg prednisone daily for ≥four days) within the past 14 days if administered to treat MM or non-MM disease • Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' syndrome, active plasma cell leukaemia at the time of screening. • Prior allogeneic SCT • Current corneal epithelial disease except mild punctate keratopathy • Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs. Prior BCMA targeted therapy. • Evidence of active mucosal or internal bleeding • Any major surgery within the last four weeks • Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect patients' safety). • Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including laboratory abnormalities) that could interfere with patient's safety, obtaining formal consent or compliance to the study procedures • Malignancies other than disease under study are excluded, except for any other malignancy from which the patient has been disease-free for more than 2 years and, in the opinion of the principal investigators and Company Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (MM).

	Patients with curatively treated non-melanoma skin cancer may be enrolled. • Pregnant or lactating female
Settings and where data were collected	58 MM specialty centres in 8 countries, including 7 centres in the UK.
Trial drugs and concomitant medications	The only trial drug included was Belamaf, at either 2.5 mg/kg Q3W, or 3.4 mg/kg Q3W. Patients received full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrhoeal, and analgesics, as appropriate. Concomitant therapy with bisphosphonates was allowed. Patients were permitted to receive local irradiation for pain or stability control.

Outcomes used in the economic model or specified in the scope, including primary outcome	**Efficacy outcomes**
	• Primary efficacy endpoint (ITT population):
	  • ORR assessed by an independent review committee (IRC)
	• Secondary efficacy endpoints (ITT population):
	  • ORR based on investigator assessment
	  • CBR
	  • DoR
	  • TTR
	  • PFS
	  • TTP
	  • OS
	  • HRQoL
	• Exploratory outcome (ITT population):
	  • MRD
	• All efficacy outcomes are defined in Table 6.
	• Additional endpoints:
	  • TTD, (safety population)*
	  • TTNT, (ITT population)*
	Safety outcomes (safety population)
	• Adverse events
	• Serious adverse events
	• Adverse events leading to discontinuation, dose delay and dose reduction of study treatment
	• Adverse events of special interest; corneal events, thrombocytopenic events, infusion-related reactions

Abbreviations: BCMA, B-cell maturation antigen; CBR, clinical benefit rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FLC, free light chain; HRQoL, health-related quality of life; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IRC, independent review committee; ITT, intent-to-treat; MM, multiple myeloma; MRD, minimal residual disease; NCI-CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; SCT, stem cell transplant; TSNT, time to start of next treatment; TTD, time to treatment discontinuation; TTP, time to progression; TTR, time to response
Source: DREAMM-2 13-months follow-up CSR[73] and Lonial et al., 2020[69]
* Please note these outcomes were analysed in a post-hoc analysis and are not reported in the CSR

Table 6. DREAMM-2 efficacy outcome measures definitions

Endpoint type	Measure	Description
Primary	Overall response rate (ORR) based on Independent Review Committee (IRC)	Based on IRC assessment of responses in patients with a confirmed response. Defined as the percentage of patients with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]), according to the International Myeloma Working Group (IMWG) response criteria.
Secondary	ORR based on investigator assessment	Based on confirmed responses where available.
	Clinical benefit rate (CBR)	Defined as the percentage of patients with a confirmed minimal response or better according to the IMWG response criteria.
	Duration of response (DoR)	Defined as the time from first documented evidence of PR or better until the earliest date of disease progression (PD) per IMWG, or death due to PD among patients who achieve a response. Responders without disease progression will be censored at the censoring timepoint for time to progression (TTP).
	Time to response (TTR)	Defined as the time between the date of randomisation and the first documented evidence of response (PR or better), among patients who achieve a response (i.e., confirmed PR or better).
	Progression-free survival (PFS)	Defined as the time from randomisation until the earliest date of PD per IMWG, or death due to any cause.
	Time to progression (TTP)	Defined as the time from randomisation until the earliest date of progression-free (PF) disease per IMWG, or death due to PD.
	Overall survival (OS)	Defined as the time from randomisation until death due to any cause. Patients who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up.
	Health-related quality of life (HRQoL)	European Organisation for Research and Treatment (EORTC) QLQ-C30 and multiple myeloma-specific EORTC-QLQ-MY20.
Exploratory	Minimal residual disease (MRD)	Defined as the percentage of patients who are MRD negative by Next Generation. It was assessed in patients who achieve ≥VGPR or better Sequencing.
Additional	Time to discontinuation (TTD)*	Defined as time on the treatment until discontinued. This is analysed from the safety population.
	Time to next treatment (TTNT)*	TTNT was not a pre-specified outcome. It was reconstructed by combining TTD to TSNT from discontinuation.

Abbreviations: CBR, clinical benefit rate; CR, complete response; DoR, duration of response; EORTC, European Organisation for Research and Treatment; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete

response; TSNT, time to start of next treatment; TTD, time to treatment discontinuation; TTNT, time to next treatment; TTP, time to progression; TTR, time to response; VGPR, very good partial response
Source: DREAMM-2 CSR
* Please note these outcomes were extracted in a separate supplementary post-hoc analysis to the CSR

B.2.3.1.2 Patient demographics and baseline characteristics

A summary of demographic and disease-relevant baseline characteristics is reported in Table 7.

A total of 97 patients receiving Belamaf 2.5 mg/kg were included in the intent-to-treat (ITT) population. Patients were predominantly white (74%), with a median age of 65 years. Patients ≥75 years of age accounted for 13% of study patients.

All patients enrolled in the study had secretory RRMM, and predominantly had IgG (67%) or IgA (23%) myeloma. Most of the patients entered the study with International Staging System (ISS) stage II or III multiple myeloma (77%), 27% of all patients had high risk cytogenetics. Extramedullary disease was present in 23% of patients.

Patients had received multiple prior lines of therapies (median = 7, range: 3 to 21).

It should be noted that in the trial population, [redacted] patients ([redacted]%) received three prior lines of therapy which is outside of the population considered in this appraisal. Besides the number of prior lines received, baseline characteristics were comparable between the 5L+ only cohort and the ITT population. In addition, when comparing the treatment effect of Belamaf 2.5 mg/kg in those patients to the efficacy in the ITT population, results were broadly comparable (Section B.2.6). Therefore, the ITT population was used to inform this appraisal and results for all study endpoints as well as in the economic analysis are based on the ITT population.

Table 7. DREAMM-2 baseline characteristics (ITT population and 5L+ subgroup)

	Belamaf Q3W	
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=[redacted]) Patients in 5L+ only**
Sex, n (%)	97	[redacted]
Male	51 (53)	[redacted]
Age (years), n	97	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	65.0 (39 to 85)	[redacted]
Age Group (years), n (%)	97	[redacted]
<18	0	[redacted]
18 to <65	45 (46)	[redacted]
65 to <75	39 (40)	[redacted]
³75	13 (13)	[redacted]
Race Detail, n (%)	95	[redacted]
Black or African American	16 (16)	[redacted]

	Belamaf Q3W	
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=[redacted]) Patients in 5L+ only**
Asian - Central/South Asian Heritage	[redacted]	[redacted]
Asian - East Asian Heritage	[redacted]	[redacted]
Asian - South East Asian Heritage	[redacted]	[redacted]
White - Arabic/North African Heritage	[redacted]	[redacted]
White - White/Caucasian/European Heritage	72 (74)	[redacted]
Mixed Asian Race	[redacted]	[redacted]
Mixed White Race	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
Weight (kg), n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
(range)	[redacted]	[redacted]
ISS disease stage at screening, n (%)		
I	21 (22)	[redacted]
II	33 (34)	[redacted]
III	42 (43)	[redacted]
Unknown	1 (1)	[redacted]
Type of multiple myeloma, n (%)		
Non-secretory	[redacted]	[redacted]
Secretory	[redacted]	[redacted]
Myeloma light chain, n (%)		
Kappa light chain	[redacted]	[redacted]
Lambda light chain	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Myeloma immunoglobulin, n (%)		
IgA	[redacted]	[redacted]
IgG	[redacted]	[redacted]
IgM	[redacted]	[redacted]
IgD	[redacted]	[redacted]
IgE	[redacted]	[redacted]

	Belamaf Q3W	
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=[redacted]) Patients in 5L+ only**
Missing	[redacted]	[redacted]
Extramedullary disease, n (%)		
Yes	22 (23)	[redacted]
No	75 (77)	[redacted]
Lytic bone lesions, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Lines of therapy completed at screening, n (%)		
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
More than 10	[redacted]	[redacted]
High risk cytogenetics n (%)		
Yes*	[redacted]	[redacted]
Other (non-high risk, not done, or missing)	[redacted]	[redacted]

Abbreviations: ISS, International Staging System; ITT, intent-to-treat; n, number; Q3W, once every three weeks; SD, standard deviation; 5L+, fifth line and beyond
*if the patient has any of the following cytogenetics: t(4;14), t(14:16) and 17p13del
Source: DREAMM-2 clinical study report primary analysis[78], Lonial 2020[69], Lonial 2021[69]

Details of the numbers of patients eligible to enter the DREAMM-2 trial are provided in Appendix D.

B.2.3.1.3 Statistical analysis

The statistical analysis undertaken in the DREAMM-2 trial is presented in Table 8.

Table 8. DREAMM-2 statistical analysis

Trial number (acronym)	**DREAMM-2, NCT03525678, primary analysis clinical study report[78], Lonial et al. 2020[69] (6-month follow-up), Lonial et al. 2021 (13-month follow-up)[74], unpublished final analysis**
Hypothesis objective	The primary study objective was to evaluate the clinical efficacy of Belamaf in patients with RRMM who had received at least 3 prior

	lines of therapy, had failed an anti-CD38 mAb, and were refractory to PIs and IMiDs. The study provides evidence with respect to ORR to either support the null hypothesis, ORR is ≤15%, or reject it in favour of the alternative hypothesis, ORR is ≥33%. The hypothesis testing was performed on all randomised patients in the 2.5 mg/kg (as well as in the 3.4 mg/kg arm separately).
Sample size, power calculation	The sample size calculation was based on a response rate of 30% or greater in each of the two Belamaf treatment arms (2·5 mg/kg or 3·4 mg/kg) compared with the historical control (≤15%). Based on the simulation results with the planned sample size of 65 patients, there was 86.90% power to reject the null hypothesis within each arm with a 1-sided type I error of 1.23%. With no change to the planned interim analysis (IA) (i.e., approximately after 25 patients/arm were evaluable for IA, and same futility boundary), simulation results showed that there was 92.38% power to reject the null hypothesis within each arm with a 1-sided type I error of 0.97% for 100 patients per arm.
Outcome populations	Outcomes are presented using the following populations for the 2.5 mg/kg cohort: • The Intent-to-Treat (ITT) Population included all randomised patients whether or not randomised treatment was administered. • The Safety Population include all randomised patients who received at least one dose of study treatment.
Statistical analysis	The primary analysis for all efficacy endpoints was based on the ITT population and is reported in Section B.2.5.1. Sensitivity analysis for ORR, DoR, and TTR as assessed by both investigator and IRC were performed using the efficacy population which consisted of the first 130 ITT patients. **Primary endpoint** ORR was analysed at interim and final analysis. Patients with best confirmed response of PR or better was considered as a responder. ORR at final analysis was based on the confirmed responses from IRC assessment in both ITT (presented in Section B.2.6) and Efficacy populations (not presented). In addition, ORR based on confirmed response from investigator assessment was performed in both ITT (presented in Section B.2.6) and Efficacy populations (not presented). The corresponding 97.5% exact CI for ORR was provided. Patients with unknown or missing response were treated as non-responders, i.e., these patients were included in the denominator when calculating percentages of response. **Secondary endpoints**

	CBR, DoR, TTR, PFS, TTP and OS were assessed using the ITT population (Section B.2.6). CBR, TTR and DoR were also assessed using the efficacy population (data not presented in Section B.2.6) Analyses conducted are as follows: - CBR – summarised in the same way as ORR. No hypothesis testing was performed for CBR. - DoR – analysed at the time of final ORR analysis - PFS – analysed at the time of final ORR analysis - OS – analysed at the time of final ORR analysis, with an updated analysis performed at the end of study - TTD – analysed in a supplementary post-hoc analysis (analysed from the safety population) - TSNT – analysed in a post-hoc analysis (analysed from the ITT population) **Exploratory endpoint:** - MRD – The MRD negative rate was calculated based on the ITT population, with the corresponding 95% exact confidence interval provided **Safety** All safety analyses were performed on the safety population. All adverse events (AEs) whether serious or non-serious, were reported from the start of treatment until 45 days after the last dose of study treatment, until the patient withdraws consent for study participation, or until the patient starts subsequent anti-cancer therapy, whichever occured first. AEs were recorded using standard medical terminology and graded according to the NCI-CTCAE, Version 4.03. AEs were summarised by frequency and proportion of total patients (Section B.2.9) To ensure a comprehensive understanding of corneal events, data were collected in the following way during DREAMM-2: - Ocular AEs were collected and coded using MedDRA PTs and events were graded for intensity/severity using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grading. **Health outcomes** *EORTC-QLQ-C30*: For summary score and each of domain scores, the following outputs will be provided: • The descriptive summary of the actual value and change from baseline by visit (baseline, every 6 weeks and end of treatment visit).

	• The number (%) of patients with improvement in score ≥ 10, and ≥ 5 points respectively by visit (baseline, every 6 weeks and end of treatment visit). *EORTC-QLQ-MY20*: For each of four domain scores, the following outputs will be provided: • The descriptive summary of the actual value and change from baseline by visit (baseline, every 6 weeks and end of treatment visit). • Summary of the number (%) of patients with improvement in score ≥ 10, and ≥ 5 points respectively by visit (baseline, every 6 weeks and end of treatment visit).
Data management and patient withdrawals	As of the data cut-off of 4th May 2022, in the 2.5 mg/kg cohort, [redacted]% of patients had died, withdrawals from the study accounted for [redacted]% of patients, and [redacted]% were still ongoing. A total of [redacted]% of patients had discontinued treatment and the most frequent reason for discontinuation was disease progression ([redacted]%).
Interim analyses	For each arm (2.5 mg/kg or 3.4 mg/kg), a single futility IA was planned for the primary endpoint ORR after approximately 25 patients out of originally planned 65 patients per arm were evaluable. The IA to assess futility was performed by an Independent Data Monitoring Committee (IDMC).

Abbreviations: AE, adverse event; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; FU, follow-up; IA, interim analysis; IDMC, Independent Data Monitoring Committee; IMiD, immunomodulatory drug; IRC, Independent Response Committee; ITT, intent-to-treat; mAb, monoclonal antibody; MRD, minimal residual disease; NCI-CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; RRMM, relapsed/ refractory multiple myeloma; TSNT, time to start of next treatment; TTD, time to death, TTR, time to response
Source: Reporting and Analysis Plan for DREAMM-2[73]

B.2.3.1.4 Critical appraisal of the DREAMM-2 trial

A complete quality assessment for the DREAMM-2 trial is provided in Appendix D.

B.2.3.2 PomDex (NCRAS study)

The NCRAS study is a Company-initiated RWE study conducted to describe the characteristics, treatments and outcomes for 5L+ TCR MM patients in the UK.

The study identified a population of patients in England (N=[redacted]), who were closely aligned with the licensed population for Belamaf, and for whom some detailed aggregated data on baseline characteristics, prognostic variables and survival outcomes were available.

It provides a real-world representation of current clinical management and key efficacy outcomes in the UK, in this difficult-to-treat patient population where there is a paucity of published literature. Accordingly, this study serves as the primary comparative efficacy evidence in this submission and informs the base-case cost-effectiveness analysis (CEA).

Additional details on the study are available in the study protocol.[60]

B.2.3.2.1 Summary of study methodology

Study design

The NCRAS study was a descriptive, retrospective, non-interventional study using routine, England patient-level health data available through the NCRAS dataset, which combines linked data from the Hospital Episode Statistics (HES), the Systemic Anti-Cancer Therapy dataset (SACT), National Radiotherapy Dataset (RTDS) and Office for National Statistics (ONS) mortality data. Data were collected for patients diagnosed with MM between 1st January 2013 and 31st December 2019, with data extraction until 31st December 2021.

Initial inclusion and exclusion criteria to identify patients with 5L+ TCR MM

Patients became eligible for inclusion into the cohort at the initiation of the first line of therapy that meets the cohort criteria (index line of therapy [LoT] as 5th line or above, as well as TCR). A series of inclusion and exclusion criteria were defined in order to narrow down the total number of patients available to only adult patients with 5L+ TCR MM for whom sufficient data were available (date of diagnosis, stage at diagnosis and age at diagnosis). These initial inclusion and exclusion criteria are detailed in Table 9.

Individuals were classed as refractory to a treatment class (PI, IMiD, anti-CD38 mAb) where a new line was initiated within 60 days of completion of the PI, IMiD or anti-CD38 mAb-containing line with the exception of Bor since it is given as a fixed treatment duration.[79]

Table 9. Initial inclusion and exclusion criteria of the NCRAS study to identify patients with 5L+ TCR MM

Inclusion criteria	Exclusion criteria
• Resident in England at the date of diagnosis of RRMM. • At least one incident primary diagnosis of RRMM between 01/01/2013 and 31/12/2019. The diagnosis dates for the study will be between 01/01/2013 and 31/12/2019. • Adult 18 years or above at the date of advanced diagnosis or recurrent disease.	• Diagnoses via death certificate only. Reason for exclusion: patients with diagnosis via death certificate only would not have had the opportunity to receive treatment and will be ineligible for inclusion in survival analyses, the objectives of this study. • No recorded date of diagnosis, negating the ability to select incident cases from the pre-specified time window; Reason for exclusion: confirmation of least one incident primary diagnosis of RRMM between 01/01/2013 and 31/12/2019 required for inclusion. • Some anti-CD38 mAb regimens are currently provided via the CDF, so the usual process will be followed with NCRAS to determine whether exclusions will need to be applied.

Abbreviations: CDF, cancer drug fund; NCRAS, national cancer registration and analysis service; RRMM, relapsed refractory multiple myeloma

Study outcomes

The clinical outcomes sought in the study are presented in Table 10.

Table 10. NCRAS outcome measures definition

Measure	Description
OS	Defined as the time from initiation of the index LoT and until failure (all-cause death) and estimated using Kaplan-Meier methodology. Patients lost to follow-up or still alive at the end of the study period were censored.

Measure	Description
TTNT	As progression is not recorded within the NCRAS database, TTNT was considered instead. This is in line with previous studies conducted using real-world datasets in multiple myeloma such as the SACT dataset in England.[30] TTNT was defined as the time from the start of line of therapy until failure (the earliest of all-cause death or the start of a new line of treatment) and estimated using Kaplan-Meier methodology. Patients lost to follow-up or still in same line of treatment at the end of the study period were censored.
TTD	Treatment discontinuation was defined as the first of death or the date of any drug administration that is followed by a gap of >60 days and was estimated using Kaplan-Meier methodology.

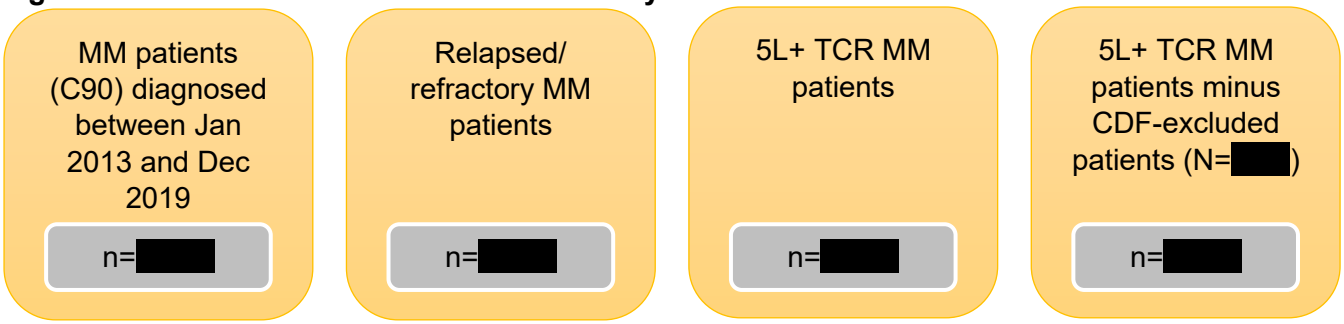
Abbreviations: LoT, line of therapy; OS, overall survival; TTD, time to discontinuation; TTNT, time to next treatment

Full methodology is presented in the study protocol.[60]

Patient numbers

A summary of the patient numbers in the NCRAS study is provided in Figure 7. The incident 5L+ TCR patient cohort (n=[redacted]) captures TCR patients that are treated with a fifth line therapy or above. This is the point in the treatment pathway where patients would first be eligible for treatment with Belamaf. Thus, this is the cohort of patients relevant to the decision problem.

Figure 7. Patients included in the NCRAS study



Abbreviations: CDF, Cancer Drugs Fund; MM, multiple myeloma; TCR, triple class refractory; 5L+, fifth line and beyond

B.2.3.2.2 Patient demographics and clinical characteristics

From the cohort of patients with 5L+ TCR MM in the NCRAS study (n=[redacted]), [redacted] patients received PomDex at a dose [redacted] (pomalidomide median index dose = [redacted], interquartile range = [redacted] at 5L and median index dose = [redacted], interquartile range = [redacted] for lines 6-8).[80]

All patients' demographics and clinical characteristics available for the PomDex arm in the NCRAS study are presented in Table 11.

Table 11. Patient characteristics in the NCRAS study

	NCRAS – PomDex index line (N=[redacted])
Sex, n (%)	

	NCRAS – PomDex index line (N=[redacted])
Male	[redacted]
Age (years), n	
Mean (SD)	[redacted]
Age Group (years), n (%)	
<18	[redacted]
18 to <65	[redacted]
65 to <75	[redacted]
75	[redacted]
Race Detail, n (%)	
Black	[redacted]
Asian	[redacted]
White	[redacted]
Other	[redacted]
Unknown*	[redacted]
Weight (kg), n	
Mean (SD)	[redacted]
ISS staging system, n (%)	
I	[redacted]
II	[redacted]
III	[redacted]
Un-staged*	[redacted]
ECOG performance status, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
3-4	[redacted]
Unknown*	[redacted]
Extramedullary plasmocytoma, n (%)	
Yes	[redacted]
No	[redacted]
Lytic bone lesions, n (%)	
Yes	[redacted]
No	[redacted]
Prior therapy exposure, n (%)	
PI	[redacted]
IMiD	[redacted]
Len	[redacted]
Anti-CD38	[redacted]
Lines of therapy completed at screening, n (%)	
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
Median (range)	[redacted]

*No imputations were carried out.

B.2.3.2.3 Statistical analysis

The statistical analysis undertaken in the NCRAS study is presented in Table 12.

Table 12. NCRAS study statistical analysis

Outcome populations	Outcomes are presented using the following populations for the 5L+ TCR cohort • PomDex arm • PanoBorDex arm, in Appendix M
Statistical analysis	**Summary statistics** Continuous variables were summarised by means, standard deviations, medians, quartiles and ranges. Frequencies and percentages were presented for categorical data. Subjects were described in terms of their baseline demographic and clinical characteristics. **Survival analyses** The Kaplan-Meier (KM) method were used to summarise time-to-event variables (OS, TTNT and TTD). Kaplan-Meier (KM) estimates (and their corresponding two-sided 95% CIs) were reported for patients at 1, 6, 12, 18, 24 and 36 months following the index date, subject to a minimum of 10 at risk participants at each interval. Estimates were presented alongside associated summary statistics, including the median survival time. Survival curves were presented graphically. **Missing data** The proportion of missing data was displayed. No imputations were carried out.

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival; PanoBorDex, Panobinostat with bortezomib and dexamethasone; PomDex, Pomalidomide with dexamethasone; TCR, tiple-class refractory; TTD, time to treatment discontinuation; TTNT, time to next therapy

B.2.3.2.4 Critical appraisal of the NCRAS study

A complete quality assessment for the NCRAS study is provided in Appendix D.

B.2.4 Method used for expert's elicitation

Three England-based consultant haematologists were engaged to validate the following components of the NICE submission: positioning of Belamaf in the treatment pathway, and indirect and mixed treatment comparisons.

Clinical experts were selected based on their expertise in MM as well as having experience with Belamaf [redacted]. Additionally, experience with the DREAMM-2 trial and the NICE Health Technology Assessment (HTA) process were considered.

The biographies of the clinical experts are presented in Appendix Q.

B.2.5 Clinical effectiveness results from DREAMM-2 and NCRAS

The following sections present the clinical effectiveness results from the DREAMM-2 trial and the NCRAS study for outcomes available in the dataset (OS, TTNT and TTD). Note that

the figures from the NCRAS dataset also present the efficacy outcomes results for PanoBorDex however, as described in Section B.1.3.3.1, it is not considered as a main comparator in this appraisal.

A summary of the data cuts available for the DREAMM-2 study is presented in Table 13.

Table 13. Summary of data cuts available

Data cut-off	**21st June 2019 Primary analysis**	**31st January 2020 13-month follow-up data cut**	**4th May 2022 Final analysis**
Publication	Lonial et al., 2020[69]	Lonial et al., 2021[74]	Unpublished
Internal Company documents	Clinical study report	Clinical study report 13-month-follow-up	Tabulated results

B.2.5.1 Belamaf – Efficacy outcomes (DREAMM-2)

B.2.5.1.1 Primary efficacy outcome: ORR

At the 13-month follow-up, the ORR as assessed by IRC was 32% (97.5%CI: 21.7, 43.6) in the Belamaf 2.5 mg/kg cohort. Over half of responders achieved deep responses of VGPR or better (58%), including two patients with a stringent complete response (sCR). (Table 14) Overall, the ORR as assessed by IRC was concordant with the assessment by investigators.

In the final analysis, the overall response rate (ORR) as assessed by IRC was consistent with the 13-month follow-up. (Table 14) There was a further deepening of response, with [redacted] additional patients achieving a CR. The 5L+ subgroup efficacy results were [redacted] with the results of the ITT population. The ORR as assessed by IRC was concordant with the assessment by investigators.

Table 14. Best confirmed response based on IRC assessment (DREAMM-2)

	Belamaf Q3W		
	13-Month follow-up (31Jan20)	**Final analysis (4May22)**	**Final analysis (4May22)**
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=97) ITT**	**2.5 mg/kg (N=[redacted]) Patients in 5L+ only**
Best Response, n (%)			
Stringent complete response (sCR)	2 (2)	[redacted]	[redacted]
Complete response (CR)	5 (5)	[redacted]	[redacted]
Very good partial response (VGPR)	11 (11)	[redacted]	[redacted]
Partial response (PR)	13 (13)	[redacted]	[redacted]
Minimal response (MR)	4 (4)	[redacted]	[redacted]
Stable disease (SD)	27 (28)	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]	[redacted]

	Belamaf Q3W		
	13-Month follow-up (31Jan20)	Final analysis (4May22)	Final analysis (4May22)
	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=[redacted]) Patients in 5L+ only
Not evaluable (NE)	[redacted]	[redacted]	[redacted]
Primary endpoint: Overall Response Rate, n (%)			
sCR+CR+VGPR+PR	31 (32)	[redacted]	[redacted]
97.5% confidence interval	(21.7, 43.6)	[redacted]	[redacted]
Clinical Benefit Rate, n (%)			
sCR+CR+VGPR+PR+MR	35 (36)	[redacted]	[redacted]
97.5% confidence interval	(25.4, 47.9)	[redacted]	[redacted]

Abbreviations: CR, complete response; IRC, Independent Review Committee; ITT, intent-to-treat; n, number; NE, not evaluable; NR, not reported; PD, progressive disease; PR, partial response; Q3W, once every three weeks; sCR, stringent complete response; VGPR, very good partial response; 5L+, fifth line and beyond
Source: DREAMM-2 13-months follow-up clinical study report[73], Lonial et al. 2021[74],

B.2.5.1.2 Duration of response (DoR)

Duration of response increased over time; the median DoR as assessed by IRC was increased from 11 months (95% CI, 4.2, -) at the 13-month follow-up[74] to [redacted] months in the final analysis with an estimated probability of having a DoR of ≥12 months of ~[redacted]%. The 5L+ subgroup efficacy results were broadly consistent with the results of the ITT population. (Table 15, Figure 8, Figure 9)

Table 15. Duration of response based on IRC assessment (DREAMM-2, final analysis)

	Belamaf Q3W	
	Final analysis (4May22)	
	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=[redacted]) Patients in 5L+ only
Number of patients, n (%)	[redacted]	[redacted]
Progressed or died due to PD (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary		
Death due to PD	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Estimates for DoR (months)		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]

	Belamaf Q3W	
	Final analysis (4May22)	
	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=[redacted]) Patients in 5L+ only
95% CI	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Probability of maintaining response		
Time-to-event endpoint at 4 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DoR, duration of response; IRC, Independent Review Committee; ITT, intent-to-treat; n, number; PD, progressive disease; Q3W, once every three weeks; 5L+, fifth line and beyond

Figure 8. Kaplan-Meier analysis of DoR based on IRC assessment (DREAMM-2, final analysis, ITT population)

Abbreviations: DoR, duration of response; IRC, Independent Review Committee; ITT, intent-to-treat

Figure 9. Kaplan-Meier analysis of DoR based on IRC assessment (DREAMM-2, final analysis, 5L+ subgroup)

Abbreviations: DoR, duration of response; IRC, Independent Review Committee; 5L+, fifth line and beyond

B.2.5.1.3 DoR by response

Duration of response with Belamaf 2.5 mg/kg also increased among the responders, with a median DoR of [redacted] months for patients achieving at least a MR (Figure 10) versus [redacted] months for those in the ITT population. (Table 15)

Figure 10. Kaplan-Meier curves of duration of response, by response category, based on independent reviewer-assessed response (MR or better) – (DREAMM-2, final analysis, ITT population)

Abbreviations: DoR, duration of response; ITT, intent-to-treat; MR, minimal response

B.2.5.1.4 Time to response (TTR)

Among responders, the time to response was short with a median of [redacted] months (95% CI: [redacted]) at the [redacted]. (Table 16)

Table 16. Time to response based on IRC assessment (DREAMM-2, ITT population)

	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=97) ITT
Estimates for time to response (months)		
N	[redacted]	[redacted]
1st Quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd Quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IRC, Independent Review Committee; ITT, intent-to-treat; N, number; Q3W, once every three weeks
Source: DREAMM-2 13-months follow-up clinical study report[73]

B.2.5.1.5 Time to progression (TTP)

At the 13-month follow-up, the median time to progression in the 2.5 mg/kg cohort was [redacted] months (95% CI [redacted]), [redacted]. (Table 17).

Table 17. Time to progression based on independent reviewer - assessed response **(DREAMM-2, ITT population)**

	Belamaf Q3W	
	13 Month follow-up (31Jan20)	**Final analysis (4May22)**
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=97) ITT**
Number of patients, n (%)		
Progressed or died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%)		
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for time variable (months)		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intent-to-treat; n, number; Q3W, once every three weeks
Source: DREAMM-2 13-months follow-up clinical study report[73]

B.2.5.1.6 Progression-free survival (PFS)

A median PFS of [redacted] months (95% CI [redacted]) was achieved for patients receiving Belamaf 2.5 mg/kg. In the final analysis, [redacted]% of patients had progressed or died. The 5L+ subgroup efficacy results are broadly consistent with the results of the ITT population (Table 18, Figure 11, Figure 12).

Table 18. Progression free survival based on IRC assessment (DREAMM-2, final analysis)

	Belamaf Q3W	
	Final analysis (4May22)	
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=[redacted]) Patients in 5L+ only**
Number of patients, n (%)		
Progressed or died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]

	Belamaf Q3W	
	Final analysis (4May22)	
	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=[redacted]) Patients in 5L+ only
Event summary, n (%)		
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for time variable (months)		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Progression-free survival probability		
Time-to-event endpoint at 6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IRC, Independent Review Committee; ITT, intent-to-treat; n, number; PFS, progression-free survival; Q3W, once every three weeks; 5L+, fifth line and beyond

Figure 11. Kaplan-Meier analysis of PFS based on IRC assessment (DREAMM-2, final analysis, ITT population)

Abbreviations: IRC, Independent Review Committee; ITT, intent-to-treat; PFS, progression-free survival

Figure 12. Kaplan-Meier analysis of PFS based on IRC assessment (DREAMM-2, final analysis, 5L+ subgroup)

Abbreviations: IRC, Independent Review Committee; PFS, progression-free survival; 5L+, fifth line and beyond

PFS by response

The median PFS in the final analysis was [redacted]. Median PFS was [redacted] months, [redacted] months, [redacted] months, and [redacted] months in the PR or better group, MR or better group, stable disease (SD) group and progressive disease (PD)/ not evaluable (NE) group respectively (Table 19, Figure 13).

Table 19. Summary of PFS by response category based on independent reviewer-assessed response (DREAMM-2, final analysis, ITT population)

	Belamaf Q3W			
	Final analysis (4May22)			
	2.5 mg/kg (N=97) ITT			
	Partial Response or better	**Minimal Response or better**	**Stable Disease**	**Progressive Disease or Not Evaluable**
Number of patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progressed or Died (event)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]	[redacted]	[redacted]
Event summary, n (%)				
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]

	Belamaf Q3W			
	Final analysis (4May22)			
	2.5 mg/kg (N=97) ITT			
	Partial Response or better	**Minimal Response or better**	**Stable Disease**	**Progressive Disease or Not Evaluable**
Estimates for time variable (months)				
1st quartile	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Progression-Free Survival probability				
Time-to-event endpoint at 6 months	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intent-to-treat; n, number; PFS, progression-free survival; Q3W, once every three weeks

Figure 13. Kaplan-Meier analysis of PFS by response (DREAMM-2, final analysis, ITT population)

Abbreviations: ITT, intent-to-treat; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

B.2.5.1.7 Overall survival (OS)

In the final analysis, the median OS in the 2.5 mg/kg cohort was [redacted] months (95% CI [redacted]) and [redacted]% of patients had died. Survival probability at 12-months was [redacted]% (95%CI: [redacted]). The 5L+ subgroup efficacy results are broadly consistent with the results of the ITT population. (Table 20, Figure 14 and Figure 15)

Table 20. Overall survival (DREAMM-2, final analysis)

	Belamaf Q3W	
	Final analysis (4May22)	
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=[redacted]) Patients in 5L+ only**
Number of patients, n (%)		
Died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%)		
Death	[redacted]	[redacted]
Estimates for time variable (months)		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

	Belamaf Q3W	
	Final analysis (4May22)	
	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=[redacted]) Patients in 5L+ only
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Survival probability		
Time-to-event endpoint at 6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intent-to-treat; n, number; Q3W, once every three weeks; 5L+, fifth line and beyond

Figure 14. Kaplan-Meier analysis of OS (DREAMM-2, final analysis, ITT population)

Abbreviations: ITT, intent-to-treat

Figure 15. Kaplan-Meier analysis of OS (DREAMM-2, final analysis, 5L+ subgroup)

Abbreviations: 5L+, fifth line and beyond

OS by response

[redacted], in the final analysis, median OS was [redacted]. Median OS was [redacted] months, [redacted] months, [redacted] months, and [redacted] months in the PR or better group, MR or better group, SD group, and PD/ NE group respectively. (Table 21, Figure 16)

Table 21. Summary of overall survival by response category based on independent reviewer-assessed response (DREAMM-2, final analysis, ITT population)

	Belamaf Q3W			
	Final analysis (4May22)			
	2.5 mg/kg (N=97) ITT			
	Partial Response or better	**Minimal Response or better**	**Stable Disease**	**Progressive Disease or Not Evaluable**
Number of patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Died (event)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]	[redacted]	[redacted]
Event summary, n (%)				
Death	[redacted]	[redacted]	[redacted]	[redacted]
Estimates for time variable (months)				

	Belamaf Q3W			
	Final analysis (4May22)			
	2.5 mg/kg (N=97) ITT			
	Partial Response or better	**Minimal Response or better**	**Stable Disease**	**Progressive Disease or Not Evaluable**
1st quartile	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
3rd quartile			[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Survival probability				
Time-to-event endpoint at 6 months	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intent-to-treat; n, number; OS, overall survival; Q3W, once every three weeks

Figure 16. Kaplan-Meier analysis of OS by response (DREAMM-2, final analysis, ITT population)

Abbreviations: ITT, intent-to-treat; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

B.2.5.1.8 Time to treatment discontinuation (TTD)

TTD was run in a post-hoc analysis of the latest data cut on 4th May 2022 (final analysis). The median TTD was [redacted] months (95% CI [redacted]) and at the data cut-off, all patients had discontinued treatment. The 5L+ subgroup efficacy results are broadly consistent with the results of the ITT population. (Table 22, Figure 17 and Figure 18)

In the final analysis, the median TTD was [redacted] than the median PFS, showing that [redacted].

Table 22. Time to treatment discontinuation (DREAMM-2, post-hoc analysis, 4May2022)

	Belamaf Q3W	
	Post-hoc analysis (4May2022)	
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=[redacted]) 5L+ subgroup
Number of patients, n (%)		
Treatment discontinued (event)	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Estimates for time variable (months)		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time to Treatment Discontinuation probability		
Time-to-event endpoint at 6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; n, number; 5L+ fifth line and beyond

Figure 17. Kaplan-Meier analysis of TTD (DREAMM-2, post-hoc analysis, 4May2022, safety population)

Abbreviations: TTD, time to treatment discontinuation

Figure 18. Kaplan-Meier analysis of TTD (DREAMM-2, post-hoc analysis, 4May2022, 5L+ subgroup)

Abbreviations: TTD, time to treatment discontinuation; 5L+, fifth line and beyond

B.2.5.1.9 Time to next treatment (TTNT)

TTNT was not a pre-specified outcome in the DREAMM-2 trial. To allow a comparison with PomDex TTNT data from the NCRAS study, this outcome was reconstructed by combining TTD to TSNT.

TTNT was run in a post-hoc analysis on 4th May 2022. The median TTNT was [redacted] months (95% CI [redacted]) and [redacted]% of patients had either received follow-up treatment or died at the

data cut-off. Of this [redacted]%, [redacted]% received follow-up treatment, and [redacted]% had died. The 5L+ subgroup efficacy results are broadly consistent with the results of the ITT population. (Table 23, Figure 19 and Figure 20)

Table 23. Time to next treatment (DREAMM-2, post-hoc analysis, 4May2022)

	Belamaf Q3W	
	Post-hoc analysis (4May2022)	
	2.5 mg/kg (N=97) ITT	2.5 mg/kg ([redacted]) 5L+ subgroup
Number of patients, n (%)		
Follow-up treatment received or Died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Event summary, n (%)		
Follow-up treatment received	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for time variable (months)		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time to Next Treatment probability		
Time-to-event endpoint at 6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intent-to-treat; n, number; Q3W, once every three weeks; 5L+, fifth line and beyond

Figure 19. Kaplan-Meier analysis of TTNT (DREAMM-2, post-hoc analysis, 4May2022, ITT population)

Abbreviations: ITT, intent-to-treat; TTNT, time to next treatment

Figure 20. Kaplan-Meier analysis of TTNT (DREAMM-2, post-hoc analysis, 4May2022, 5L+ subgroup)

Abbreviations: TTNT, time to next treatment; 5L+, fifth line and beyond

Summary of follow-up anti-cancer therapy is presented in Table 24. The results from the final analysis showed that [redacted] are the more commonly used subsequent therapy, followed by [redacted] and then [redacted]. The median time from study treatment discontinuation to start of subsequent therapy was [redacted] days, [redacted] from [redacted] days in the primary analysis.

Table 24. Summary of follow-up anti-cancer therapy (DREAMM-2, ITT population)

	Belamaf Q3W
	Final analysis (4May22)
	2.5 mg/kg (N=97) ITT
Any anti-cancer therapy n (%)	
Yes	
No	[redacted]
Type of anti-cancer therapy by drug class n (%)	[redacted]
Steroids	
Proteasome inhibitor	[redacted]
Carfilzomib	[redacted]
Bortezomib	[redacted]
Ixazomib	[redacted]
Chemotherapy	[redacted]
Immunomodulator	[redacted]
Pomalidomide	[redacted]
Lenalidomide	[redacted]
Thalidomide	[redacted]
Monoclonal antibody	[redacted]
Daratumumab	[redacted]
Elotuzumab	[redacted]
TAK-573	[redacted]
Other	[redacted]
Stem cell transplant	[redacted]
HDAC inhibitor	[redacted]
Engineered T cell therapy	[redacted]
Time from study treatment discontinuation to start of subsequent anti-cancer therapy (days)	[redacted]
N	
Min.	[redacted]
1st quartile	[redacted]
Median	[redacted]
3rd quartile	[redacted]
Max.	[redacted]

Abbreviations: HDAC, histone deacetylase; ITT, intent-to-treat; n, number; Q3W, once every three weeks

B.2.5.1.10 Minimal residual disease (MRD)

At the 13-month follow-up, results of MRD negativity at the $1x10^{-5}$ sensitivity level were available for 13 patients; five patients (36%) achieved MRD negativity, including two patients with a sCR (100% among the two sCR patients with MRD results), two patients with a CR (40% among the five CR patients with MRD results) and one patient with a VGPR (17% among the six VGPR patients with MRD results).[74]

Similar results were reported in the final analysis, with results of MRD negativity at the $1x10^{-5}$ sensitivity level available for [redacted] additional patient (N=[redacted]); [redacted] patients ([redacted]%) achieved MRD negativity, including [redacted] patients with a sCR ([redacted]% among the [redacted] sCR patients with MRD results), [redacted] patients with a CR ([redacted]% among the [redacted] CR patients with MRD results) and [redacted] patient with a VGPR ([redacted]% among the [redacted] VGPR patients with MRD results).

B.2.5.1.11 Health-related quality of life

EORTC-QLQ-C30

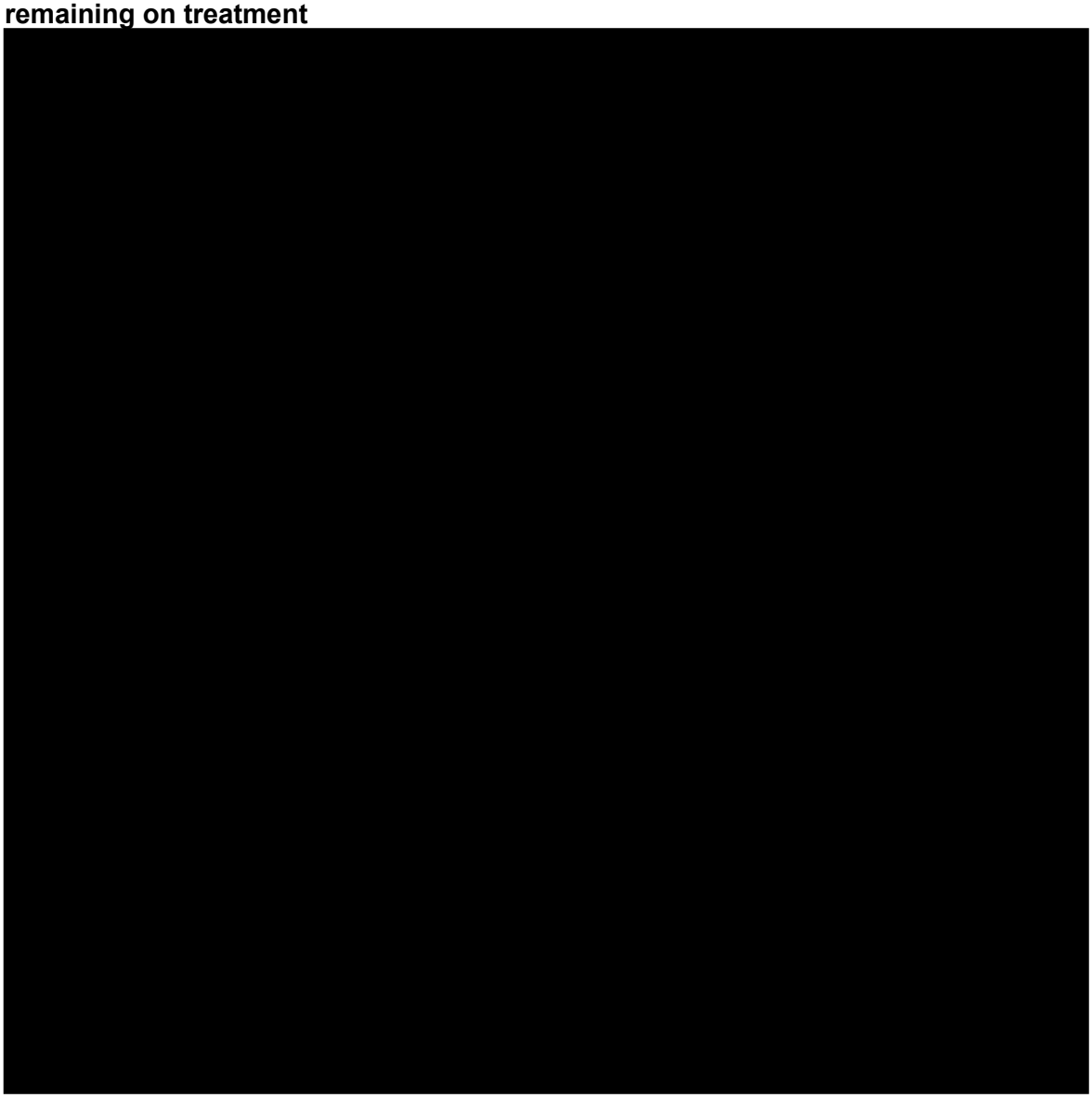
The HRQoL results as elicited by the EORTC-QLQ-C30 are presented in Figure 21 and Figure 22.[81]

The EORTC-QLQ-C30 questionnaire was completed by [redacted]% of DREAMM-2 patients at baseline. Both 'Physical Functioning' and 'Global Health Status/ QoL' remained consistent during treatment with Belamaf. 'Fatigue', 'Nausea/Vomiting' and 'Pain' were stable over time, as were the three 'Functioning' domains; 'Role', 'Social', and 'Cognitive'. 'Future Perspective' similarly showed stability. (Figure 21)

At Week 7, [redacted] patients remained on treatment. Improvements in score ≥10 points (a meaningful improvement) from baseline were seen in [redacted]% of patients for 'Physical Functioning', [redacted]% of patients remained stable, and [redacted]% reported they had worsened. 'Fatigue' and 'Pain' scores were shown to improve in [redacted]% and [redacted]% of patients respectively, scores remained stable in [redacted]% and [redacted]% respectively, and were reported to worsen in [redacted]% and [redacted]% of patients respectively.

At Week 25, [redacted] patients remained on treatment. Meaningful improvements were seen in 'Physical Functioning', 'Fatigue' and 'Pain' scores in [redacted]% [redacted]% and [redacted]% of patients respectively, [redacted]%, [redacted]% and [redacted]% of patients remained stable, respectively, and [redacted]%, [redacted]% and [redacted]% experienced worsening, respectively. (Figure 22)

Figure 21. DREAMM-2 HRQoL change from baseline in EORTC-QLQ-C30 in patients remaining on treatment



Source: Popat R et al. (2022)[82] 13-month follow-up. Data cut-off date: January 31, 2020. Error bars show 95% CIs.
Abbreviations: BL, baseline; CI, confidence interval; GHS/QoL, global health status/quality of life; 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 Quality of Life Questionnaire-Myeloma 20; WK, week.

Figure 22. DREAMM-2 HRQoL distribution of patients with meaningful changes from baseline in EORTC-QLQ-C30 and EORTC-QLQ-MY20 domain scores*

Source: Popat R et al. (2022)[82] 13 -month follow-up. Data cut-off date: January 31, 2020. Data shown above bars are the number of patients with improvement/number of patients assessed at each study visit.
*'Improved': patients with >10-point improvement; 'Stable': patients with scores between 10-point improvement and 10-point deterioration; 'Worsened': patients with ≥10-point deterioration. †Pain in different locations.
Abbreviations: 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 Quality of Life Questionnaire-Myeloma 20; WK, week.

EORTC-QLQ-MY20

The HRQoL results as elicited by the EORTC-QLQ-MY20 are presented in Figure 23 to Figure 25.

The EORTC-QLQ-MY20 questionnaire was completed by 74% or patients at baseline. 'Disease Symptoms' demonstrated stability during treatment with Belamaf (Figure 23 and Figure 24). Improvements in score ≥10 points for 'Disease Symptoms' (defined as meaningful improvements) were seen in 38% and 29% of patients on treatment with Belamaf at weeks 7 and 13 respectively, 40% and 46% of patients remained stable, and 22% and 25% experienced worsening, respectively. At week 25, meaningful improvements were seen in 37% of patients, whilst 21% remained stable and 42% experienced worsening (Figure 25). 47% of patients reported no bone pain at week 31, which was an improvement compared to 25% who reported no bone pain at baseline. A slight improvement was also seen in the proportion of patients who reported 'Very Much' bone pain; 12% at week 31, compared with 15% at baseline.

Figure 23. DREAMM-2 HRQoL change from baseline in EORTC-QLQ-MY20 item

Source: Popat R et al. (2022) [82,83]
The item was graded on the scale of 1 to 4, where 1 indicates 'Not at all'; 2, 'A little'; 3, 'Quite a bit'; and 4, 'Very much'.
Abbreviations: BL, baseline; EORTC-QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20; WK, week.

Figure 24. DREAMM-2 HRQoL response category for EORTC-QLQ-MY20 item

Source: Popat R et al. (2022) [82,83]
Abbreviations: EORTC-QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20.

Figure 25. DREAMM-2 HRQoL response category for EORTC-QLQ-MY20 item

Source: Popat R et al. (2022) [81]
No patients worsened by 3 categories.
Abbreviations: EORTC-QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Myeloma 20.

Core MM disease symptoms, patient functioning and overall HRQoL were stable over time with treatment with Belamaf, as shown by the EORTC-QLC-30 and EORTC-QLQ-MY20 collected in DREAMM-2.

B.2.5.2 PomDex – Efficacy outcomes (NCRAS)

B.2.5.2.1 Overall Survival (OS)

In the cohort of 5L+ TCR patients included in the NCRAS dataset, median OS with PomDex was [redacted] months (95% CI: [redacted]), with a survival probability of [redacted] at 12 months (95% CI: [redacted]). (Table 25, Figure 26)

Table 25. Overall survival for PomDex (aggregate data)

PomDex			**N=[redacted]**	
Number of events			[redacted]	
Number censored			[redacted]	
Median (95% CI) survival; months			[redacted]	[redacted]
Months from Line start	N at risk	Survival probability	Lower 95% CI	Upper 95% CI
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]			

Abbreviations: CI, confidence interval; n, number; PomDex, pomalidomide plus dexamethasone

Figure 26. Overall survival, PomDex (Kaplan-Meier analysis)

Notes: The KM curves cannot be drawn when number at risk falls below 10. The graph includes PD (PomDex) and PANOVD (PanoBorDex) which is presented as an exploratory comparator only in Appendix M.

B.2.5.2.2 Time to treatment discontinuation or death (TTD)

Median TTD with PomDex was [redacted] (95% CI [redacted]), with a discontinuation probability of [redacted] at 9 months. (Table 26, Figure 27).

Table 26. Time to treatment discontinuation or death for PomDex (aggregate data)

PomDex			**N=[redacted]**	
Number of events			[redacted]	
Number censored			[redacted]	
Median (95% CI) survival; months			[redacted]	[redacted]
Months from Line start	N at risk	Survival probability	Lower 95% CI	Upper 95% CI
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]			
15	[redacted]			
18	[redacted]			

Abbreviations: CI, confidence interval; n, number; PomDex, pomalidomide plus dexamethasone

Figure 27. Time to treatment discontinuation or death, PomDex (Kaplan-Meier analysis)

Notes: The KM curves cannot be drawn when number at risk falls below 10. The graph includes PD (PomDex) and PANOVD (PanoBorDex) which is presented as an exploratory comparator only in the Appendix M.

B.2.5.2.3 Time to next treatment (TTNT)

Median TTNT with PomDex was [redacted] (95%CI [redacted]), with a probability of receiving the next treatment at 9 months of [redacted]. (Table 27, Figure 28)

Table 27. Time to next treatment, PomDex (aggregate)

PomDex			N=[redacted]	
Number of events			[redacted]	
Number censored			[redacted]	
Median (95% CI) time to next treatment; months			[redacted]	
Months from Line start	N at risk	Survival probability	Lower 95% CI	Upper 95% CI
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]			
18	[redacted]			

Abbreviations: CI, confidence interval; n, number; PomDex, pomalidomide plus dexamethasone

Figure 28. Time to next treatment, PomDex (Kaplan-Meier analysis)

Notes: The KM curves cannot be drawn when number at risk falls below 10. The graph includes PD (PomDex) and PANOVD (PanoBorDex) which is presented as an exploratory comparator only in Appendix M.

B.2.6 Subgroup analysis

In the DREAMM-2 trial, the primary outcome, ORR based on IRC, was analysed according to the pre-specified subgroups listed in Table 28.

Table 28. Pre-specified subgroup analyses in DREAMM-2

Subgroup	Categories
Age group (at screening)	18 to <65, 65 to < 75, ≥ 75
Sex	Male, Female
Ethnic background	White, Black, Other
ISS staging at screening	I, II, III, Other (Unknown or Missing)
Baseline renal impairment status per eGFR (ml/min/1.73 m^2)	Normal (≥ 90), Mild (≥ 60, < 90), Moderate (≥ 30, < 60), Severe (≥ 15, < 30)
Number of prior lines of therapy	≤4, >4
Type of myeloma	IgG, Non-IgG
Cytogenetics risk [1]	High, Other (non-high risk – all others)
Refractory to prior anti-cancer therapy	Any proteasome inhibitor (PI) Bortezomib Carfilzomib

Subgroup	Categories
	Ixazomib
	Any immunomodulatory drug (IMiD)
	Thalidomide
	Lenalidomide
	Pomalidomide
	Any Monoclonal Antibodies
	Elotuzumab
	Isatuximab
	Daratumumab
	Daratumumab alone [2]
	Daratumumab in combination [3]
	PI+IMiD
	Daratumumab+PI+IMiD
	Penta-refractory [4]

[1] A subject is considered as high risk if the subject has any of the following cytogenetics: t(4;14), t(14;16), and 17p13del.
[2] Defined as prior CTX regimen with Daratumumab as the only drug in the regimen.
[3] Defined as prior CTX regimen with Daratumumab and other drugs.
[4] Defined as refractory to: Bortezomib, AND Carfilzomib AND Lenalidomide AND Pomalidomide AND Daratumumab

In addition to these pre-specified subgroup analyses, a post-hoc analysis was conducted for the 5L+ TCR patients receiving Belamaf 2.5 mg/kg in DREAMM-2, the licensed population of Belamaf. This population is based on the ITT population minus the five patients who received three prior lines of treatment.

Full results of the subgroup analyses can be found in Appendix E.

B.2.7 Meta-analysis

A meta-analysis was not conducted as the only relevant clinical trial identified was the DREAMM-2 trial.

B.2.8 Indirect and mixed treatment comparisons

This section presents the indirect treatment comparison (ITC) for Belamaf versus PomDex.

As discussed in Section B.1.3.3.1, PomDex is the most relevant comparator for this appraisal. Therefore, the results of the ITC comparing Belamaf to PomDex are presented below, while the results of the ITC comparing Belamaf to PanoBorDex are presented in Appendix O.

B.2.8.1 Overview of indirect treatment comparisons considered

B.2.8.1.1 Comparative effectiveness data sources

As described in Section B.2.1 and Appendix D, there are currently no head-to-head studies comparing Belamaf to PomDex, and the SLR found no relevant studies assessing the efficacy and safety of PomDex in 5L+ TCR MM for inclusion in an ITC versus Belamaf.

In addition, a targeted literature review was performed to identify relevant studies and/or NICE submissions in RRMM presenting 4L+ post-progression survival data to inform efficacy for the comparator arms; however, no relevant studies were retrieved.

Therefore, the NCRAS study described in Section B.2.3.2 is considered as the only source of comparative efficacy evidence in this submission since it reports efficacy outcomes for PomDex in the relevant population of 5L+ TCR MM patients.

B.2.8.1.2 Choice of ITC

As no head-to-head studies for Belamaf and PomDex are available, indirect comparison is required. In the absence of individual patient data (IPD) available for PomDex, and since the studies considered for the ITC are not randomised and do not form a connected network, unanchored methods are the only methods feasible for comparison. Therefore, the options considered to inform the comparative efficacy data for Belamaf versus PomDex were unanchored matched adjusted indirect comparison (MAIC), and naïve comparison.

There is precedent for the use of a MAIC; the approach has been used in a number of oncology HTAs submitted to and accepted by NICE, most recently the evaluation of Daratumumab (TA783) for the treatment of RRMM, for which a MAIC was conducted on OS.[30] The analyses considered in this submission are outlined below:

- Unanchored MAIC of Belamaf 2.5 mg/kg versus PomDex based on the DREAMM-2 trial and the NCRAS study including 3 covariates for OS, TTNT and TTD. The feasibility assessment and methodology for the unanchored MAIC are presented in Appendix O and summarised in Section B.2.8.2

- Naïve comparison of Belamaf 2.5 mg/kg versus PomDex based on the DREAMM-2 trial and NCRAS study.

B.2.8.1.3 Comparison of patients' characteristics between the DREAMM-2 trial and the NCRAS dataset

Several differences in patients' characteristics were noted across the DREAMM-2 trial and the NCRAS study (Table 7 described in Section B.2.3.1.2 and Table 11 in Section B.2.3.2.2, respectively).

While all patients in the DREAMM-2 trial had an ECOG performance status (PS) of 0-2 (as per the trial inclusion criteria), only [redacted]% of patients in the NCRAS study had an ECOG of 0-2. In addition, [redacted] patients ([redacted]%) had an ECOG PS 3-4 and [redacted] patients ([redacted]%) had an unknown ECOG PS in NCRAS.

Baseline characteristics suggest that certain markers could indicate a generally poorer prognosis for patients from the DREAMM-2 trial, for instance a higher proportion of patients presented with extramedullary disease (23% in DREAMM-2, [redacted]% in NCRAS) and lytic bone lesions ([redacted]% in DREAMM-2, [redacted]% in NCRAS) at baseline.

In addition, patients in the NCRAS study received fewer prior lines of therapy than in the DREAMM-2 trial; around [redacted]% of patients received four prior lines of therapy in the NCRAS study with a median of [redacted] prior lines, while 11% of patients received four prior lines of therapy in the DREAMM-2 trial with a median of seven prior lines.

Patients' ISS staging system differed between the NCRAS study and the DREAMM-2 trial however, this was mainly due to the vast majority ([redacted]%) of patients being un-staged in the NCRAS study. With this considered, the proportion split between stages 1, 2 and 3 aligned well with fewest patients at stage [redacted], followed by stage [redacted], and the majority at stage [redacted].

The proportion of males, age, age group split, and ethnicity characteristics were broadly aligned between both datasets. A higher proportion of males than females was observed in both datasets: [redacted]% male in the NCRAS study and 53% male in the DREAMM-2 trial. The average age was [redacted] years in the NCRAS study and [redacted] years in the DREAMM-2 trial respectively, with the age group split similar across both datasets ([redacted] aged 18 to <75). Ethnicity showed that most patients were white ([redacted]% and 80% respectively), with the inclusion of Black and Asian ethnicities too ([redacted]% and 16%, [redacted]% and 2%, respectively).

The differences between populations in the DREAMM-2 and NCRAS datasets support the need for a MAIC, to allow a more accurate estimate of the relative efficacy of Belamaf versus PomDex in more closely aligned populations.

B.2.8.2 Unanchored MAIC

B.2.8.2.1 Outcomes

An unanchored MAIC was conducted using IPD from the DREAMM-2 trial and aggregate data from the NCRAS study for the endpoints of interest for the cost-effectiveness model (

Table 29).

Table 29. Outcomes used in the MAIC

Endpoints of interest in the cost-effectiveness model	Outcomes used from DREAMM-2 (IPD)	Outcomes used from NCRAS (aggregate data)	Justification
OS	OS	OS	Collected in both NCRAS and DREAMM-2
PFS	TTNT (TTD+TSNT)*	TTNT	As PFS is not collected in the NCRAS dataset, a comparison of TTNT was considered instead (used as a proxy for PFS in the CEM)
TTD	TTD	TTD	Collected in both NCRAS and DREAMM-2

*As TTNT was not reported in DREAMM-2, TTNT was derived by combining TTD and TSNT from discontinuation
Abbreviations: NCRAS, National Cancer Registration and Analysis Service; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation; TSNT, time to the start of next therapy; TTNT, time to next therapy

B.2.8.2.2 Methodology

The methodology used in the MAIC followed the guidance produced by NICE Decision Support Unit (DSU) in the Technical Support Document (TSD) 18.[84]

MAIC models generate estimates for comparative effectiveness by re-weighting IPD from one source to match the population of another, based on its aggregate baseline characteristics data. By generating this adjusted dataset, MAICs aim to eliminate any bias due to differences in the baseline characteristics of patients, such that the differences across the datasets are driven by treatment effect alone.

MAIC modelling was deemed appropriate to explore in this submission given its less restrictive data requirements compared to other ITC methods. A MAIC requires IPD to be available for at least one of the treatments included in the comparison, with aggregate data being sufficient for all other treatments. This is the case in this submission, where IPD are available from the DREAMM-2 trial and aggregate data are available from the NCRAS study. Furthermore, in an unanchored MAIC analysis, a common comparator does not need to be present within the evidence base, which is the case across DREAMM-2 and the NCRAS study.

B.2.8.2.3 Covariates selection

The following treatment effect modifiers and prognostic variables in relation to OS, TTNT and TTD were identified through a review of previous appraisals in MM and validated with UK MM clinical experts: age, number of prior lines of therapy, extramedullary disease, ECOG PS, (R-)ISS, cytogenetic risk, renal impairment, median time to diagnosis, prior ASCT, lytic bone lesions at baseline and sex.

Only three of the most important factors identified by clinical experts, could be included in the MAIC, based on the availability of baseline characteristics in the NCRAS dataset: age [mean, years], prior lines of therapy [median], and extramedullary disease [yes or no] and the subsequent impact of the effective sample size (ESS). Results

The baseline characteristics for Belamaf before and after matching are presented in Table 30.

It should be noted that differences between baseline characteristics persist between the adjusted Belamaf and PomDex cohorts and may impact the comparability of evidence.

In the re-weighted Belamaf arm [redacted]% have an ISS stage III while on the PomDex arm most of the patients had no records of ISS staging ([redacted]% unknown ISS stage). Lytic bone lesions were present in [redacted]% of patients in the re-weighted Belamaf arm while most patients had no lytic bone lesions in the PomDex arm ([redacted]%).

Missing baseline characteristics may also impact the comparability of the datasets. For instance, high cytogenetic risk, identified as a key prognostic factor and treatment effect modifier by clinical experts, was not reported in the NCRAS dataset.

Table 30. Belamaf patient characteristics before and after matching versus PomDex

Baseline characteristic	**DREAMM-2 N = 97 Unmatched**	**DREAMM-2 ESS = [redacted] Matched**	**PomDex N=[redacted]**
Age (mean, years)	[redacted]	[redacted]	[redacted]
Race: white (%)	[redacted]	[redacted]	[redacted]
Race: black (%)	[redacted]	[redacted]	[redacted]
Race: Asian (%)	[redacted]	[redacted]	[redacted]
Race: other (%)	[redacted]	[redacted]	[redacted]
Race: unknown (%)	[redacted]	[redacted]	[redacted]
Sex (% male)	52.6	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]
Lytic bone lesions (% with)	[redacted]	[redacted]	[redacted]
High risk cytogenetics (% with)	[redacted]	[redacted]	[redacted]
Prior stem cell transplant (% with)	[redacted]	[redacted]	[redacted]
ECOG status = 0-2 (%)	[redacted]	[redacted]	[redacted]
ECOG status = 3-4 (%)	[redacted]	[redacted]	[redacted]
ECOG status = unknown (%)	[redacted]	[redacted]	[redacted]
Extramedullary disease (% with)	22.7	[redacted]	[redacted]
ISS Stage = 1 (%)	22.7	[redacted]	[redacted]
ISS Stage = 2 (%)	34.0	[redacted]	[redacted]
ISS Stage = 3 (%)	43.3	[redacted]	[redacted]
Prior lines of therapy (median)	6.7	[redacted]	[redacted]

Abbreviations: ESS, effective sample size; N, number.

A summary of the efficacy results for OS, TTNT and TTD is presented in Table 31 and in Figure 29 to Figure 31.

Table 31. MAIC results: summary Belamaf versus PomDex

Endpoint	HR	95% CI	p-value
OS	[redacted]	[redacted]	[redacted]
TTNT	[redacted]	[redacted]	[redacted]
TTD	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, effective sample size; CI, confidence interval; HR, hazard ratio; OS, overall survival; TTD, time to treatment discontinuation; TTNT, time to next treatment.
HR<1 favours Belamaf. P-value<0.05 indicates statistical significance. 95% CIs that do not cross 1 indicate statistical significance.

Figure 29. MAIC results versus PomDex: OS Kaplan-Meiers

Abbreviations: OS, overall survival.

Figure 30. MAIC results versus PomDex: TTNT Kaplan-Meiers

Figure 31. MAIC results versus PomDex: TTD Kaplan-Meiers

Abbreviations: TTD, time to treatment discontinuation.

The analyses showed that, once the Belamaf and PomDex populations are more closely aligned, a a [redacted] was observed for Belamaf compared to PomDex. [redacted] results produced by the MAIC were [redacted].

B.2.8.2.4 Limitations

The MAIC represents an alternative source of comparative effectiveness for the patient population of interest to this appraisal, aiming to adjust where feasible, for cross-study differences in patient characteristics. Nonetheless, in light of the unresolvable limitations and considerable uncertainty associated with the MAIC discussed below, this analysis is considered as a scenario in this appraisal.

Firstly, the NCRAS dataset censor data on patients who are receiving treatments not currently available on NHS routine commissioning but instead are funded through the CDF. This impacts the sample size available for the analysis and may affect the generalisability of the cohort; however, it is difficult to predict the magnitude of impact and direction of the potential resulting bias.

Some differences in the definition of outcomes and population are observed between the DREAMM-2 trial and the NCRAS study. In the absence of routine data collection for progression, relapse or refractoriness within the NCRAS dataset, there was a need to use proxy measures (e.g., TTNT for disease progression) or algorithms (e.g., to estimate whether patients are refractory to a treatment class). As such, the definition of refractoriness and progression varies across the DREAMM-2 and NCRAS datasets. As described in Section B.2.3.2.1, refractoriness in the NCRAS dataset is defined based on previous exposure without further details on the response status. The use of TTNT as a proxy for PomDex PFS was considered to estimate the relative PFS between Belamaf and PomDex; however, this assumption was deemed not appropriate in the context of MM. Indeed, in the MM treatment paradigm, a delay may be observed between disease progression and the initiation of a subsequent line of therapy to allow for the completion of a treatment cycle, a ‘wash-out’ period to recover from toxicities or for a treatment decision to be implemented.

A MAIC requires much stronger assumptions than an anchored comparison, for instance that all important prognostic and effect modifiers can be accounted for. Due to limitations in the data reported in the NCRAS dataset, it was not possible to adjust for all imbalances in the important prognostic factors and treatment effect modifiers identified by UK clinicians. Specifically, comorbidities, high cytogenetic risk and renal impairment at baseline were not reported in the NCRAS dataset and therefore could not be adjusted for. In addition, it is not possible to compare the cohorts for those baseline characteristics and thus, it is difficult to assess how differences, if any, may impact the results.

As highlighted in Section B.2.8.2.3, the baseline ECOG PS differed between the two populations; [redacted] patients in the PomDex arm had ECOG PS 3-4 (which is an exclusion criterion in DREAMM-2) and [redacted]% of PomDex patients had an unknown status. A censoring of the patients with ECOG PS 3-4 from the PomDex cohort was explored, however, it did not meet the Information Standards Board anonymisation standard (the standard anonymisation processes for health and social care data to assess the risk of extra information being used to try to reveal the identity of individuals) and was therefore not feasible. Similarly, data for ISS staging was unavailable for [redacted]% of PomDex patients in the NCRAS study.

Upon matching, including ECOG PS and/or ISS staging would dramatically reduce the ESS, and affect the reliability of results. As such, matching the patients in the DREAMM-2 trial to those in the NCRAS study on these variables was not considered and the impact of potential bias resulting from unknown ECOG PS and un-staged ISS is difficult to estimate.

Disparities in the number of prior lines of therapy received by patients in both cohorts have been noted, as outlined in Section B.2.8.1.3. First, [redacted] patients in the DREAMM-2 trial had received three prior lines however, since the baseline characteristics and efficacy outcomes were broadly similar between the 5L+ TCR only and ITT populations, and to maximise the sample sizes, the whole ITT population of the DREAMM-2 trial was considered in the MAIC. Then, the distribution of prior lines of therapy varied between the NCRAS and DREAMM-2 populations. Over half of the patients in the DREAMM-2 trial had seven or more lines of prior therapies, whereas the maximum number of prior lines reported in the NCRAS study was [redacted] (for [redacted]% of PomDex patients). Patients in the DREAMM-2 trial were, on average more heavily pre-treated, which could affect the comparability of the populations and result in bias.

Finally, owing to covariates matching, the Belamaf population size was reduced from 97, to an ESS of [redacted], an indication that there is little overlap in the populations being compared. Consequently, results for OS and TTNT outcomes comparison produced [redacted] results (p=[redacted] and p=[redacted] for OS and TTNT, respectively).

This indicates that the results, produced from such small sample sizes combined with the remaining areas of uncertainty generate plausible but unreliable estimates of the relative efficacy of Belamaf versus PomDex.

In light of the MAIC limitations described above, especially the partial adjustment only for effect modifiers and prognostic variables, a naïve comparison of the efficacy data from the DREAMM-2 trial and the NCRAS study was deemed more appropriate, and consequently, was used to inform the clinical parameters in the base-case economic analysis (Section B.3.3). Nonetheless, the results of the unanchored MAIC are included in a scenario to validate the results of the CEA. (Appendix M)

When naively compared, a [redacted] associated with Belamaf versus PomDex was suggested ([redacted] months versus [redacted] months respectively), despite [redacted] indicating that patients treated with Belamaf had [redacted]).

B.2.9 Adverse reactions

B.2.9.1 Adverse events (AE) overview

At the 13-month follow-up, 98% of patients in the 2.5 mg/kg cohort reported an AE, of which 83% experienced a Grade 3 or 4 AE, [redacted]% had a serious AE (SAE) and 3% a fatal AE. In the final analysis, the proportion of patients who experienced AEs and SAEs was [redacted]. (Table 32)

Table 32. Adverse event overview (DREAMM-2, safety population)

	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan2020)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any AE, n (%)	93 (98)	[redacted]
AEs related to study treatment	84 (88)	[redacted]
AEs leading to permanent discontinuation of study treatment	9 (9)	[redacted]
AEs leading to dose reduction	33 (35)	[redacted]
AEs leading to dose interruption/delay	51 (54)	[redacted]
AEs related to study treatment and leading to permanent discontinuation of study treatment	[redacted]	[redacted]
Grade 3 or 4 AEs	[redacted]	[redacted]
Grade 3 or 4 AEs related to study treatment	54 (57)	[redacted]
Any SAE, n (%)	[redacted]	[redacted]
SAEs related to study treatment	[redacted]	[redacted]
Fatal SAEs	3 (3)	[redacted]
Fatal SAEs related to study treatment	[redacted]	[redacted]

Abbreviations: AE, adverse event; n, number; Q3W, once every 3 weeks; SAE, serious adverse event
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74]Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74], Lonial, supplement 2021[85]

B.2.9.2 AEs by severity

At the 13-month follow-up, the most frequent Grade ≥3 AEs reported were keratopathy ([redacted]%), thrombocytopenia ([redacted]%), anaemia (21%) and lymphocyte count decreased (13%). (Table 33)

In the final analysis, the incidence of the most commonly reported AE of Grade ≥3 was [redacted]. (Table 33) In general, the extended exposure [redacted].

Table 33. Adverse events grade ≥3 reported in ≥5% of patients (DREAMM-2, safety population)

Preferred term	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any Event, n (%)	80 (84)	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	20 (21)	[redacted]
Keratopathy	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Lymphocyte count decreased	12 (13)	[redacted]
Platelet count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Hypercalcemia	7 (7)	[redacted]

Abbreviations: n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74]

B.2.9.3 Adverse events leading to discontinuation of Belamaf

The incidence of AEs leading to discontinuation was 9% at the 13-month follow-up, and [redacted]% in the final analysis. The most common AE leading to permanent discontinuation was keratopathy, at 1% at the 13-month follow-up and [redacted]% in the final analysis. (Table 34)

Table 34. Adverse events leading to permanent discontinuation of study treatment (safety population)

Preferred term	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any event, n (%)	9 (9)	[redacted]
Keratopathy	1 (1)	[redacted]
Cardiac arrest	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Herpes simplex pneumonia	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Urine albumin/creatinine ratio increased	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Preferred term	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Vision blurred Visual acuity reduced Hypoxia		

Abbreviations: n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74], Lonial, supplement 2021[85]

B.2.9.4 Adverse events leading to dose reduction of Belamaf

Overall, 35% of patients had an AE leading to dose reduction at the 13-month follow-up, which [redacted]% in the final analysis. The most common AEs leading to dose reduction were keratopathy ([redacted]% and [redacted]%), thrombocytopenia ([redacted]% and [redacted]%), and vision blurred ([redacted]% and [redacted]%) at the 13-month follow-up and in the final analysis respectively. (Table 35)

Table 35. Adverse events leading to dose reduction (DREAMM-2, safety population)

Preferred term	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any event, n (%)	33 (35)	[redacted]
Keratopathy	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]

Abbreviations: n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74], Lonial, supplement 2021[85]

B.2.9.5 Adverse events leading to dose delays of Belamaf

At the 13-month follow-up, 54% of patients had AEs leading to dose delays, this percentage [redacted] in the final analysis. The most common AEs leading to dose delays were keratopathy ([redacted]), vision blurred ([redacted]), pneumonia ([redacted]) and dry eye ([redacted]%, [redacted]%, in the 13-month follow-up and final analysis respectively). All other AEs leading to dose delay occurred in <3% of patients. (Table 36).

Table 36. Adverse events leading to dose delays (DREAMM-2, safety population)

Preferred Term	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any event, n (%)	51 (54)	[redacted]
Keratopathy	45 (47)	[redacted]
Vision blurred	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urine albumin/creatinine ratio increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]

Abbreviations: n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74], Lonial, supplement 2021[85]

B.2.9.6 Adverse events of special interest (AESI)

B.2.9.6.1 Keratopathy

At the 13-month follow-up, [redacted]% of patients experienced keratopathy at any grade, and [redacted]% of patients experienced keratopathy at grade 2+. The extended exposure [redacted]. There were minor [redacted] in incidence of keratopathy-related events, namely keratitis ([redacted]%, [redacted]%), ulcerative keratitis ([redacted]%, [redacted]%), punctate keratitis ([redacted]%, [redacted]%), and infective keratitis ([redacted]%, [redacted]%) reported in the 13-month follow-up and final analysis respectively. (Table 37)

Table 37. Keratopathy events (CTCAE) (DREAMM-2, safety population)

Preferred term	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any event, n (%)	[redacted]	[redacted]
Keratopathy	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]

Preferred term	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Limbal stem cell deficiency	[redacted]	[redacted]
Ulcerative keratitis	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]
Infective keratitis	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; n, number; Q3W, once every 3 weeks

B.2.9.6.2 Blurred vision

To ensure a comprehensive evaluation of blurred vision, events in this section include the following MedDRA AE preferred terms (PTs) that the Company considered to be related to blurred vision: blindness, diplopia, glare, halo vision, night blindness, vision blurred, visual acuity reduced, visual acuity tests abnormal, visual field defect, and visual impairment (Table 38).

Table 38. Blurred vision events (CTCAE) (DREAMM-2, safety population)

Preferred term	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any Event, n (%)	24 (25)	[redacted]
Vision blurred	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]
Diplopia	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74]

B.2.9.6.3 Dry eye

To ensure a comprehensive evaluation of dry eye, events in this section include the following MedDRA AE PTs that the Company considered to be related to dry eye: dry eye, ocular discomfort, eye pruritus and foreign body sensation in eyes (Table 39).

Table 39. Dry eye events (CTCAE) (DREAMM-2, safety population)

Preferred term	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any Event, n (%)	14 (15)	[redacted]
Dry eye	[redacted]	[redacted]
Eye pruritus	[redacted]	[redacted]
Ocular discomfort	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74]

Thrombocytopenic events and infusion-related reactions were also AEs of special interest and are reported in Table 40 and Table 41 below.

B.2.9.6.4 Thrombocytopenic events

Table 40. Thrombocytopenic events (DREAMM-2, safety population)

Preferred term	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any Event, n (%)	36 (38)	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]

Abbreviations: n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74]

B.2.9.6.5 Infusion-related reactions

Table 41. Infusion-related reactions (DREAMM-2, safety population)

Preferred term	Number (%) of patients	
	Belamaf Q3W	
	13-Month follow-up (31Jan20)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Any Event, n (%)	20 (21)	[redacted]
Infusion-related reaction	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Lethargy	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]

Abbreviations: n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74]

B.2.9.6.6 Recovery and resolution of keratopathy and best corrected visual acuity (BCVA)

At the final analysis, the median time to the onset of the first keratopathy examination finding was [redacted] days (range, [redacted] days), with [redacted] patients who had keratopathy experiencing their first finding by [redacted]. As of the final analysis and where data were available, [redacted] patients ([redacted]%) recovered (resolution or return to baseline) from their first keratopathy examination finding of grade ≥2 according to the keratopathy and visual acuity (KVA) scale, and [redacted] of [redacted] patients ([redacted]%) recovered from their last events. The median time to recovery of the first examination finding was [redacted] days (range, [redacted] days), and it was [redacted] days (range, [redacted] days) for the last event. [redacted] patients whose recovery had yet to be recorded from their last event [redacted] as of this analysis.

In patients with normal or near-normal vision at baseline, change to a Snellen Visual Acuity score of 20/50 indicates a meaningful reduction in visual acuity and is used as a threshold for legal driving in many countries.[86] [redacted] of [redacted] patients ([redacted]) recovered (BCVA improvement to better than a Snellen Visual Acuity of 20/50) from their last event, with the remaining [redacted] patients not completing follow up as of the final analysis.[87] The median duration of these declines in BCVA was [redacted] days (range, [redacted] days); therefore, [redacted] patients recovered after one [redacted] assessment interval. [redacted] permanent complete loss of vision (irreversible BCVA decline worse than a Snellen Visual Acuity of 20/200) has been reported from DREAMM-2 as of the final analysis.

B.2.9.6.7 Deaths

At the final analysis, [redacted]% of patients had died (Table 42).

Table 42. Summary of deaths (safety population)

	Belamaf Q3W	
	13-Month follow-up (31Jan2020)	Final analysis (4May22)
	2.5 mg/kg (N=95) Safety	2.5 mg/kg (N=95) Safety
Patient status, n (%)		
Dead	47 (49)	[redacted]
Alive at the last contact, follow-up ended	[redacted]	[redacted]
Alive at the last contact, follow-up ongoing	[redacted]	[redacted]

Abbreviations: n, number; Q3W, once every 3 weeks
Source: DREAMM-2 13-month follow-up clinical study report[73], Lonial et al. 2021[74]

B.2.10 Ongoing studies

DREAMM-3 (NCT04162210) is an ongoing phase 3, open-label, randomised multi-centre study to evaluate the efficacy and safety of single agent Belamaf compared with PomDex in patients with RRMM who received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and a proteasome inhibitor (given separately or in combination), and who have failed their last line of treatment. The study is being conducted in 19 countries in 184 sites, including 10 UK sites.

There is likely

[redacted]

11

B.2.11 Interpretation of clinical effectiveness and safety evidence

B.2.11.1 Principal findings from the clinical evidence base

B.2.11.1.1 Clinical effectiveness

In the heavily pre-treated TCR patient population enrolled in DREAMM-2, clinically meaningful (overall responses achieved by [redacted]% of patients as assessed by IRC) and deep ([redacted]% of responders with ≥VGPR) responses with single agent Belamaf 2.5 mg/kg were sustained at the final analysis. Time to response was short, at a median of [redacted] months. The median OS was [redacted] months in this analysis, which is substantially longer than that reported in a similar population. [29] The median DoR in the 2.5 mg/kg group was [redacted] months in the ITT population and increased to [redacted] months for patients achieving at least a MR. The median PFS was [redacted] months in the ITT population and increased to [redacted] months in patients who achieved a MR or better. In those with deep responses (≥VGPR) who were tested for MRD status, five patients (38%) achieved MRD negativity after a median follow-up

of 13 months. Median TSNT was [redacted] months, and median TTD was [redacted] months, [redacted] in the post-hoc analysis run on 4th May 2022.

The EORTC-QLQ-C30 Global Health Status/QoL scores demonstrated [redacted] quality of life overall [redacted] the 13-month follow-up period. [redacted] were seen in 'Physical Functioning', 'Fatigue' and 'Pain' in [redacted]%, [redacted]% and [redacted]% respectively at week 25.

The EORTC-QLQ-MY20 QoL scores during treatment with Belamaf [redacted], with a [redacted] over time.

Based on those results reported in the DREAMM-2 trial, Belamaf represents a clinically meaningful step change in the management of 5L+ TCR MM in the UK.

B.2.11.1.2 Safety

Overall, the DREAMM-2 trial demonstrated a manageable safety profile. As of the final data analysis, the most frequent Grade ≥3 adverse events (AEs) reported were keratopathy ([redacted]), anaemia ([redacted]), thrombocytopenia ([redacted]), and lymphocyte count decreased ([redacted]). The incidence of the most commonly reported AE of Grade ≥3 was consistent between the 13-month follow-up and the final analyses. In general, the extended exposure did not lead to a significant increase in severity of keratopathy events. Few patients permanently discontinued treatment due to AEs ([redacted]), with keratopathy being the most common AE leading to discontinuation ([redacted]). Dose reductions and dose delays were most commonly due to keratopathy ([redacted] and [redacted] respectively) in the final analysis and are the primary mitigation strategy for AEs.

Recovery and resolution of keratopathy and best corrected visual acuity (BCVA)

At the final analysis, the median time to the onset of the first keratopathy examination finding was [redacted] days, with [redacted] of [redacted] patients who had keratopathy experiencing their first finding by treatment cycle [redacted], [redacted] of [redacted] patients ([redacted]%) recovering (resolution or return to baseline) from their first keratopathy examination finding of grade ≥2, and [redacted] of [redacted] patients ([redacted]%) recovering from their last events. The median time to recovery of the first examination finding was [redacted] days. [redacted] of [redacted] patients ([redacted]%) recovered (BCVA improvement to better than a Snellen Visual Acuity of 20/50) from their last event, with the remaining [redacted] patients not completing follow up as of the final analysis.[87] The median duration of these declines in BCVA was [redacted] days; therefore, [redacted] patients recovered after [redacted] 21-day assessment interval. No permanent complete loss of vision (irreversible BCVA decline worse than a Snellen Visual Acuity of 20/200) has been reported from DREAMM-2 as of the final analysis.

B.2.11.1.3 Comparative efficacy

Although the observed durable response in highly pre-treated patients whose disease is refractory to three classes of agents is considered a clinically meaningful benefit, there is a need to quantify the relative efficacy of Belamaf versus relevant comparators in a 5L+ TCR myeloma population.

An unanchored MAIC was conducted, using the PomDex arm of the NCRAS study and adjusting for three of the most important prognostic factors and treatment effect modifiers

identified by clinical experts (age, number of lines of prior therapies and extramedullary disease). Further adjustment was explored but deemed unfeasible due to limitations in the NCRAS study, and therefore differences in patients' characteristics persisted after matching. The results of the adjusted comparison between Belamaf (DREAMM-2 trial) and PomDex (NCRAS study) suggested that patients treated with Belamaf may experience an increased OS, with a hazard ratio of [redacted], representing a reduction in the risk of death of [redacted]% (95% CI [redacted], [redacted]; p=[redacted]) compared to PomDex. Superiority was also suggested for TTNT (HR [redacted]; 95% CI [redacted], [redacted]; p=[redacted]) and TTD (HR [redacted]; 95% CI [redacted], [redacted]; p=[redacted]) compared to PomDex, with statistical significance reached for TTD.

However, in light of the limitations resulting from the partial covariates adjustment and small effective sample size, the robustness of the MAIC outcomes is limited. Thus, a naïve comparison of OS, TTNT and TTD outcomes of Belamaf from the DREAMM-2 trial to the PomDex arm of the NCRAS study was preferred to inform the base-case CEA. The naïve comparison showed a [redacted]OS in patients treated with Belamaf than in those treated with PomDex ([redacted] months versus [redacted] months), [redacted].

B.2.11.2 Strengths and limitations of the clinical evidence base

B.2.11.2.1 Strengths of the clinical evidence base

DREAMM-2 trial

DREAMM-2, a single-arm, open-label trial, was the only clinical trial identified for Belamaf in a population of patients with 5L+ TCR MM. Survival data were mature at the point of the final analysis presented in this appraisal, with [redacted]% patients having experienced progression and [redacted]% patients having died.

The results of the DREAMM-2 trial are relevant to the decision problem specified in the NICE final scope proposing the use of Belamaf for patients who have received at least four prior lines of therapy and are refractory to a PI, an IMiD and an anti-CD38 mAb.

The external validity and generalisability of the DREAMM-2 trial to UK clinical practice is supported by:

- **Population**: most patients in the DREAMM-2 trial had previously received at least four prior lines of therapy and were refractory to a PI (bortezomib, carfilzomib), an IMiD (lenalidomide) and an anti-CD38 mAb (Daratumumab for all patients with or without isatuximab). Thus, the results of the DREAMM-2 trial provide robust supportive evidence for the use of Belamaf in the patient population specified in the decision problem. In addition, DREAMM-2 was a multi-centre, international study and patients were enrolled across seven UK trial sites, increasing the generalisability to the UK population of patients with 5L+ TCR MM.
- **Intervention**: Belamaf 2.5 mg/kg was evaluated in line with its licensed indication.
- **Comparators**: Not applicable due to the single-arm nature of the DREAMM-2 trial. However, the most appropriate comparator for this appraisal, PomDex, was selected

based on the findings of the NCRAS study which also reported data for relevant efficacy outcomes.

- **Outcomes**: All the key outcomes relevant for decision making were assessed in the DREAMM-2 trial and used in the economic analysis (OS, TTD, TTNT, adverse events, HRQoL).

Comparative efficacy evidence

To mitigate the impact of the lack of data available in the literature for PomDex, the Company conducted a RWE study using the NCRAS dataset to identify a cohort of 5L+ TCR MM patients receiving PomDex, as detailed in Section B.2.3.2.

The NCRAS study provides the most robust and only evidence identified for PomDex in a population of 5L+ TCR MM patients. The NCRAS database collects quality-assured data with complete coverage of all patients diagnosed with cancer in England, meaning that this cohort is representative of patients in UK clinical practice. Data was reported for an extended period from the 1st January 2013 until the 31st December 2021, representing another key strength, particularly for the evaluation of survival endpoints.

In addition to key clinical outcomes (OS, TTNT, TTD), patient characteristics and data for a number of prognostic variables were available in the NCRAS study allowing a comparison of the population in both cohorts.

Given the generalisability of this RWE cohort to patients with 5L+ TCR MM in UK clinical practice and based on the strengths described above, this study represents the most robust source of evidence to inform PomDex efficacy in this appraisal.

B.2.11.2.2 Limitations of the clinical evidence base

As previously outlined, the lack of comparator arm in the DREAMM-2 trial and the absence of published evidence to inform the efficacy of PomDex in 5L+ TCR MM patients were two key limitations of the clinical evidence base.

While the NCRAS study provides the most robust source of comparative evidence to address this data gap, it is associated with limitations. Differences in population and outcomes definition may result from the non-inclusion of data for progression, remission or recurrence of disease and proxy or assumptions were required. For instance, while OS was reported in the NCRAS dataset, no PFS data was available and instead, TTNT was compared to DREAMM-2 TTNT to ensure a consistent and fair comparison of clinical outcomes.

Furthermore, while a number of baseline characteristics were available in the NCRAS dataset, some key prognostic factors and treatment effect modifiers were incomplete or not reported. This impacts the assessment of population comparability and the feasibility of ITCs. In addition, some differences in baseline characteristics across both datasets were noted and could not be adjusted for such as the exclusion of patients with ECOG 3-4 from the DREAMM-2 trial and the proportion of patients with an unknown ECOG PS or ISS stage in the NCRAS study.

In both the NCRAS study and the DREAMM-2 trial, patient numbers were small which represents an important challenge when attempting to derive comparative efficacy data of

Belamaf versus PomDex. Hence, whilst performing a MAIC improved the comparability of populations, it significantly reduced the sample sizes which consequently impacted the quality and reliability of the relative efficacy estimates.

As such, the MAIC results were deemed too uncertain to draw conclusions. Instead, all data available was used and in light of the populations difference for markers of poor prognosis it is reasonable to assume that the naïve comparison provides a conservative estimate of the relative efficacy of Belamaf versus PomDex.

B.2.11.3 Conclusion

The efficacy and safety of Belamaf in 5L+ TCR MM patients was demonstrated in the DREAMM-2 trial, the most robust source of evidence generalisable to the UK population. When comparing the unadjusted results of the DREAMM-2 and NCRAS study cohorts, a [redacted] OS associated with Belamaf was observed [redacted], which implies that the naïve comparison may be conservative. Despite the methodological limitations, the MAIC suggested that when compared to PomDex, the most relevant comparator in the UK, Belamaf may offer clinical benefits to patients with 5L+ TCR MM.

Considering the few alternative treatment options and exquisitely high unmet medical need, Belamaf (as the first BCMA targeted treatment) would provide hope for the heavily pre-treated, TCR MM patients who currently feel hopeless and face a poor prognosis with limited options at 5L and beyond. Belamaf is a clinically effective novel treatment option in this population and as such has the potential to shift the NICE MM treatment paradigm.

B.3 Cost effectiveness

Summary of cost-effectiveness analysis

- A *de novo* partitioned survival model was developed to evaluate the cost-effectiveness of Belamaf versus PomDex in adult patients with RRMM who have had at least 4 prior therapies, and whose disease is refractory to at least one PI, one IMiD, and an anti-CD38 mAb, and whose disease has progressed on the last therapy.

- The model structure consisted of four health states: progression-free on treatment, progression-free off-treatment, progressed disease and death.

- Clinical outcomes (TTD, TTNT as a proxy for PFS and OS), adverse events incidence and subsequent treatments for Belamaf were derived from the ITT population of the final analysis of the DREAMM-2 trial.

- Clinical outcomes and subsequent treatments for PomDex were based on the NCRAS study and adverse events incidence was sourced from the MM-010 trial.

- Health state utilities for the PFS and PD health states were informed by DREAMM-2 EORTC-QLQ30 mapped to the EQ-5D-3L instrument and AE related disutilities were sourced from the literature.

- Costs associated with drug acquisition and administration, the management of AEs, disease monitoring, concomitant therapies and supportive care, subsequent treatments and end of life were included for all modelled treatments. All unit costs were sourced from the relevant national UK sources. Healthcare resource use and other aggregate costs were sourced from previous NICE TAs, with any missing data provided by clinical opinion.

Summary of cost-effectiveness results

- The base-case deterministic results predict that Belamaf is associated with higher average QALYs ([redacted]) and lower average costs (£[redacted] cost savings) when compared to PomDex suggesting that Belamaf (at PAS price) is dominant vs PomDex (at list price) over a 25-year time horizon.

- A [redacted]% proportional QALY shortfall was calculated based on the model population. The heterogeneity of the population and the closeness of the estimate to the 95% shortfall, supports the application of a 1.7x multiplier and a willingness to pay threshold of £36,000 to £51,000.

- The mean PSA results were consistent with the deterministic base-case results and the probability of Belamaf being cost-effective at a WTP of £51,000 per QALY was [redacted]%. In the deterministic OWSA, the parameters with the greatest impact on the base-case ICERs were the RDI for pomalidomide and Belamaf, followed by OS and TTD for both Belamaf and PomDex.

- The validity of the base-case analysis results was further supported by the scenario analyses results which indicated that Belamaf continued to dominate PomDex across all scenarios.

- All key model inputs and modelling assumptions have been validated by UK clinicians, with internal, external and cross-validation steps taking place also.

- Overall, and mindful of NHS resources, these results demonstrate that Belamaf, a much-needed new mechanism of action, would be a valuable addition to the treatment pathway for patients with 5L+ TCR MM in England and Wales who are currently faced with very limited treatment alternatives towards the end stages of their disease.

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted in July 2019 and updated in August 2022 to identify relevant cost-effectiveness studies from the published literature. The population considered in this submission is patients with 5L+ TCR MM. The evidence available in this setting is usually limited, therefore the scope of the economic SLR was broadened to patients with 4L+ RRMM to identify all relevant data that could inform the development of the cost-effectiveness model.

Full details of the SLR strategy, study selection process and results are presented in Appendix G. The SLR identified ten economic evaluation publications of which nine were CEA in 4L+ RRMM and one was a cost-minimisation analysis. Of the nine CEAs identified, six were based on a partitioned survival model (PSM) structure, two were semi-Markov PSMs and the other a Markov model. The Markov model considered on a 12-month time horizon and therefore has limited generalisability the decision problem.

B.3.2 Economic analysis

None of the nine studies identified assessed the cost-effectiveness of Belamaf versus PomDex, therefore a *de novo* cost-effectiveness model was constructed for the purpose of this appraisal, as described in the following sections.

For completeness, a CEA versus PanoBorDex is presented in Appendix M.

B.3.2.1 Patient population

In line with the final NICE scope for this appraisal, and with the licensed indication for Belamaf in the UK, the cost-effectiveness model considers adult patients with RRMM who have had at least four prior therapies, and whose disease is refractory to at least one PI, one IMiD agent, and an anti-CD38 mAb, and whose disease has progressed on the last therapy, referred to as 5L+ TCR MM.[89]

As discussed in Section B.2.2.1, the model is based on the 2.5 mg/kg arm of the ITT population of DREAMM-2 which is broader than the licensed indication of Belamaf as DREAMM-2 included 5 patients who received three prior therapies and are therefore at 4L on entry into the study. The 5L+ only and the ITT population are broadly aligned when comparing the baseline characteristics and clinical outcomes (B.2.3.1.2 and B.2.6). The ITT was considered in the CEA.

B.3.2.2 Model structure

A *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of Belamaf versus PomDex in patients with 5L+ TCR MM.

The developed model was a cohort-based PSM consisting of four mutually exclusive health states:

- Progression-free (PF) on treatment (on-tx)
- PF off-treatment (off-tx),

- Progressed disease (PD)
- Death

The proportion of patients occupying each health state over time was estimated from parametric distributions fitted to the OS, PFS and TTD data from the DREAMM-2 trial and NCRAS dataset, for Belamaf and PomDex, respectively. In the absence of PFS reported in the NCRAS study, TTNT from DREAMM-2 and NCRAS was used as a proxy to inform PFS in the cost-effectiveness model. State membership for the PF on-tx state was estimated from the extrapolated TTD KM curves. State membership for the PF off-tx state was estimated by subtracting the TTD curve from the extrapolated PFS KM curve for each treatment (i.e., PFS off-tx = PFS-TTD). State membership for the death state was estimated using the extrapolated OS KM curves (Death=1-OS) and the PD state membership was estimated to be the difference between the OS and PFS curves (PD=OS-PFS). Model schematics are provided in Figure 32 and Figure 33.

For each weekly cycle, costs and QALYs were calculated based on the state membership of patients across the modelled health states and death. Costs and QALYs were accumulated over the lifetime model time horizon to calculate total costs and QALYs for the two cohorts entering the model to receive Belamaf and PomDex, respectively, with the data used to calculate incremental results and the cost per QALY for Belamaf versus PomDex. In addition, the cost per life year gained was calculated.

This model structure was deemed appropriate for the decision problem since PSMs are considered standard practice for oncology modelling in the UK[90] and it is consistent with the approach considered in previous appraisals in late-stage MM.[97,90]

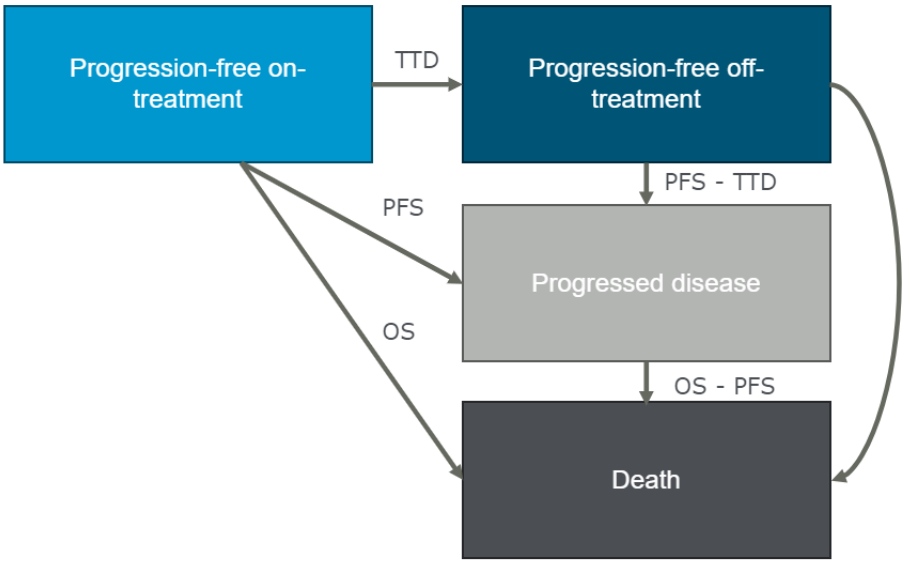
The PSM approach requires fewer inputs than methods requiring time- and state-specific transition probabilities to be estimated, such as Markov models.[90] Patient distributions between health states are derived directly from trial endpoints thus, modelled state populations are well aligned with the DREAMM-2 data over the observed trial period, and complexities that may be associated with deriving transition probabilities are avoided.

The four health states in the PSM are mutually exclusive, meaning that patients must occupy one of the states at any given time. PF (on- and off-tx) and PD health states are intended to capture the differences in costs and quality of life within MM. PF (on- and off-tx) captures the costs and consequences of treatment, administration, concomitant therapies and supportive care, monitoring, and adverse events, whilst PD captures the costs and consequences of subsequent treatments, monitoring and end of life care. Therefore, the model captures the key elements of care for patients with 5L+ TCR MM from the time they begin treatment to when they complete subsequent treatment and enter terminal care.

The PF on- and off-treatment split was chosen based on the rationale that some patients in DREAMM-2 withdraw from active treatment before disease progression (Section B.2.5.1.8). This is aligned with clinical opinion and the posology guidance in the SmPC, which states that treatment with Belamaf '*should be continued until disease progression or unacceptable toxicity*'.[1] Moreover, the ERG accepted this model structure in TA427[66] and TA783[30] which allowed the possibility to model patients on PomDex who stop therapy prior to disease progression.

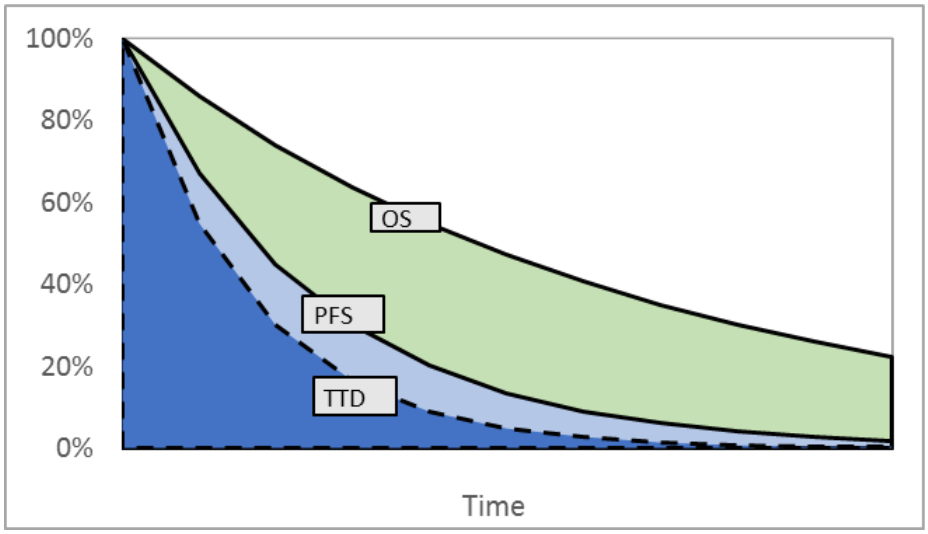
Structural uncertainty has been tested in a scenario analysis using a three-health state model (PF, PD and death). Results are presented in Section B.3.11.3.

Figure 32: Diagram of model structure



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

Figure 33: Distribution of patients in progression-free and on treatment, progression-free and off-treatment, progressed and death health states



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

B.3.2.2.1 Model settings

An overview of the key features from previous NICE TAs and for the *de novo* economic model are presented in Table 43. Parameter selection was consistent with the NICE Reference Case [91] and UK clinical practice.

Table 43. Features of the economic analysis

Previous appraisals				Current appraisal	
Factor	**TA427[66]**	**TA510/TA783[30]**	**TA658[93]**	**Chosen values**	**Justification**
Population and treatment	4L+ Intervention: POM+LoDEX Comparators: BorThalDex, PanoBorDex and conventional chemotherapy	4L+ Intervention: Daratumuab Comparators: PomDex and PanoBorDex	4L+ Intervention: Isatuximab in combination with PomDex Comparator: PomDex	5L+ TCR Intervention: Belamaf Comparator: PomDex	See Section B.1.1.
Time horizon	15 years (lifetime)	15 years (lifetime)	15 years	Lifetime - 25 years	Sufficiently long to be considered a lifetime horizon for 5L+ TCR MM patients with a mean age of 64.1 years and aligned with NICE reference case[91]
Perspective	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	In line with NICE reference case[91]
Discounting	3.5% per annum for costs and outcomes	3.5% per annum for costs and outcomes	3.5% per annum for costs and outcomes	3.5% per annum for costs and outcomes	In line with NICE reference case[91]
Cycle length	1 week	1 week	1 week	1 week	This allows the model to capture the differences in treatment cycle length across Belamaf and PomDex since 1 week is a common denominator. In addition, a short cycle length captures the rapid progression of TCR MM.

Previous appraisals				Current appraisal	
Factor	**TA427[66]**	**TA510/TA783[30]**	**TA658[93]**	**Chosen values**	**Justification**
Health states	Four state PSM: pre-progression on treatment, PF off-treatment, PD and death	Semi-Markov partitioned survival cohort model. Four health states; two PF disease states (defined by treatment status), one PD state, and a state for death	In the initial submission: Four state PSM: PF on treatment, PF off-treatment, PD, death. During the clarification process: the model operates as a 3-state PSM	Four health state model: PF on-tx, PF off-tx, PD, death	Health states aligned with previous NICE appraisals and are consistent with the natural disease progression in MM patients.
Source of utilities	Utility data from the MM-003 trial (EQ-5D estimates).	Utility scores were mainly taken from the MM-003 trial.	Utility data sourced from ICARIA study	Utility data sourced from DREAMM-2	PF on-tx, PF off-tx and PD health states mapped from EORTC-QLQ-C30 and QLQ-MMY20
Source of costs	Source of cost data included NHS reference costs, BNF, Emit, MIMS			Sources of cost data included the BNF for drug costs, and NHS Reference Costs	In line with NICE reference case[91]

Abbreviations: 4L+, fourth line and beyond; 5L+, fifth line and beyond; BNF, British National Formulary; EORTC,The European Organisation for Research and Treatment of Cancer; EQ-5D; EuroQoL Five Dimension; MIMS, The Monthly Index of Medical Specialities; MM, multiple myeloma; NHS, National Health Services; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; PSM, partitioned survival model; TA, technology appraisal; TCR, triple class refractory; tx, treatment; UK, United Kingdom

B.3.2.3 Intervention technology and comparators

The intervention, Belamaf, is modelled as per the licensed dosing regimen. The license states that Belamaf should be administered until disease progression or unacceptable toxicity and patients in DREAMM-2 withdrew from active treatment before disease progression (Section B.2.5.1.8).[1] As such, Belamaf treatment costs are modelled until the end of the TTD period to align with the recommendation in the SmPC and feedback from clinicians (see B.3.5.1.1).

PomDex is deemed to be the most relevant comparator for the economic analysis (Section B.1.1) and is modelled as per its marketing authorisation and licensed dosing regimen until the end of the TTD period (see B.3.5.1.1).

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

Baseline characteristics for the modelled cohort were based on the statistical analysis of the 2.5 mg/kg Belamaf dosing arm of DREAMM-2 (see Table 44).

Table 44. Patient baseline characteristics for the base-case economic analysis

Baseline demographics	Belamaf 2.5 mg/kg (ITT) N = 97	Reference
Mean age, years (SD)	[redacted]	DREAMM-2
Male, n (%)	51 (53)	
Mean weight, kg (SD)	[redacted]	
Mean BSA, m^2 (SD)	[redacted]	

Abbreviations: ITT, intention-to-treat; SD, standard deviation

B.3.3.2 Data sources for survival endpoints

The key outcomes used in the economic model are TTD, PFS and OS. As described in section B.2.3.2.1, in absence of PFS reported in NCRAS, TTNT was selected as the next best available source to model PFS for both Belamaf and PomDex. While PFS is available for Belamaf in the DREAMM-2 trial, TTNT was used for both treatment arms to ensure a fair and appropriate comparison between Belamaf and PomDex.

As described in Section B.2.8.2, an unanchored MAIC analysis was performed and partially adjusted the Belamaf population for some covariates; however, it resulted in small effective sample sizes and thus produced non-statistically significant and unreliable results. Instead, a naïve (unadjusted) comparison of clinical outcomes from the DREAMM-2 trial and NCRAS study was considered as the best approach to form the base-case CEA as it considers all clinical data available in this population. In addition, the remaining differences in population characteristics suggests that the NCRAS PomDex cohort may be healthier than the DREAMM-2 Belamaf cohort which implies that the model uses a conservative estimate of the relative efficacy of Belamaf vs PomDex (as detailed in Section B.2.8.1.3).

Efficacy data for Belamaf and PomDex was sourced from the open-label, Belamaf 2.5 mg/kg dose single-arm from DREAMM-2 and observational, retrospective NCRAS dataset, as described in Section B.2.3.1 and Section B.2.3.2, respectively. The naïve comparison used patient-level data (PLD) from DREAMM-2 to model clinical efficacy for Belamaf and reconstructed Kaplan-Meier (KM) data from NCRAS to model clinical efficacy for PomDex.

For Belamaf, DREAMM-2 PLD were available for OS, TTNT and TTD. For PomDex, only aggregate data for OS, TTNT and TTD were available in the form of KM plots, and as such, these plots were digitised using WebPlotDigitizer software to generate reconstructed KM data.

Table 45 summarises the clinical efficacy input data used in the cost-effectiveness model.

Table 45. Clinical input data for the naïve (unadjusted) comparison

Endpoint	Source of clinical effectiveness	
	Belamaf	**PomDex**
OS	OS PLD from DREAMM-2	OS reconstructed KM from NCRAS
PFS	TTNT PLD from DREAMM-2	TTNT reconstructed KM from NCRAS
TTD	TTD PLD from DREAMM-2	TTD reconstructed KM from NCRAS

Abbreviations: KM, Kaplan-Meier; NCRAS, national cancer registration and analysis service; OS, overall survival; PLD, patient-level data; PFS, progression-free survival; TTD, time to treatment discontinuation; TTNT, time to next treatment.

B.3.3.3 Parametric survival modelling

Parametric survival modelling was implemented to extrapolate survival curves over a lifetime horizon of the cost-effectiveness model. Survival analyses were carried out in line with the NICE TSD 14.[56] Multiple analyses were used to test for proportional hazards (PH):

- A visual assessment of log cumulative hazard plots to assess whether the PH assumption is likely to hold. The PH assumption may not hold if the hazard plots show non-parallel or uneven lines between the two treatments arms. In this case independent distributions were fitted to each arm.
- An assessment of Schoenfeld residual plots to test the correlation between Schoenfeld residuals and survival time. The test for non-proportionality used p-values extracted from the Grambsch and Therneau test, where a significant p-value (<0.05) showed that the null hypothesis could be rejected, and the alternative hypothesis of non-proportionality could be assumed.
- An assessment of the Cox-Snell plot to assess the overall goodness of fit of the Cox model. In cases where the line did not have a unit slope, this was considered a violation of the PH assumption.

Six standard parametric distributions were fitted to KM data using R (Exponential, Weibull, log-logistic, log-normal, Gompertz and Generalised Gamma). The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to estimate the goodness of fit for each parametric distribution.

Furthermore, UK clinical experts were consulted to validate the clinical plausibility of the long-term extrapolations generated by each of the distributions, specifically of patients who would be progression-free following treatment with Belamaf and PomDex at 6-months, 1-, 2-, 5- and 10-years).

Finally, visual goodness of fit and clinical validation was used to determine the chosen parametric curves in the cost-effectiveness model.

The parametric survival modelling approach considered for the scenario using the MAIC efficacy estimates is described in Appendix P with results presented in Section B.3.11.3.

B.3.3.3.1 Progression-free survival

The cumulative log-log plot, the Schoenfeld residual plot and the Cox-Snell plots for PFS are presented in Figure 34 (A-C), respectively.

Figure 34. PFS diagnostic plots naïve comparaison

(A) Top left: Cumulative log-log plot DREAMM-2/NCRAS, (B) Top right: Schoenfeld plot DREAMM2/NCRAS, (C) Bottom: Cox-Snell DREAMM-2/NCRAS

Initial inspection of the log cumulative hazard plot (Figure 34 (A)) suggests the PH assumption can be rejected as the lines cross. In contrast, the Schoenfeld residual plot (Figure 34 (B)) shows an approximate 0 slope with a p-value of 0.2575 suggesting the PH assumption cannot be rejected. Similarly, the Cox-Snell plot Figure 34 (C) has a unit slope, signifying the PH assumption cannot be rejected. Based on the violation of the PH assumption in at least one of the diagnostic plots reported, independent parametric models were fitted to both treatment arms.

Belamaf progression-free survival

The six parametric distributions were fitted to the PFS KM collected from DREAMM-2 to extrapolate PFS in the economic model. The AIC/BIC statistical goodness of fit for these six distributions are shown in Table 46. Extrapolations of PFS using each model up to 60-months is presented in Figure 35 to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility. The landmark survival estimates from each of the PFS extrapolations are presented in Table 47.

Table 46. Base-case: AIC and BIC statistical goodness of fit data for PFS from DREAMM-2 (independent models)

Goodness of fit statistics: Belamaf, PFS		
Parametric survival model	**AIC**	**BIC**
Exponential	553.06	555.63
Weibull	553.79	558.94
Gompertz	548.60	553.75
Log-logistic	542.06	547.21
Lognormal	**538.30**	**543.45**
Generalised gamma	538.31	546.04

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; NR, not reported; PFS, progression-free survivalNote: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 35. Belamaf PFS extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Table 47. Base-case: Belamaf landmark PFS rates

Distribution	Proportion of patients who are progression-free at:				
	6 months	1-year	2-years	5-years	10-years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival

According to the AIC and BIC, the lognormal appeared to provide the best statistically fitting model for Belamaf PFS (Table 46). Within the observed period, all extrapolated parametric models yielded reasonable visual predictions (Figure 35). Landmark rates show the [redacted] curve estimates that [redacted]% and [redacted]% of patients are progression-free at 5-years and 10-years, respectively (Table 47). This falls between the most optimistic (Generalised Gamma) and pessimistic curves (Weibull).

PomDex progression-free survival

The same approach was adopted to extrapolate PFS data from the PomDex arm of the NCRAS study. The AIC/BIC goodness of fit for these six distributions are shown in Table 48.

Figure 36 depicts the PFS extrapolations up to 35-months (to aid visual assessment) and Table 49 summarises the landmark survival estimates from each of the PFS extrapolations.

Table 48. Base-case: AIC and BIC statistical goodness of fit data for PFS from NCRAS (independent models)

Goodness of fit statistics: PomDex, PFS		
Parametric survival model	**AIC**	**BIC**
Exponential	**186.3**	**188.5**
Weibull	187.8	192.2
Gompertz	NR	NR
Log-logistic	187.3	191.7
Lognormal	186.8	191.2
Generalised gamma	188.4	194.9

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; NR, not reported; PFS, progression-free survival
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 36. Base-case: PomDex PFS extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Table 49. Base-case: PomDex landmark PFS rates

	Proportion of patients progression-free at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Proportion of patients progression-free at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival

According to the AIC and BIC, the Exponential distribution was the best statistically fitting model for PomDex PFS (Table 48). Despite this, within the observed period, the tail in the [redacted] distribution appears to overestimate PFS (Figure 36). The landmark survival rates from all six distributions show that, at 2-years, between [redacted]% and [redacted]% of patients are progression-free. Furthermore, statistical fit data for Gompertz was not reported such that this aspect could not be assessed (Table 49).

According to clinical expert opinion, all the landmark rates overestimate PomDex PFS from 2 years onwards as, in clinical practice, it is not expected that patients would be progression-free beyond this time point.

Progression-free survival conclusions

Considering the visual fit, statistical fit and clinical plausibility, expert clinical opinion confirmed the [redacted] curve represents the most appropriate distribution to extrapolate PFS and therefore was selected for both treatment arms in the base-case analysis.

The [redacted] provides one of the lowest proportions of PomDex patients progression-free at 2 years ([redacted]%) however, feedback from clinical expert indicated that no patients receiving PomDex would be expected to be progression-free beyond 2 years. Accordingly, PFS was capped so that after 2-years, 0% of PomDex patients remain progression-free. In addition, PFS was capped by OS i.e., PFS modelled to not exceed OS.

Figure 37 shows the chosen base-case PFS distribution for both treatment arms alongside the KM curves from the respective data sources. A scenario was explored to test the impact of not applying the cap at 2-years and using the [redacted] curve to the end of the time horizon instead (see Section B.3.11.3).

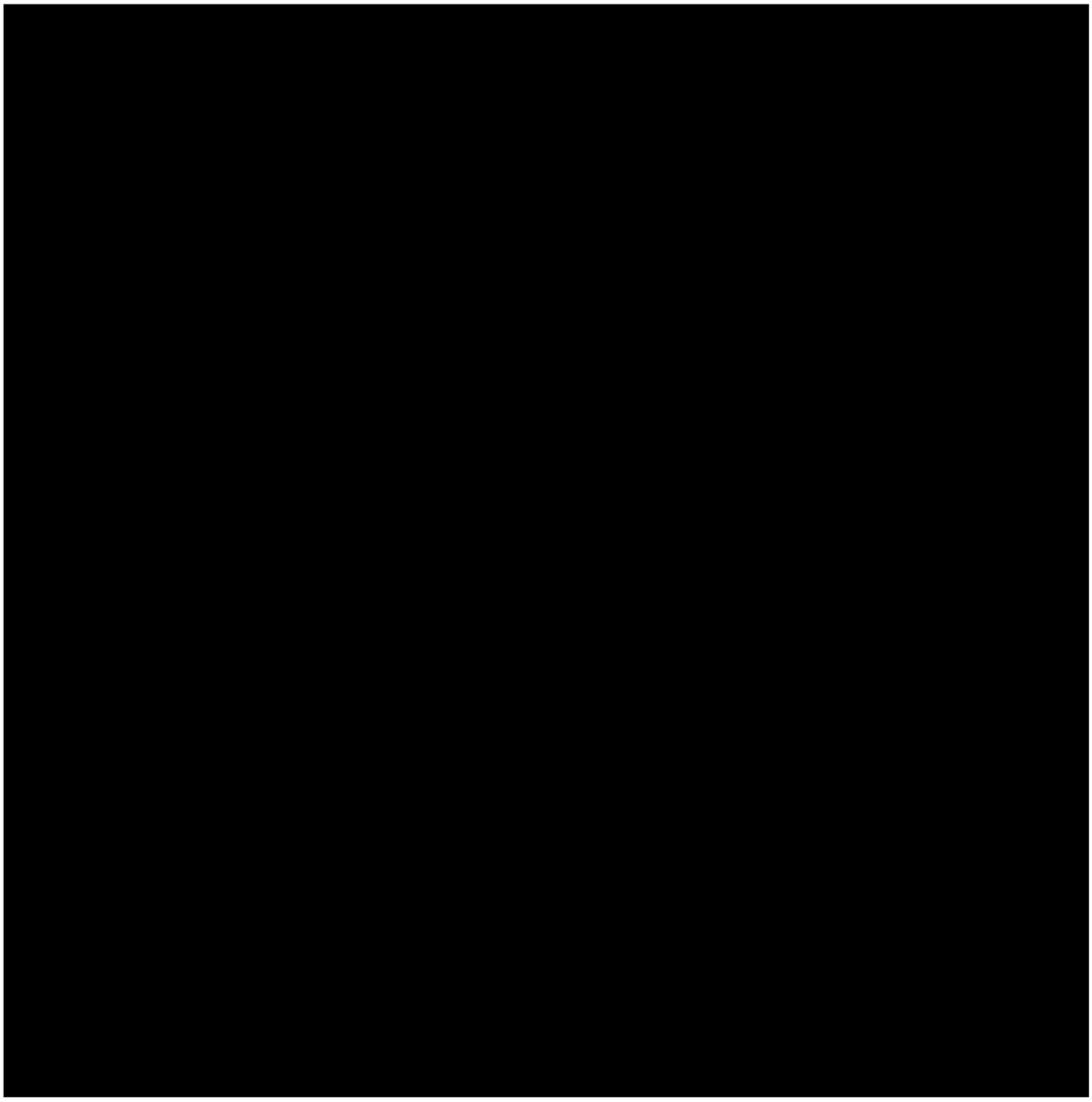
Figure 37. Belamaf and PomDex PFS KM and Weibull curve (base-case)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

B.3.3.3.2 Overall survival

The cumulative log-log plot, the Schoenfeld residual plot and the Cox-Snell plots for PFS are presented in Figure 38 (A-C), respectively.

Figure 38: OS diagnostic plots naïve comparison



(A) Top left: Cumulative log-log plot DREAMM-2/NCRAS, (B) Top right: Schoenfeld plot DREAMM2/NCRAS, (C) Bottom: Cox-Snell DREAMM-2/NCRAS

Initial inspection of the log cumulative hazard plot (Figure 38 (A)) suggests the PH assumption can be rejected as the lines cross. In contrast, the Schoenfeld residual plot (Figure 38 (B)) shows an approximate 0 slope with a p-value of 0.277 suggesting the PH assumption cannot be rejected. Similarly, the Cox-Snell plot Figure 38 (C) has a unit slope, signifying the PH assumption cannot be rejected. Based on the violation of the PH assumption in at least one of the diagnostic plots reported, independent parametric models were fitted to both treatment arms.

Belamaf overall survival

Similar to the PFS modelling, six parametric independent models were fitted to OS KM collected from DREAMM-2. The AIC/BIC goodness of fit for these six distributions are shown

in Table 50. Extrapolations up to 100 months are presented in Figure 39. To validate the clinical plausibility of the extrapolations presented, the predicted number of patients alive at 6-months, 1, 2, 5 and 10 years based on each parametric extrapolation were presented to UK clinical experts, to select the estimates that most closely align with their clinical observations. The corresponding landmark survival estimates are reported in Table 51.

Table 50. Base-case: AIC and BIC statistical goodness of fit data for OS from DREAMM-2 (independent models)

Goodness of fit statistics: Belamaf, OS		
Parametric survival model	**AIC**	**BIC**
Exponential	580.26	**582.83**
Weibull	580.78	585.93
Gompertz	580.61	585.76
Log-logistic	580.96	586.11
Lognormal	**579.15**	584.30
Generalised gamma	580.83	588.55

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; OS, overall survival
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 39. Belamaf OS extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Table 51. Base-case: Belamaf survival landmarks for OS

	Proportion of patients alive at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS; overall survival

According to the AIC and BIC, the lognormal and Exponential are the best statistically fitting curves for Belamaf OS (Table 50). The [redacted] has a steeper decline beyond the observed period (Figure 39) whereas the [redacted] has the largest tail over time, potentially under and overestimating the survival for Belamaf, respectively.

The landmark survival rates estimate a 5-year survival probability between [redacted]% ([redacted]) and [redacted]% ([redacted]). The [redacted] curve, which estimated a 5- and 1-year survival probability of [redacted]% and [redacted]% respectively, was considered to provide the most clinically plausible overall survival results for Belamaf according to clinical experts (Table 51).

PomDex overall survival

The same approach was adopted to extrapolate OS data from the PomDex arm of the NCRAS study. The AIC/BIC goodness of fit for these six distributions are shown in Table 52. Figure 40 show the extrapolations using each model up to 70-months and the landmark survival estimates up to 10-years are reported in Table 53.

Table 52. Base-case: AIC and BIC statistical goodness of fit data for OS from NCRAS (independent models)

Goodness of fit statistics: PomDex, OS		
Parametric survival model	**AIC**	**BIC**
Exponential	**180.6**	**182.8**
Weibull	182.3	186.6
Gompertz	Not reported	Not reported
Log-logistic	184.3	188.6
Lognormal	185.9	190.2
Generalised gamma	184.2	190.7

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; OS, overall survival
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 40. Base-case: PomDex OS extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; OS; overall survival

Table 53. Base-case: PomDex landmark OS rates

	Proportion of patients alive at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS; overall survival

According to the AIC and BIC, the Exponential distribution was the best statistically fitting model for PomDex OS (Table 52). Despite this, the tail in the [redacted] distribution appears to potentially overestimate OS compared to clinical expert expectations (Figure 40).

Landmark survival estimates at 2-years show a variation from [redacted]% to [redacted]%of patients are expected to be alive based on the distribution selected (Table 53). The conclusion from clinical opinion suggest that the Weibull distribution produced the most clinically plausible results with [redacted]% of patients expected to be alive at 2-years and [redacted]% alive at 5-years.

Overall survival conclusions

Considering the visual fit, statistical fit and expert clinical opinion, the [redacted] curve was chosen as the base-case distribution for both treatment arms. Figure 41 shows the chosen base-case OS distribution for both treatments where OS is capped by general mortality i.e., OS is modelled to not exceed general population survival.

Figure 41. Belamaf and PomDex OS KM and Weibull curves

Abbreviations: OS, overall survival

B.3.3.3.3 Time to treatment discontinuation

The cumulative log-log plot, the Schoenfeld residual plot and the Cox-Snell plots for PFS are presented in Figure 42 (A-C), respectively.

Figure 42: TTD diagnostic plots

(A) Top left: Cumulative log-log plot DREAMM-2/NCRAS, (B) Top right: Schoenfeld plot DREAMM2/NCRAS, (C) Bottom: Cox-Snell DREAMM-2/NCRAS

Initial inspection of the log cumulative hazard plot (Figure 42 (A)) suggests the PH assumption can be rejected as the lines cross. The Schoenfeld residual plot (Figure 42 (B)) shows an approximate 0 slope however the p-value of 0.0117 suggests the PH assumption can be rejected. Similarly, the Cox-Snell plot Figure 42 (C) has a unit slope, signifying the PH assumption cannot be rejected. Based on the violation of the PH assumption in at least one of the diagnostic plots reported, independent parametric models were fitted to both treatment arms.

Belamaf time to treatment discontinuation

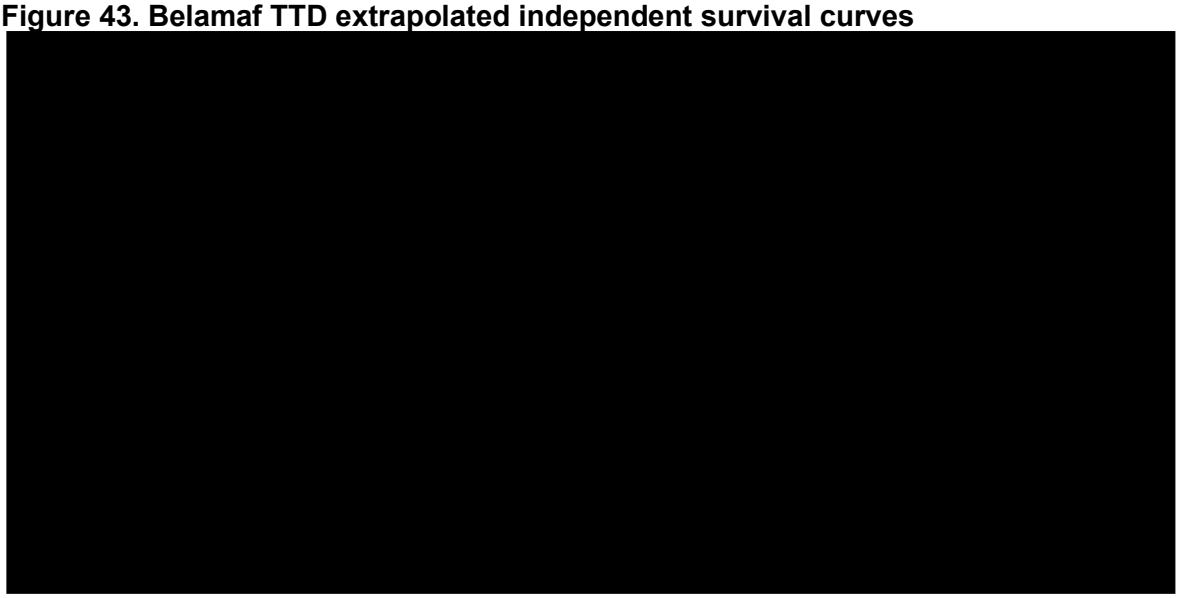
In line with the approach for PFS and OS, six parametric independent models were fitted to the TTD KM collected from DREAMM-2. The AIC/BIC goodness of fit for these six distributions are shown in Table 54. Figure 43 presents the TTD extrapolations from each models up to 30-months and Table 55 summarises the TTD landmark estimates from each of the distributions up to a 10-year timepoint.

Table 54. Base-case: AIC and BIC statistical goodness of fit data for TTD from DREAMM-2 (independent models)

Goodness of fit statistics: Belamaf, TTD		
Parametric survival model	**AIC**	**BIC**
Exponential	521.06	523.61
Weibull	520.18	525.29
Gompertz	514.72	519.83
Log-logistic	499.35	504.46
Lognormal	495.40	500.51
Generalised gamma	**487.83**	**495.49**

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; TTD, time to treatment discontinuation
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 43. Belamaf TTD extrapolated independent survival curves



Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

Table 55. Base-case: Belamaf landmark TTD rates

	Proportion of patients who discontinued at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Proportion of patients who discontinued at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD, time to treatment discontinuation

According to the AIC and BIC, the Generalised Gamma provides the best statistically fitting curve for Belamaf TTD (Table 54). Despite this, the tail appears to potentially overestimate TTD compared to the TTD KM curve. (Figure 43)

Landmark rates indicate that [redacted] patients remain on treatment at 5 and 10 years when the [redacted] distributions are chosen. This is consistent with the landmark rates of the Weibull distribution for PFS which suggests that [redacted]% are progression-free beyond 5-year.

PomDex time to treatment discontinuation

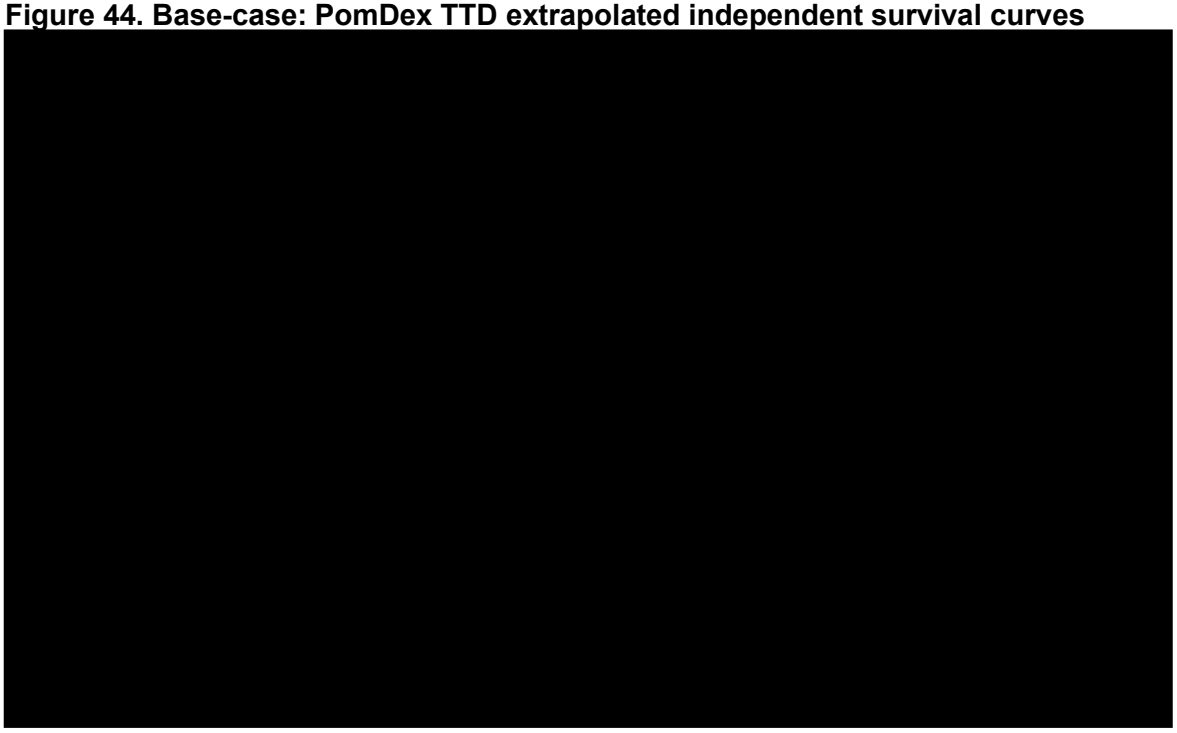
The six parametric independent models were similarly fitted to TTD KM collected from the NCRAS study for PomDex. The AIC/BIC goodness of fit for these six distributions are shown in Table 56. Figure 44 shows the TTD extrapolations from each model up 30-months and Table 57 summarises the TTD landmark estimates from each of the distributions.

Table 56. Base-case: AIC and BIC statistical goodness of fit data for TTD from NCRAS (independent models)

Goodness of fit statistics: PomDex, TTD		
Parametric survival model	**AIC**	**BIC**
Exponential	257.59	259.62
Weibull	**255.51**	**259.56**
Gompertz	256.26	260.31
Log-logistic	258.20	262.25
Lognormal	256.80	260.85
Generalised gamma	256.89	262.97

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; TTD, time to treatment discontinuation
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 44. Base-case: PomDex TTD extrapolated independent survival curves



Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

Table 57. Base-case: PomDex landmark TTD rates

	Proportion of patients progression-free at:				
Distribution	**6 months**	**1-year**	**2-year**s	**5-years**	**10-years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD, time to treatment discontinuation

According to the AIC and BIC, the Weibull distribution is best statistically fitting curve for PomDex TTD (Table 56). In addition, the [redacted] is one of the curves that provide the closest fit to the KM data up to the end of the observed period. (Figure 44). Landmark rates, as presented in Table 57, show that the [redacted] distribution estimates the lowest proportion of patients on treatment beyond 1 year and closest to the observed data.

Time to treatment discontinuation conclusions

Considering the visual fit, statistical fit and clinical plausibility expert clinical opinion confirmed the [redacted] curve as most appropriate to model both treatment arms and was chosen as the base-case. Figure 45 shows the chosen base-case TTD distribution for both treatments.

Figure 45. Belamaf and PomDex KM and Weibull TTD curves (base-case)

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

B.3.3.3.4 Survival modelling summary

The survival models used for all endpoints for both Belamaf and PomDex are summarised in Table 58. Alternative next best fitting curves were explored in a scenario analysis with the [redacted] curve selected for PFS and OS and the [redacted] for TTD (see Section B.3.11.3).

Table 58. Summary of survival models used in base-case and scenario analysis

Endpoint	Base-case (naïve comparison)		Scenario (naïve comparison)	
	Belamaf	PomDex	Belamaf	PomDex
TTD	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]	[redacted]

B.3.3.4 Safety

The incidence of treatment-emergent AEs of Grade 3 or 4 occurring in ≥5% of patients was considered for both treatment arms in the economic analysis to derive disutilities and costs associated with AEs, as described in the following section.

B.3.3.4.1 Belamaf

The DREAMM-2 safety data was used to inform the AEs associated with Belamaf in the economic model (see Section B.2.9 and Table 59).

B.3.3.4.2 PomDex

As no safety data were reported in the NCRAS study, AE incidence rates for PomDex reported in the phase 3 MM-010 trial were selected and included in the economic analysis and are presented in Table 59. MM-010 is the largest trial to date evaluating the safety and efficacy of PomDex (n=676, safety population). The median number of prior regimens (5 [range: 2-18]) and double refractory status (n=547, 80.2%) are broadly aligned with DREAMM-2 population. Thus, this trial was selected as the most accurate source of evidence for PomDex safety data in the absence of data specific to the 5L+ TCR MM population. Furthermore the dose in MM-010 is aligned with the dose modelled for PomDex (4 mg pomalidomide and 40 mg dexamethasone, daily).[94]

The AEs included within the base-case CEA for Belamaf and PomDex are presented in Table 59.

Table 59: Incidence of Grade ≥3 adverse events reported in ≥5% of patients in either the Belamaf arm from DREAMM-2 or PomDex arm from MM-010

Event	Belamaf (n = 95, safety population)	PomDex (n = 676, safety population)
	Number of patients (percent)	
Thrombocytopenia	[redacted]	163 (24)
Anaemia	[redacted]	223 (33)
Keratopathy	[redacted]	0 (0)
Pneumonia	[redacted]	87 (13)
Neutropenia	[redacted]	336 (50)
Lymphocyte count decreased	[redacted]	0 (0)
Platelet count decreased	[redacted]	0 (0)
Neutrophil count decreased	[redacted]	0 (0)
Hypercalcemia	[redacted]	0 (0)
Fatigue	[redacted]	40 (6)
Leukopenia	[redacted]	54 (8)
Source	DREAMM-2	MM-010[94]

The sum product of these incidence rates and disutilities or costs associated with AEs, described in Sections B.3.4.4 and B.3.5.3, respectively, was calculated to obtain the total AE disutility and total AE cost per treatment. Disutilities and unit costs associated with the AEs are assumed to be the same for both treatment arms, therefore the difference in terms of total AE disutility and AE cost is driven by the AE incidence rates. The total AE disutility was attributed to the first four weeks of the model and AE cost applied as a one-off episode cost, under the assumption that AEs were likely to occur very soon after treatment and only require acute care. This approach to modelling a one-off AE cost is consistent with the approach used in NICE TA658 in MM.

B.3.4 Measurement and valuation of health effects

The HRQoL of patients with 5L+ TCR MM is heavily impacted due to the late-stage of disease since outcomes diminish as patients relapse or become refractory and move to later treatment lines. HRQoL is expected to worsen over time such that overall prognosis in PF health states is better than PD.[95] Upon entering PD, patients receive subsequent treatment, monitoring and end of life care.

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

Since DREAMM-2 did not report EQ-5D data, EORTC-QLQ-C30 and EORTC-QLQ-MY20 instruments were mapped to the EQ-5D-3L instrument to generate the health state utility values used in the cost-effectiveness model and to align with the NICE Reference Case. The mapping algorithm is described in Section B.3.4.2.

B.3.4.2 Mapping

B.3.4.2.1 Mapping algorithm

The utility values of the model health states (PF on-tx, PF off-tx and PD) were based on statistical analyses of DREAMM-2 HRQoL data using Stata and R softwares. The analyses were conducted on the 13-month follow-up data (Section B.2.5.1.11) and considered data from patients with at least one complete set of EORTC measurements.

EORTC data collected in DREAMM-2 were converted into EQ-5D-3L utility scores using the mapping algorithm published by Proskorovsky et al. 2014.[96] This algorithm was originally developed by fitting a multiple linear regression model to HRQoL data of patients with MM who had participated in a multi-centre cohort study in the United Kingdom or Germany. This method was used in the NICE HTA submission for PomDex and the utility scores derived from mapped EQ-5D analysis were used in a scenario analysis (TA427).[66] Two equations were proposed by Proskorovsky et al. 2014; one using only the QLQ-C30 alone and a second using QLQ-C30 in combination with QLQ-MY20. Given the availability of both scores in DREAMM-2, the second equation was considered and is described in Equation 1.

Equation 1. Mapping Equation Based on EORTC-QLQ-C30 and QLQ-MY20 Scores

Mapped EQ-5D-3L utility score = 0.25763 + 0.00165 × Global Health Status/QoL Score + 0.00467 × Physical Functioning Score - 0.00293 × Pain Score + 0.00089197 × Insomnia Score + 0.00157 × Future Perspective Score

B.3.4.2.2 Descriptive analysis of missing data

Among the 97 patients of the DREAMM-2 trial randomised to receive the 2.5 mg/kg dose of Belamaf, 89 had at least one PRO assessment visit. At baseline, EORTC-QLQ-C30 assessments were available for 76 (85.4%) of these 89 patients. As 3 patients had incomplete EORTC-QLQ-MY20 assessments at baseline, a total of 73 (82%) of these assessments (with complete EORTC-QLQ-C30 and QLQ-MY20 records) could be converted successfully to EQ-5D-3L utility scores. The number and proportion of missing/non-missing

PRO assessments and EQ-5D-3L utility scores with/without baseline utility scores available for modelling are summarised in Table 60 at all scheduled visits and at the end of treatment (EOT) visit. Non-missing utility scores at baseline was summarised to understand the sample size available for inclusion in the regression models of utilities;covariate adjustment for baseline utilities was required to ensure unbiased estimates of mean utilities by health state. In addition, 7 patients had at least one unscheduled visit; some of them had multiple unscheduled visits (12 observations in total).

The number of PRO measurements at scheduled visits dropped rapidly during the study. [redacted] ([redacted]%) patients had utility observations at both baseline and Week 7. In addition, [redacted] ([redacted]%) patients had utility observations at both baseline and Week 13, and [redacted] ([redacted]%) at both baseline and Week 19. [redacted] ([redacted]%) patients had utility observations at both baseline and EOT visit. As the proportion of missing data increased rapidly over time, regression analyses were carried out using data recorded up to Week 7 or at the EOT visit. Furthermore, all analyses were carried out based on available data without any imputations for missing data.

Table 60. Summary of missing/non-missing data for Belamaf from DREAMM-2

Visit	Missing PRO assessment, N (%)	Non-Missing PRO assessment, N (%)	Non-missing EQ-5D-3L utility scores, N (%)	Non-missing EQ-5D-3L utility scores with baseline utility, N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]
Week 25	[redacted]	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]
Week 43	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EOT, end of treatment; EQ-5D-3L, EuroQol-5 dimensions-3 levels questionnaire; PRO, patient-reported outcome

B.3.4.2.3 Mixed-Effects Model

An analytical dataset was created including one record per patient per visit. Each record contained information on time-dependent variables regarding the patients' health at each visit. Health status indicators were derived based on time to progression (TTP) and time to response (TTR), both assessed by an independent review committee. Specifically, two variables were derived categorising patients' health status at each visit into three states as follows:

- Three States: Progression-free, not in response / Progression-free, in response / Progressed

In absence of the analysis performed based on an indicator for treatment discontinuation, response was considered as a proxy for determining the utility of patients on- and off-treatment. To test the uncertainty of this assumption a scenario analysis explores the impact of applying the PFS on-tx utility to both the PFS on-tx and PFS off-tx health states (i.e., assuming the same utility across progression-free health states; see Section B.3.11.3).

The EQ-5D-3L utility scores were analysed by fitting a mixed-effects linear model. A random intercept (random effect) for each patient was included in the model to account for the clustering of multiple observations for each patient. Since the effect of Belamaf on utilities manifests after the baseline visit only, the utility scores observed at baseline were excluded from the analyses. However, baseline utility scores were included as explanatory variables in the mixed-effect model to take into account the differences at the starting point of patients' utility trajectories. Specifically, these baseline utilities were centered to their mean value to improve the interpretation of regression coefficients in the fitted model. Centering makes the interpretation of the other model coefficients easier: a value of zero represents the "average" patient with a baseline utility equal to the average utility at baseline. Therefore, the intercept term of the model corresponds to the utility of the reference category for a patient in the DREAMM-2 study with "average" EQ-5D utility at baseline. The estimated regression coefficient for the centered baseline utility represents how deviations from the average utility at baseline affect utility at later visits.

Utility analyses including PF with no response, PF in response and PD health states showed that utility [redacted] by [redacted] (p-value[redacted]) compared with the PF with no response health state. However, the [redacted] in utility when patients achieve response was [redacted] ([redacted], p-value=[redacted]). This may be affected by the low sample size of only [redacted] patients ([redacted] observations) contributing to the estimation of this utility increment. Table 61 presents the fitted mixed-effect model. The mean utility values for patients with average baseline utility predicted by the three-state utility model are presented in Table 62. These mean utility values are used in the base-case with scenario analyses performed using utility values identified from the SLR (see details in Section B.3.4.3).

Table 61. Summary of three-state utility model on data from visits up to Week 7 and the EOT Visit

Covariate	Nr. of Patients	Nr. of Obs.	Coef.	P-value	95% LCI	95% UCI
Progression-free, response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline utility (centered)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, no response (Ref.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LCI = lower limit of confidence interval; Nr = number; Obs = observations; UCI = upper limit of confidence interval.

Table 62. Utility estimates by health state in the economic model

Health state	Mean utility	SE	95% LCI	95% UCI

Progression-free, no response (proxy for progression-free off-tx)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, response (proxy for progression-free on-tx)	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LCI = lower limit of confidence interval; SE = standard error; UCI = upper limit of confidence interval.

B.3.4.3 Health-related quality of life studies

The economic SLR introduced in Section B.3.1 also aimed to identify relevant HRQoL studies from the published literature.

Full details of the SLR strategy, study selection process and results are presented in Appendix H. Overall, 22 publications reporting HRQoL studies in 4L+ RRMM were included. One US cost-effectiveness study reported utilities from DREAMM-2 for progression-free and progressed disease health states which are aligned with those reported in Table 63.[97] NICE TA427[66] and NICE TA658[93] reported PomDex treatment-specific utilities and were tested in a scenario analysis.

The remaining studies identified were not deemed appropriate to inform the cost-effectiveness model as they were either based on interventions not relevant for the decision problem or were baseline utilities rather than health state specific.

Table 63 provides a summary of the utility results from DREAMM-2 and prior NICE TAs identified via the SLR used to inform the base-case or scenario analyses. There are inevitable differences amongst the utilities from DREAMM-2 and the utilities used in prior technology appraisals.[30,66,93] These may be due to differences in trial designs, trial populations, the availability of EQ-5D observations, mapping algorithms, and different modelling approaches for utilities. To test the model sensitivity to utility data, alternative values reported in prior TAs for PomDex were tested in scenario analyses applying treatment-specific utilities (see Section B.3.11.3).

Table 63. Comparison of utilities used in prior technical appraisals

Appraisal	Current	TA427[66]	TA658[93]	TA510 / TA783[30]
Data Source	DREAMM-2	MM-003	ICARIA-MM	MM-003 + EAP
Treatment	Belamaf	PomDex	IsaPomDex and PomDex	Dara
Utility model	Alternative Model (3-state)	Base-case	Base-case	Base-case
Progressed	[redacted]	0.62	0.649 (on treatment) 0.553 (off-treatment)	0.57
Progression-free	NA	NA	NA	0.65 (active) and 0.61 (for comp)

Appraisal	Current	TA427[66]	TA658[93]	TA510 / TA783[30]
Progression-free, on treatment	[redacted]	0.76	0.731 (on IsaPomDex treatment) 0.717 (on PomDex treatment)	NA
Progression-free, off treatment	[redacted]	0.66	0.473 (off IsaPomDex treatment) 0.621 (off PomDex treatment)	NA
Comments	Utility increase in the response was not significant.	Utilities above are without AEs and hospitalisations for which disutilities were calculated separately.	Utility decrease off-treatment was significant and utilities varied per treatment arm.	Utilities from MM-003 were too low for Dara because it is better tolerated.

Abbreviations: AE, adverse event; EAP, Early Access Programme; GEE, generalised estimating equation; MM, multiple myeloma; NA, not applicable; TA, technology appraisal.

B.3.4.4 Adverse reactions

The rates of AEs for patients on Belamaf and PomDex in the model are detailed in Section B.3.3.4.

A published analysis of PomDex safety data from MM-010 showed the most common Grade 3 or 4 AEs occurred within the first few cycles of treatment based on a median time to onset of less than 4 weeks.[94] Accordingly, AE disutilities were applied to the first four weeks of treatment for patients entering the model for both treatment arms.

The disutility associated with treatment-emergent AEs were sourced from NICE TA510 and published literature and are presented in Table 64.[30] In the absence of disutility values specific for keratopathy clinical experts were consulted and advised that severe dry eyes would be an appropriate proxy to estimate HRQoL impairment associated with keratopathy. The disutility for severe dry eye was extracted from NICE TA369 for treating dry eye disease and is also reported in Table 64.[98] Lymphocyte, platelet and neutrophil count decrease are generally asymptomatic and therefore were assumed to have no disutility.

These were then applied via a sum product to the proportion of patients experiencing each event (Table 59) and applied to the first four cycles in the PF on-tx health state.

Table 64. Adverse event disutilities

Adverse event	Disutility (mean)	Disutility (95% confidence interval)	Source
Thrombocytopenia	0.31	0.20, 0.44	TA510[30]
Anaemia	0.31	0.20, 0.44	TA510[30]

Keratopathy	0.16	NR	TA369[98]
Pneumonia	0.19	0.12, 0.27	TA510[30]
Lymphocyte count decreased	0.00	0	Assumption; lymphocyte, platelet and neutrophil count decrease is generally asymptomatic and so does not attribute a disutility
Platelet count decreased	0.00	0	
Neutrophil count decreased	0.00	0	
Hypercalcemia	0.52	0.48, 0.56	Milne et al. 2006[99]
Fatigue	0.12	0.07, 0.16	TA510[30]
Leukopenia	0.07	0.04, 0.09	TA510[30]

Abbreviations: NR, not reported

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

The utility estimates used in the base-case analysis were sourced from the DREAMM-2 trial and therefore provide a robust estimate of the health state utilities for a population of 5L+ TCR MM, aligned with the decision problem. A scenario analysis explores the impact of applying the PFS on-tx utility to both the PFS on-tx and PFS off-tx health states (i.e., assuming the same utility across progression-free health states). Further scenario analyses tested treatment-specific utilities where DREAMM-2 utilities were applied to the Belamaf arm and PomDex utilities were sourced from previous TAs in MM (see Section B.3.11.3). Table 65 summarises the utility values used in both the base-case and scenario analyses.

Disutilities for AEs were sourced from the literature and previous appraisals (see Table 64). A scenario analysis explores the impact of excluding AE disutilities (see Section B.3.11.3).

As described in Section B.3.5.2.1, all patients require frequent monitoring, including physician visits, complete blood counts and biochemistry. This monitoring coincides with when Belamaf would be administered via a short 30-minute infusion and on this basis clinical experts do not expect hospital visits and administration to negatively impact HRQoL. Thus, no IV disutility is applied for Belamaf in the model.

Age-related utility decrements were applied in the model to incorporate the natural decline in HRQoL associated with increasing age and to ensure the utility of 5L+ TCR MM patients does not exceed that of the general population. This was implemented in the model using the regression equation published by Ara and Brazier et al. 2010.[100] The impact of removing this age-adjustment was explored as a scenario analysis (see Section B.3.11.3).

Table 65. Summary of utility values for cost-effectiveness analysis

Health state	Health state utility value		Reference in submission (section and page number)	Justification
	Mean	95% confidence interval		
Base-case: DREAMM-2 13-month data cut				
PF: on treatment	[redacted]	[redacted]	Section B.3.4.2.3 Page 114	This data was collected in the DREAMM-2 trial and is the most relevant HRQoL data for the population
PF: off-treatment	[redacted]	[redacted]		
PD	[redacted]	[redacted]		
Scenario 1: Same utility across progression-free health states				
PF: on and off-treatment	[redacted]	[redacted]	Section B.3.4.2.3 Page 114	To test assumption of response considered as a proxy for determining the utility of patients on- and off-treatment.
PD	[redacted]	[redacted]		
Scenario 2: TA427				
Belamaf PF: on treatment	[redacted]	[redacted]	Section B.3.4.2.3 Page 114	This data was collected in the DREAMM-2 trial and is the most relevant HRQoL data for Belamaf
Belamaf PF: off-treatment	[redacted]	[redacted]		
Belamaf PD	[redacted]	[redacted]		
PomDex PF: on treatment	0.750	Not reported	Section B.3.4.3 Page 116	Used in TA427[66]
PomDex PF: off-treatment	0.650	Not reported		
PomDex PD	0.610	Not reported		
Scenario 3: TA658				
Belamaf PF: on treatment	[redacted]	[redacted]	Section B.3.4.2.3 Page 114	This data was collected in the DREAMM-2 trial and is the most relevant HRQoL data for Belamaf
Belamaf PF: off-treatment	[redacted]	[redacted]		
Belamaf PD	[redacted]	[redacted]		
PomDex PF: on treatment	0.717	0.677, 0.758	Section B.3.4.3Page 116	Used in TA658[93]
PomDex PF: off-treatment	0.621	0.527, 0.714		
PomDex PD	0.649	0.591, 0.707		

Table 65. Summary of utility values for cost-effectiveness analysis

Health state	Health state utility value		Reference in submission (section and page number)	Justification
	Mean	95% confidence interval		
Adverse event disutilities				
Thrombocytopenia	0.31	0.20, 0.44	Section B.3.4.4 Page 117	Used in TA510[30]
Anaemia	0.31	0.20, 0.44		
Keratopathy	0.16	Not reported		Disutility for severe dry eyes [98] used as a proxy for keratopathy based on expert clinical opinion.
Pneumonia	0.19	0.12, 0.27		Used in TA510[30]
Lymphocyte count decreased	0.00	0		Assumption; lymphocyte, platelet and neutrophil count decrease is generally asymptomatic and so does not attribute a disutility
Platelet count decreased	0.00	0		
Neutrophil count decreased	0.00	0		
Hypercalcemia	0.52	0.48, 0.56		Used in Milne et al. 2006[99]
Fatigue	0.12	0.07, 0.16		Used in TA510[30]
Leukopenia	0.07	0.04, 0.09		

Abbreviations: PD – Progressed disease; PF – progression-free

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

The economic analysis was conducted from an NHS and personal social services (PSS) perspective and therefore only included costs that would be incurred by the NHS and PSS. Appropriate sources of unit costs, such as NHS reference costs 2020/21,[101] the British National Formulary (BNF),[102] and Personal Social Services Research Unit (PSSRU)[103] 2021 costs were used to inform the cost inputs in the model. In the absence of any additional sources of evidence, assumptions were made where necessary for specific cost/resource inputs included in the model and validated through discussions with UK clinical experts.

The economic SLR described in Section B.3.1 and Appendix G also identified relevant cost and resource use studies from the published literature.

Full details of the SLR strategy, study selection process and results are presented in Appendix I. The SLR identified 19 publications related to cost and resource use studies in 4L+ RRMM. Three of the studies were NICE TA submissions, cost and resource use estimates were used from these submissions where appropriate with more recent costs sourced from the UK cost databases described above where possible.[30,92,93] One study was an SMC submission in RRMM however granular costs were not reported and therefore not used in the cost-effectiveness model.[104] None of the remaining studies were used to inform inputs in the cost-effectiveness model as they were either based on countries other than the UK or costs were not provided in Great British Pounds (GBP).

B.3.5.1 Intervention and comparators' costs and resource use

For each regimen included in the cost-effectiveness model, drug costs were estimated using drug costs per pack and administration schedules. Drug acquisition costs for Belamaf and PomDex were sourced from the BNF[105–108] Dosing regimens for each therapy were sourced from the Summary of Product Characteristics (SmPC).[,33]

B.3.5.1.1 Drug acquisition costs

Intervention: Belamaf

Belamaf is available as a 100 mg powder for concentration solution at a list price of £5,707.83.[108] A confidential simple Patient Access Scheme (PAS) discount of [redacted]% has been proposed to NHS England/Patient Access Schemes Liaison Unit (PASLU). At a list price of £5,707.83 for 1 vial of 100 mg powder for concentration solution, this results in a PAS price of £[redacted]. The recommended dose is 2.5 mg/kg administered as an intravenous infusion once every three weeks. Mean patient weight (Section B.3.3.1) from DREAMM-2 was used to calculate the dose of Belamaf. In addition, dose reductions and dose delays were modelled via the relative dose intensity (RDI) from DREAMM-2 to reflect the true dose patients have received in the trial (see Appendix P for RDI calculations).[76] No wastage was modelled assuming vial sharing can take place in clinical practice. A scenario analysis explored an alternative assumption of 50% wastage (see Section B.3.11.3). The duration of treatment with Belamaf was modelled using TTD from DREAMM-2 as described in Section B.3.3.3.

Table 66 reports the drug acquisition cost of Belamaf applied every three weeks in the model until treatment discontinuation and assuming no wastage; including unit cost, dose, mean patient weight, RDI and drug acquisition cost every three weeks.

Table 66. Belamaf drug acquisition cost

Treatment	Vial size	Cost per unit	Required dosage	Mean patient weight	Relative dose intensity	Drug acquisition cost every three weeks	Source
Belamaf	100 mg	£5,707.83 (list price) £[redacted] (PAS price)	2.5 mg/kg every three weeks	[redacted]kg	[redacted]	£6,568.93 (list price) £[redacted] (PAS price)	R: DREAMM-2[76] D: DREAMM-2[15,36] C: BNF[12] P: Data on File

Abbreviations: C, costs; D, dose; kg, kilogram; mg, milligram; P, PAS; PAS, patient access scheme; R, relative dose intensity.

Comparator: PomDex

Pomalidomide is available as 4 mg tablets and the list price per 21-day supply is £8,884.00 (note that the simple PAS discount is in place for PomDex is confidential hence, the list price is considered in the analyses).[105] The recommended dose of pomalidomide is 4 mg orally administered once daily for three weeks followed by a week break every four week cycle. Dexamethasone is available as 20 mg tablets and the list price per 10-day supply is £20.00.[106] The recommended dose of dexamethasone is 40 mg orally administered once a week.[110] This is consistent with the observed dose of PomDex in the NCRAS study.

The NCRAS study does not provide details on the doses received by each patients in the PomDex cohort. The median pomalidomide dose reported in the overall 5L+ TCR cohort was [redacted] (interquartile range [redacted] mg at 5th line and [redacted] mg for line 6-8), which is in line with the recommended posology in the SmPC.[110] However, a number of administrations has no dose values reported and therefore there is some uncertainty associated with the pomalidomide RDI from NCRAS. In addition, dexamethasone use is not systematically reported which may also contribute to the uncertainty.[60] Therefore, the MM-010 trial was selected as the next best source of evidence to inform the RDI for PomDex.[94] Drug wastage was not applicable since the recommended dose aligns with the tablet sizes available. The duration of treatment with PomDex was modelled using TTD from NCRAS as described in Section B.3.3.3.

Table 67 reports the drug acquisition cost of pomalidomide applied weekly for three weeks followed by a week break every four-week cycle and dexamethasone applied weekly; including unit cost, dose, RDI and drug acquisition cost per week.

Table 67. PomDex drug acquisition cost

Regimen	Drug	Cost per unit	Required dose	Relative dose intensity	Weekly drug acquisition cost	Source
PomDex	Pomalidomide	£423.05 /4mg	4 mg daily	90.1%	£2,668.16 (3 weeks on, 1 week break)	R: MM-010 C: BNF[105] D: SmPc[110]
	Dexamethasone	£2.00 /20mg	40 mg weekly	90.1%	£3.60 (weekly)	R: MM-010 C: BNF[106] D: SmPc[110]

Abbreviations: C, cost; D, dose; mg, milligram; NA, not applicable; PomDex, pomalidomide and dexamethasone; R, relative dose intensity.

B.3.5.1.2 Administration costs

Belamaf and PomDex are administered via a short 30-minute IV infusion and oral administration, respectively. No administration costs were assumed for PomDex as an orally administered treatment. The unit costs of IV infusion administration were sourced from the 2020/21 NHS reference costs and are provided in Table 68.[101] These IV infusion administration unit costs were applied to Belamaf treatment once every three weeks until treatment discontinuation, aligned with the application of the drug acquisition cost according to the treatment schedule and is reported in Table 69. The cost of first IV administration was £361.53 followed by £237.21 for subsequent IV administrations.

Table 68. Administration unit costs

Administration type	Cost (£)	Source
Admin cost, first infusion (£)	361.53	SB12Z - Deliver Simple Parentral Chemotherapy at First Attendance. NHS Reference cost 2020-21[101]
Admin cost, subsequent infusions (£)	237.21	SB97Z, Regular same day chemotherapy admission. NHS Reference cost 2020-21[101]

Table 69. Belamaf and PomDex administration costs

Treatment	Week	Administration cost (£)
Belamaf	Week 1	361.53
	Week 4+ (applied once every 3 weeks until treatment discontinuation)	237.21
PomDex	Weekly until treatment discontinuation	0.00

Abbreviations: mg, milligram; PomDex, pomalidomide and dexamethasone.

B.3.5.2 Health state unit costs and resource use

B.3.5.2.1 Routine monitoring unit costs and resource use

The approach to health state costs was based on NICE TA510.[30] It was assumed that patients receiving RRMM treatments require frequent monitoring, including physician visits, complete blood counts and biochemistry. It is assumed that all treatment arms would require the same resource use. Routine monitoring resources per weekly cycle for each health state included in the model are presented in Table 70.

Table 70. Routine monitoring resource use

Resource	Health state	Resource use (per weekly cycle)
Physician visit	PFS on-tx	0.23
	PFS off-tx	0.08
	PD	0.08
Complete blood count test	PFS on-tx	0.21
	PFS off-tx	0.21
	PD	0.39
Blood chemistry	PFS on-tx	0.19
	PFS off-tx	0.19
	PD	0.33

Source: NICE TA510[30]
Abbreviations: NICE, National Institute for Health and Care Excellence; PD, progressed disease; PFS, progression-free survival; tx, treatment

The unit costs of monitoring resources as shown in Table 71 were identified from NICE TA510[30] and subsequently sourced from the 2020/21 NHS reference costs.[101] The monitoring cost for each treatment was calculated as the sum product of the monitoring resources required per week and unit cost of monitoring resources and applied to all patients in the corresponding health states across the model time horizon.

Table 71. Routine monitoring unit costs

Resource	Unit cost (£)	Reference	Source
Physician visit	193.24	2020/21 NHS reference costs (Services code 303: Clinical Haematology)[101]	Via NICE TA510[30]
Complete blood count test	3.63	2020/21 NHS reference costs (DAPS05: Haematology) [101]	
Blood chemistry	1.85	2020/21 NHS reference costs (DAPS04: Clinical biochemistry) [101]	

Abbreviations: NICE, National Institute for Health and Care Excellence

B.3.5.3 Adverse reaction unit costs and resource use

Only Grade ≥3 AEs were expected to have an impact on the treatment costs and resource use of patients. Grade ≥3 AEs occurring in ≥5% of patients in the 2.5 mg/kg arm of DREAMM-2 for Belamaf or MM-010 for PomDex are included in the model as presented in Table 59.

The unit cost of a keratopathy AE episode was determined from eye care professional feedback and is calculated based on the unit cost and resource use of an ophthalmologist visit and a pack of 10ml preservative free artificial tear eye drops for treating artificial tears.

Patients with mild/moderate keratopathy are assumed to visit an ophthalmologist (including an ophthalmic examination with a visual acuity and slit lamp examination) every 3 weeks during an event. In contrast, patients with more severe keratopathy are expected to visit an ophthalmologist every week until resolution of the event (assumed to take up to 5 weeks). Furthermore, those with mild/moderate keratopathy are assumed to need 1 pack of 10 ml eye drops (4 drops [0.05 ml] per eye per day) whereas patients with severe keratopathy are assumed to need 5 packs of 10 ml eye drops (1 drop [0.05 ml] in each eye every two hours during the event).

As shown in Table 72, the unit cost of keratopathy is then calculated based on the average of the total cost per year for patients with mild, moderate, and severe keratopathy.

Unit costs for all other AEs were sourced from the 2020/21 NHS Reference Costs and are presented in Table 73.[101] Lymphocyte, platelet and neutrophil count decrease are generally asymptomatic and therefore were assumed to not attribute a cost.

Unit costs were then applied via a sum product to the AE incidence rates to evaluate the total costs associated with AEs by treatment and incorporated as a one-off episode cost when patients enter the model under the assumption that AEs are likely to occur very soon after treatment initiation and only require acute care.

Table 72. Adverse event cost of keratopathy

Resource use	Unit cost (£)	Source	Frequency per patient (Quantitative - Per episode)		
			Mild	Moderate	Severe
Ophthalmologist outpatient attendance	168.24	2020/21 NHS reference costs (Service code 130) [101]	[redacted]	[redacted]	[redacted]
Artificial tears 10 ml pack (Hypromellose eye drops, preservative free)	1.98	BNF[111]	[redacted]	[redacted]	[redacted]
Total (£)			170.22	170.22	851.10
Average cost (£)			397.18		

Source: GSK Data on File

Table 73. Unit costs of treating AEs

Grade ≥3 AE	Cost (£)	Source
Thrombocytopenia	1,069.63	NHS reference cost 2020/21 (SA12G-SA12K) [101]
Anaemia	1,030.40	NHS reference cost 2020/21 (SA04G-SA04L) [101]
Keratopathy	397.18	GSK Data on file
Pneumonia	2,651.59	NHS reference cost 2020/21 (DZ11K-DZ11V) [101]
Neutropenia	1,568.24	NHS reference cost 2020/21 (SA08G, SA08H, SA08J) [101]
Lymphocyte count decreased	0.00	Assumption; lymphocyte count decrease is generally asymptomatic and so does not attribute cost
Platelet count decreased	0.00	Assumption; platelet count decrease is generally asymptomatic and so does not attribute cost
Neutrophil count decreased	0.00	Assumption; neutrophil count decrease is generally asymptomatic and so does not attribute cost
Hypercalcemia	1,802.71	NHS reference cost 2020/21 (KC05G-KC05N) [101]
Fatigue	2,116.59	NHS reference cost 2020/21 (SA01G-SA01K) [101]
Leukopenia	1,568.24	NHS reference cost 2020/21 (SA08G, SA08H, SA08J) [101]

Abbreviations: AE, adverse event; BNF, British National Formulary; NICE, National Institute for Health and Care Excellence; NHS, National Health Service.

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 the approach taken in TA427. [66] In TA427, a one-off cost to account for the costs of the last eight weeks prior to death based on the Kings Fund's estimate of £5,363 (2007 cost year) was applied.[112] This is based on retrospective data of 40 cancer patients in the UK. This cost was uplifted using the inflation indices from PSSRU 2021[103] to give an end of life care cost of £6,834. This cost is applied in the model as a one-off cost when a patient enters the death health state.

B.3.5.4.2 Concomitant therapies and supportive care

The approach to concomitant therapies and supportive care was aligned to the approach used in the economic model of NICE TA510 and TA783.[30] Whilst patients are on treatment, a proportion of patients on Belamaf and PomDex require granulocyte stimulating factor (GCSF), red blood cell and platelet transfusions. The unit costs for these concomitant

therapies and supportive care resources are presented in Table 74 and were sourced from NICE TA510 uplifted using the inflation indices from PSSRU 2021.[103]

The resource use estimates for GCSF, red blood cell and platelet transfusions are also presented in Table 74. The proportion of patients receiving transfusions and GCSF treatments for Belamaf and PomDex were based on expert clinical opinion and the MM-010 trial, respectively. As described in Section B.3.3.4 MM-010 was considered the most appropriate data source for PomDex in absence of NCRAS data and aligns with the source used to inform PomDex AEs and RDI.

The unit costs were multiplied by the resource use for these concomitant therapies and supportive care to derive a one-off cost for Belamaf and PomDex which was applied in the model to each respective treatment upon patients' entry in the model.

Table 74. Supportive care costs

Treatment	Resource	% patients receiving	Number per patient per treatment course	Unit cost (£)	One-off cost applied (3)	Source
Belamaf	GCSF	[redacted]	[redacted]	58.68	151.63	Expert clinical opinion TA510[30] uplifted via PSSRU 2021[103]
	RBC transfusion	[redacted]	[redacted]	135.68		
	Platelet transfusion	[redacted]	[redacted]	219.32		
PomDex	GCSF	43%	1.00	58.68	434.80	MM-010 TA510[30] uplifted via PSSRU 2021[103]
	RBC transfusion	49%	3.00	135.68		
	Platelet transfusion	20%	4.79	219.32		

Abbreviations: GCSF, granulocyte stimulating factor; NICE, National Institute for Health and Care Excellence.

Moreover, a proportion of patients on PomDex are assumed to receive acetylsalicylic acid and anti-coagulation therapy while on treatment. The unit costs, resource use and total costs for these concomitant therapies are given in Table 75 and were applied every cycle when patients received PomDex.

Table 75. PomDex concomitant therapies

Resource	Cost per pack (£)	Unit size (mg)	Units per pack	Administration per weekly cycle	Proportion of patients on concomitant treatment (%)	Total costs per cycle (£)	Source
Acetylsalicylic acid	0.86	75.00	28.00	7	33%	0.22	C: BNF[113] D: SmPC[114] P: Clinical opinion
Anti-coagulation therapy (enoxaparin)	30.27	40.00	1.00	7	67%	211.89	C: BNF[113] D:SmPC[115] P:Clinical opinion
Total costs (£)						141.33	

Abbreviations: BNF, British National Formulary; C, Cost; D, Dose; P; Proportion of patients; SmPC, Summary of Product Characteristics

As described in Section B.1.2 and aligned with the SmPC for Belamaf,[1] patients receiving Belamaf are assumed to attend ophthalmology appointments (including an ophthalmic examination with visual acuity and slit lamp examination) and administer artificial tears.[1] The unit costs, resource use and total cost for these concomitant therapies applied in the first year and subsequent years while receiving Belamaf treatment are provided in Table 76.

Table 76. Belamaf concomitant therapies

Resource	Unit cost (£)	Source	Administration	Frequency per year	Proportion of patients on concomitant medication
Ophthalmologist outpatient attendance	168.24	2020/21 NHS reference costs (Service code 130)[101]	Every 3 weeks until the fourth cycle, then one per year	[redacted]	100%
Artificial tears 10 ml pack (Hypromellose eye drops, preservative free)	1.98	BNF[118]	4 eye drops per day for the duration of therapy	[redacted]	100%
			Total cost first year (£)		702.66
			Total cost subsequent years (£)		197.94

B.3.5.4.3 Subsequent treatments

The base-case economic analysis included the costs of subsequent therapies that might be received by patients upon progression from treatment with Belamaf or PomDex. Average time on subsequent treatment was sourced from Gandhi et al. 2019[29] and was assumed to be the same for all treatment regimens. The acquisition costs and dosing for each subsequent treatment regimen were sourced from the BNF and corresponding SmPC, respectively.

Data from DREAMM-2 and NCRAS reported that [redacted]% and [redacted]% of patients who progressed on Belamaf and PomDex went on to receive subsequent treatments, respectively.[60] The weighted cost associated with subsequent treatments was calculated by multiplying the cost per treatment by the treatment duration and applied as a one-off cost upon disease progression.

Subsequent treatments after Belamaf

The subsequent treatments mix and dose for patients on Belamaf at 5L are based on the data from DREAMM-2. The following regimens were received upon disease progression: chemotherapy, steroids, carfilzomib, bortezomib, pomalidomide, lenalidomide, thalidomide, Dara, elotuzumab and other.

To align with UK clinical practice, treatments not commissioned in the UK (carfilzomib and elotuzumab) were excluded from the analysis. Moreover, to reflect the recommendation of Dara monotherapy at 4L it was removed from the subsequent treatments list. The remaining treatments were re-weighted to sum up to 100% (Table 77).

Table 77. Subsequent treatment resource use following Belamaf treatment

Subsequent regimen	Proportion of Belamaf patients switching, re-weighted (%)
Chemotherapy	[redacted]
Steroids	[redacted]
Bortezomib (IV)	[redacted]
Pomalidomide	[redacted]
Lenalidomide	[redacted]
Thalidomide (oral)	[redacted]
Other	[redacted]

To model subsequent treatments in DREAMM-2 classified as ‘Chemotherapy’, ‘Steroid’ and ‘Other’ the approach adopted in the scenario analysis based on UK expert clinical opinion was taken (described below). On this basis, it was assumed that chemotherapy, steroids and other would be costed assuming patients receive:

- 25%: melphalan + prednisolone
- 25%: thalidomide + dexamethasone
- 25%: dexamethasone monotherapy

- 25%: cyclophosphamide and dexamethasone

The resulting total acquisition and administration costs per patient per regimen per duration are detailed in Table 78 and Table 79. A summary of the subsequent treatment costs applied as a one-off cost upon disease progression is presented in Table 81.

Table 78. DREAMM-2 chemotherapy, steroids and other unit costs

Regimen	Drug	Cost per pack (£)*	Unit size in pack (mg)	Units per pack	Dose (mg)	Administration	Treatment duration (weeks)[29]	Acquisition cost per treatment duration (£)	Administration cost per treatment duration (£)
Melphalan + prednisolone	Melphalan	26.64	50	1	7	4 days of 28-day cycle	13.47	50.24	6,395.15
	Prednisolone	29.12	30	28	60	4 days of 28-day cycle	13.47	28.02	0.00
Thalidomide + dexamethasone	Thalidomide	298.48	50	28	50	Daily	13.47	1,005.13	0.00
	Dexamethasone	20	20	10	40	Once a week (28-day cycle)	13.47	53.88	0.00
Dexamethasone monotherapy	Dexamethasone	20	20	10	40	Once a week (28-day cycle)	13.47	53.88	0.00
Cyclophosphamide + dexamethasone	Cyclophosphamide	8.21	500	1	500	Once a week (28-day cycle)	13.47	110.59	6,395.15
	Dexamethasone	20	20	10	40	Once a week (28-day cycle)	13.47	53.88	0.00
Chemotherapy, steroids and other total costs		£3,536.48							

*All costs taken from BNF entries for each drug

Table 79. Subsequent treatment unit costs for Belamaf

Subsequent drug or regimen	Cost per pack (£)	Source	Unit size in pack (mg)	Units per pack	Dose (mg)	Cost per dose (£)	Treatment duration (weeks)	Admin schedule	Acquisition cost per treatment duration (£)	Administration cost per treatment duration (£)
Chemotherapy	See Table 78								£3,536.48	
Other										
Steroids										
Bortezomib (IV)	217.82	BNF[116]	1	1	1.87	407.32	13.47	Twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment	£7,315.53	£8,508.24
Pomalidomide	8884.00	BNF[117]	4	21	4	423.05	13.47	Daily on days 1-21 of 28-day cycles	£29,916.87	£0.00
Lenalidomide	3712.80	BNF[118]	21	25	25	176.80	13.47	Daily on days 1-21 of 28-day cycles	£12,502.85	£0.00
Thalidomide	298.48	BNF[119]	50	28	200	42.64	13.47	Dosed once daily on Days 1 to 42 of each 42-day cycle	£4,020.53	£0.00

Abbreviations: BNF, British National Formulary; IV, intravenous; mg, milligram

Subsequent treatments after PomDex

In the base-case, the proportion and dosage of subsequent treatments at 6L for patients who received PomDex at 5L were based on the NCRAS study. The following subsequent regimens were reported: bortezomib with panobinostat, cyclophosphamide (with or without thalidomide), melphalan (with or without thalidomide), bendamustine (with or without thalidomide), pomalidomide (with or without cyclophosphamide) and bortezomib (with or without cyclophosphamide).

To align with UK clinical practice, treatments not commissioned in the UK (bendamustine, bendamustine + thalidomide), were excluded from the analysis and the remaining treatments re-weighted to 100% (Table 80).

The resulting total acquisition and administration costs per patient per regimen per duration are detailed in Table 82. A summary of the subsequent treatment costs applied as a one-off cost upon disease progression is presented in Table 81.

Table 80. Subsequent treatment resource use following PomDex treatment

Regimen	6L – Following PomDex treatment
Bortezomib Panobinostat	[redacted]
Melphalan Thalidomide	[redacted]
Cyclophosphamide	[redacted]
Melphalan	[redacted]
Bortezomib	[redacted]

Source: NCRAS[60]
Abbreviations: NCRAS, National Cancer Registration and Analysis Service; PomDex, Pomalidomide and dexamethasone.

Table 81. Summary of one-off subsequent treatment costs for Belamaf and PomDex

Index treatment	Subsequent treatments received	Subsequent treatment one-off cost (£)
Belamaf	[redacted]%	[redacted]
PomDex	[redacted]%	[redacted]

Abbreviations: PomDex, Pomalidomide and dexamethasone

Table 82. Subsequent treatment costs unit costs for PomDex

Subsequent regimen	Drug	Cost per pack (£)*	Unit size in pack (mg)	Units per pack	Dose, based on NCRAS (mg)	Cost per dose (£)	Treatment duration (weeks)	Acquisition cost per treatment duration (£)	Administration cost per treatment duration (£)
Bortezomib + panobinostat	Bortezomib (IV)	217.82	1	1	2.45	532.59	13.47	8,630.65	7,682.30
	Panobinostat	4,656.00	20	6	16.63	645.05	13.47	17,377.65	
Cyclophosphamide + thalidomide	Cyclophosphamide (IV)	8.21	500	1	500.00	8.21	13.47	774.12	997.14
	Thalidomide	298.48	50	28	50.00	10.66	13.47	1,005.13	
Cyclophosphamide	Cyclophosphamide (IV)	8.21	500	1	500.00	8.21	13.47	774.12	997.14
Melphalan + thalidomide	Melphalan (IV)	298.48	50	28	50.00	10.66	13.47	1,005.13	1,640.71
	Thalidomide (oral)	26.64	50	1	10.47	5.58	13.47	18.79	0
Melphalan	Melphalan (IV)	26.64	50	1	10.47	5.58	13.47	18.79	1640.71
Bortezomib	Bortezomib (IV)	217.82	1	1	2.45	532.59	13.47	8,630.65	7,682.30

*All drug costs taken from BNF
Abbreviations: BNF, British National Formulary; IV, intravenous; mg, milligram; NCRAS, National Cancer Registration and Analysis Service; NICE, National Institute for Health and Care Excellence.

Subsequent treatment as per clinical opinion (scenario analysis)

In addition to the base-case considering subsequent treatments based on DREAMM-2 and the NCRAS study, a scenario was explored to model the costs incurred by subsequent treatments as defined by UK clinical experts. UK haematologists were asked to describe what treatments Belamaf and PomDex patients would likely receive upon disease progression as presented in Table 83.

The resulting administration and acquisition costs per patient per regimen per duration are detailed in Table 84, with one-off costs given in Table 85.

Table 83. Subsequent treatment mix according to UK clinical expert opinion (used as a scenario analysis)

Subsequent treatments received upon disease progression	5L+ TCR treatment: Belamaf	5L+ TCR treatment: PomDex
Palliative care (including chemotherapy and a steroid with or without thalidomide)	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]
PomDex	[redacted]	[redacted]
PanoBorDex	[redacted]	[redacted]

Abbreviations: 5L+, fifth line and beyond; TCR, triple class refractory.

Table 84. Subsequent treatment unit costs (scenario analysis based on UK clinical expert opinion)

Subsequent regimen	Drug	Dose, based on SmPC (mg)	Cost per dose (£)	Source	Treatment duration (weeks)[29]	Acquisition cost per treatment duration (£)	Administration cost per treatment duration (£)
Palliative care (including chemotherapy with a steroid)	Assumed split 33% Melphalan + prednisolone 33% Thalidomide + dexamethasone 33% Dexamethasone monotherapy (See Table 78)				13.47	397.05	2,131.72
Conventional chemotherapy	Cyclophosphamide (IV)	500	8.21	BNF[120] SmPC[121]	13.47	110.59	6,395.15
	Dexamethasone	40	4.00	BNF[122] SmPC[123]	13.47	53.88	0
Pomalidomide	Pomalidomide	4	423.05	BNF[117] SmPC[80]	13.47	29,917.73	0
PomDex	Pomalidomide	4	423.05	BNF[117] SmPC[80]	13.47	29,917.13	0
	Dexamethasone	20	2.00	BNF[124] SmPC[110]	13.47	53.88	0
PanoBorDex	Panobinostat	20	776.00	BNF[124] SmPC[125]	13.47	20,906.04	0
	Bortezomib	1	217.82	BNF[116] SmPC[123]	13.47	9,510.46	4,226.29
	Dexamethasone	20	2.00	BNF[123]	13.47	71.84	0

Abbreviations: mg, milligram; SmPC, Summary of product characteristics.

Table 85. Subsequent treatment one-off costs (scenario analysis based on expert clinical opinion)

Index treatment	Subsequent treatments received	Subsequent treatment one-off cost (£)
Belamaf	See Table 83	13,976.13
PomDex	See Table 83	4,006.75

Abbreviations: PomDex, Pomalidomide and dexamethasone

B.3.6 Severity

Based on the QALY shortfall calculator published by Schneider *et al.*, [126] Belamaf meets the criteria to be assessed against an increased willingness-to-pay (WTP) threshold reflecting the severity of 5L+ TCR MM. In light of the considerations described below, it was concluded that the most appropriate severity modifier is 1.7x indicating that a WTP threshold of £36,000 to £51,000 should be considered for this appraisal (see Appendix P for calculations).

Existing treatment options in 5L+TCR MM, offer limited QALY gain, suggesting that Belamaf is a candidate for a QALY shortfall multiplier.

Younger patients have a higher remaining QALYs without the disease, therefore the age of individual 5L+ TCR MM patients is a key factor to determine the severity modifier selection. Patient characteristics from DREAMM-2 were considered consistently with the base-case CEA and reported a mean age at baseline of 64.1 years with a standard deviation of 10.01.[76] The main features of the QALY shortfall analysis are summarised in Table 86.

PomDex and PanoBorDex were considered, and the proportion of usage reported in the NCRAS study was used to calculate an average proportional shortfall of [redacted]%, as described in Table 87. It should be noted that the 95% confidence interval around this point estimate is [redacted]% - [redacted]% which therefore includes both the 1.2x and the 1.7x multiplier.

Moreover, a [redacted]% proportional QALY shortfall lies on the frontier between the 1.7x multiplier (i.e. a 95% shortfall) and the 1.2x multiplier (i.e. an 85% shortfall). The NICE Methods state that in this situation the higher modifier should be applied: "*If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply*".[127] Thus, the estimated proportional shortfall supports the application of the 1.7x multiplier.

Table 86. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference
Sex distribution	53% male	B.3.3.1
Starting age	[redacted] years	B.3.3.1
Proportion of patients receiving PomDex (vs PanoBorDex)*	[redacted]%	B.1.3.3.1
Discount rate	3.5%	Reference Case[91]

Factor	Value (reference to appropriate table or figure in submission)	Reference
PFS on treatment	[redacted]	B.3.4.2.3
PFS off-treatment	[redacted]	
PD	[redacted]	
Remaining LY of population	UK life tables	[128]
Remaining QALY of population	UK population utility norms	[129,130]

Abbreviations: LY, life years; PFS, progression-free survival; PD, progressed disease; QALY, quality-adjusted life year.
*PomDex and PanoBorDex included to identify the WTP threshold to apply across all CEA results.

Table 87. Summary of average QALY shortfall analysis

Factor	Mean QALY in expectation	Absolute shortfall	Proportional shortfall
No disease	[redacted]	[redacted]	[redacted]
PomDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
PanoBorDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
Weighted average of real-world usage of PomDex and PanoBorDex	[redacted]	[redacted]	[redacted]

Abbreviations: MM, multiple myeloma; QALY, quality-adjusted life year; TCR, triple class refractory
Source for calculations: GSK Economic Model, details in Appendix P

An alternative method to estimate the severity modifiers for this appraisal considered the number of individual patients for whom the 1.7x modifier should be applied using the probabilistic sensitivity analysis (PSA) within the cost-effectiveness model. Figure 46 below demonstrates that the 1.7x severity modifier could be applied to approximately [redacted]% of patients, the 1.2x modifier to [redacted]% of patients and the 1.0x modifier to approximately [redacted]%. This suggests a heterogeneity of the population within the 5L+ TCR MM setting. Figure 46 depicts the distributions of patients eligible to each of the severity modifiers, derived from the PSA analysis (1,000 iterations); Table 88 provides example calculations corresponding to the first five simulations from the PSA. Further details of the calculations are given in Appendix P.

Figure 46. Graphical demonstration of heterogeneity in the 5L+ TCR MM population, and related severity modifiers

Table 88. Example calculations for severity modifier from five PSA simulations

Background treatment	Age	Remaining QALY for healthy population	Absolute QALY shortfall	Proportional QALY shortfall	Severity modifier
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	1.2x
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	1.2x
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	1.7x
PanoBorDex	[redacted]	[redacted]	[redacted]	[redacted]	1.7x
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	1.2x

B.3.7 Uncertainty

There is uncertainty around the comparative effectiveness used within the economic analysis, the treatment regimens for subsequent treatment, paucity of safety data collected in the NCRAS study and lack of evidence for costs/resource use and HRQoL associated with keratopathy. The limitations associated with these aspects are described in Section B.2.11.2.2 and Section B.3.15.1.3 with uncertainty explored in Section B.3.11 in order to determine the impact of various scenarios on the ICER.

B.3.8 Managed access proposal

Under the base case assumptions (and scenario analyses) Belamaf was cost-effective below the WTP thresholds considered by NICE for cost-effectiveness analysis, particularly when considering a fifth line TCR population and the appropriate application of severity modifiers described in Section B.3.6.

Nevertheless, we identify that an important uncertainty in the submission is whether a naïve or matched-adjusted comparison leads to more reliable estimates of relative efficacy and cost-effectiveness of Belamaf vs PomDex. In this appraisal, the naïve comparison was considered as the most reliable source to inform the CEA, although it should be noted that the MAIC suggests that the comparative efficacy observed in the naïve comparison may be conservative when key prognostic factors and treatment effect modifiers are accounted for (and therefore costs the NHS more, as patients stay alive and on treatment for longer).

Consequently, Belamaf is well positioned as a candidate for the Cancer Drugs Fund if the Committee agree that Belamaf is potentially cost-effective but that the naive comparison is unsuitable for decision-making.

Navigating access for patients via the CDF would allow RWE collection (through SACT and Bluteq) in an NHS setting which would improve the feasibility of a comparison with the PomDex efficacy outcomes.

Table 89 summarises the opportunity presented by the CDF.

Table 89. List of uncertainties and the data that could be collected to resolve them

Clinical uncertainty	Outcome data	Data source
How will Belamaf perform in a real-world NHS setting (vs a trial setting)?	OS TTD TTNT	SACT

The expected duration of the CDF managed access agreement is of three years There are no anticipated barriers to data collection since the existing NCRAS data in this submission proves that the data collection is possible and of high enough quality to make a CDF entry plausible.

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

B.3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 90.

Table 90. Summary of variables applied in the base-case economic analysis

Parameter	Value	OWSA			Within PSA varied by	Reference to location in submission
		SE	Lower bound	Upper bound		
Model set up						
Cohort size	1000	-	-	-	-	-
Time horizon (years)	25	-	-	-	-	B.3.2.2.1
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	Gamma	B.3.3.1
Percentage male (%)	53	11	32	73	Beta	B.3.3.1
Discount rate costs (%)	3.5	-	-	-	-	B.3.2.2.1
Discount rate outcomes (%)	3.5	-	-	-	-	
Drug acquisition costs						
Belamaf cost per cycle (£)	[redacted]	-	-	-	-	B.3.5.1.1
Belamaf relative dose intensity (%)	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Pomalidomide acquisition cost per cycle (£)	2,961.33	-	-	-	-	
Dexamethasone acquisition cost per cycle (£)	4.00	-	-	-	-	
Pomalidamide relative dose intensity (%)	90	18	32	100	Beta	
Dexamethasone relative dose intensity (%)	90	18	32	100	Beta	
Drug administration costs						
Administration cost per cycle with Belamaf (cycle 1) (£)	361.53	72.31	233.96	516.41	Gamma	B.3.5.1.2
Administration cost per cycle with Belamaf (cycle 4+) (£)	237.21	47.44	153.51	338.83	Gamma	

Parameter	Value	OWSA			Within PSA varied by	Reference to location in submission
		SE	Lower bound	Upper bound		
Administration cost per cycle with pomalidomide (£)	0.00	-	-	-	-	
Administration cost per cycle with dexamethasone (£)	0.00	-	-	-	-	
Subsequent treatments						
Belamaf subsequent tx (% patients)	[redacted]	[redacted]	[redacted]	[redacted]	Beta	B.3.5.4.3
PomDex subsequent tx (% patients)	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Belamaf subsequent tx cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	Gamma	
PomDex subsequent tx cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	Gamma	
Concomitant therapies						
Belamaf concomitant therapies/supportive care one-off cost (£)	151.63	30.33	98.13	216.59	Gamma	B.3.5.4.2
PomDex concomitant therapies/supportive care one-off cost (£)	400.52	80.10	259.20	572.11	Gamma	
PomDex concomitant therapies/supportive additional cost per cycle (£)	141.33	28.27	91.46	201.88	Gamma	
Belamaf ocular concomitant therapies cost first year (£)	702.66	140.53	454.72	1003.68	Gamma	
Belamaf ocular concomitant therapies cost subsequent years (£)	197.94	39.59	128.10	282.74	Gamma	
Routine monitoring costs						
Belamaf routine monitoring PFS on-tx total cost (£)	45.56	9.11	29.48	65.08	Gamma	B.3.5.2.1

Parameter	Value	OWSA			Within PSA varied by	Reference to location in submission
		SE	Lower bound	Upper bound		
Belamaf routine monitoring PFS off-tx total cost (£)	16.57	3.31	10.73	23.67	Gamma	
Belamaf routine monitoring PD total cost (£)	17.49	3.50	11.32	24.98	Gamma	
PomDex routine monitoring PFS on-tx total cost (£)	45.56	9.11	29.48	65.08	Gamma	
PomDex routine monitoring PFS off-tx total cost (£)	16.57	3.31	10.73	23.67	Gamma	
PomDex routine monitoring PD total cost (£)	17.49	3.50	11.32	24.98	Gamma	
End of life costs						
End of life cost (£)	6,833.97	1,366.79	4,422.58	9,761.67	Gamma	B.3.5.4.1
Quality of life						
Belamaf adverse event total cost (£)	1,058.00	211.60	684.68	1,511.25	Gamma	B.3.5.3
PomDex adverse event total cost (£)	1,969.07	393.81	1,274.28	2,812.63	Gamma	
Utility: PFS on-tx	[redacted]	[redacted]	[redacted]	[redacted]	Beta	B.3.4.5
Utility: PFS off tx	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Utility: PD	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Belamaf adverse event total disutility	0.24	0.05	0.15	0.34	Beta	
PomDex adverse event total disutility	0.29	0.06	0.18	0.41	Beta	

Abbreviations: OWSA, one-way sensitivity analysis; PD, progressed disease; PFS, progression-free survival; PSA, probability sensitivity analysis; SE, standard error; tx, treatment

B.3.9.2 Assumptions

A summary of modelling assumptions is provided, divided by aspect of the cost-effectiveness model, in Table 91.

Table 91. List of assumptions for the base-case cost-effectiveness analysis

Category	Assumption	Justification
Population and comparators	The 2.5 mg/kg arm of the ITT population of DREAMM-2 is representative of the 5L+ TCR MM patient population modelled	The model uses efficacy data from the 2.5 mg/kg arm of the DREAMM-2 ITT population which included [redacted] patients at 4L (instead of 5L+). There is a limited impact on the baseline characteristics and outcomes when these [redacted] patients are removed (B.2.3.1.2 and B.2.6), therefore the ITT population is chosen for the economic analysis.
Model structure and settings	The progression-free health state was divided into on- and off-treatment in order to differentiate costs and utility based on treatment status	The PF on- and off-treatment split was chosen based on the observation that some patients in DREAMM-2 withdraw from active treatment before disease progression, which was also aligned with previous NICE TAs[66,30] A scenario analysis using a 3-state model structure (with a single PFS health state) was explored.
	Lifetime horizon of 25 years	The mean age of the population is [redacted] years (based on the mean age in DREAMM-2) therefore a 25-year time horizon was considered long enough to capture the clinical and economic impacts of RRMM in a 5L+ setting. Alternative time horizons (10 and 15 years) are considered in scenario analyses.
	No half cycle correction applied	The one-week cycle length was assumed to be sufficiently short to capture model transitions.
Clinical effectiveness	TTNT is used as a proxy for PFS in the economic analysis	PFS was not reported in NCRAS therefore TTNT was considered for both treatment arms and was used as a proxy for PFS in the economic model.
	The naïve comparison was used to inform the efficacy for Belamaf (DREAMM-2) to PomDex (NCRAS)	Given the challenges in estimating the relative efficacy between Belamaf and PomDex, the naïve comparison was selected as the most appropriate source of evidence. A scenario analysis using the MAIC results is also presented.

Category	Assumption	Justification
	PFS is capped at 2-years for PomDex	Clinical experts have indicated that in practice patients are unlikely to remain progression-free after 2-year when receiving PomDex therefore the PFS curves for PomDex were capped at this timepoint. A scenario removing the PomDex PFS cap is presented to test this assumption.
	PomDex AE incidence rates sourced from MM-010 in absence of NCRAS data	It was assumed that the population of the NCRAS study and MM-010 were broadly comparable, despite some differences between the median number of prior lines and the proportion of TCR patients.
Cost and resource use inputs	Health state specific resource use is assumed the same for all treatment arms	This is consistent with previous MM TAs[30] and has been validated with clinicians.
	Grade ≥3 AEs costs and disutilities are applied as a one-off cost and during the first four weeks on treatment, respectively	AEs are likely to occur very soon after treatment initiation and only require acute care. This is consistent with other modelling approaches in MM TAs.[131]
	PomDex RDI sourced from MM-010 given the limited NCRAS data	RDI was taken from MM-010[94] given the data for actual doses received from NCRAS was limited.
	No wastage of doses assumed	No wastage was modelled by assuming vial sharing will take place in clinical practice. An alternative assumption of assuming that 50% of patients do not share vials is presented as a scenario analysis.
	Subsequent treatments were informed by DREAMM-2 trial while NCRAS was used to determine PomDex subsequent treatments	The NCRAS study and DREAMM-2 trial were considered to inform the subsequent treatments for PomDex and the DREAMM-2, respectively. The subsequent treatment mix was re-weighted to reflect interventions available in the UK. An alternative subsequent treatment mix based on UK clinical expert opinion is presented as a scenario analysis.
	Average time on subsequent treatment was sourced from the literature and was assumed to be the same for all treatment regimens. The efficacy and HRQoL impact of subsequent treatments was not included in the CEA.	Time on subsequent treatment was not reported in either DREAMM-2 nor NCRAS. Therefore, the value of 3.1 months (or, 13.47 weeks) as reported in Gandhi et al. (2019) was used.[29] A treatment sequencing model was not selected as the model structure, and as such, only the costs of subsequent treatments are modelled.

Category	Assumption	Justification
Health-related quality of life	EQ-5D-3L utility data obtained via a mapping from EORTC-QLQ-C30 and QLQ-MMY20	EQ-5D data were not collected in the DREAMM-2 clinical trial. In absence of these data, in line with the NICE Reference Case[91], EORTC data collected in DREAMM-2 were converted into EQ-5D-3L utility scores using the mapping algorithm published by Proskorovsky et al. 2014.[96]
	Utilities on- and off-treatment are based on response and non-response utilities	In absence of the HRQoL utility analysis performed based on an indicator for treatment discontinuation, response was assumed to be an acceptable proxy for determining the utility of patients on- and off-treatment. An alternative approach is considered in a scenario analysis by applying the same utility for PF for the on- and off-treatment health states.
	Severe dry eye disutility was used as proxy for disutility associated with keratopathy AEs	In the absence of disutility values specific for keratopathy clinical experts were consulted and advised that severe dry eyes would be an appropriate proxy to estimate HRQoL impairment associated with keratopathy. The disutility for severe dry eye was extracted from NICE TA369.[98]
	Age-related utility decrements are applied	Age-related utility decrements were applied in the model to incorporate the natural decline in HRQoL associated with increasing age and to ensure the utility of 5L+ TCR MM patients does not exceed that of the general population.
	No IV disutility applied for Belamaf	The IV administration is not expected to add further monitoring compared to current management of MM. Belamaf is administered via a short 30 minutes infusion (in the absence of any IRRs) and on this basis clinical experts do not expect administration to negatively impact HRQoL. Therefore no IV disutility is applied for Belamaf in the model.

Abbreviations: 5L, fifth line; AE, adverse event; CEA, cost-effectiveness analysis; EORTC-QLQ-C30/ MM-Y20, EORTC Core Quality of Life questionnaire/myeloma module; EQ-5D-3L, Euro-QoL-5 dimensions-3 levels; HRQoL, health-related quality of life; IV, intravenous; MM, multiple myeloma; NCRAS, National cancer registration and analysis service; PF, progression-free; RWE, real-world evidence; TA, technology appraisal; TCR, triple class refractory; UK, United Kingdom

B.3.10 Base-case results

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

This section presents the base-case results for the CEA comparing Belamaf to PomDex in a population of 5L+ TCR MM patients.

The base-case results are presented using the list price for PomDex and the confidential simple PAS discount of [redacted]% for Belamaf as described in Section B.1.2. Results using the list price for Belamaf are provided in Appendix N.

Total costs, life years gained (LYG), quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) for Belamaf versus PomDex are presented in Table 92. In the deterministic base-case analysis, Belamaf was associated with higher average QALYs ([redacted]) and lower average costs ([redacted] cost savings) when compared to PomDex suggesting that Belamaf is dominant vs PomDex over a 25-year horizon. Disaggregated base-case results are presented in Appendix J.

The net health benefit is displayed in Table 93. The threshold for net health benefit (NHB) has been updated to align with the WTP outlined in Section B.3.6. The NHB at £36,000 and £51,000 of [redacted] and [redacted], respectively, implies that overall population health would be increased as a result of introducing Belamaf.

Table 92. Deterministic base-case results for Belamaf versus PomDex

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
PomDex	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 93. Net health benefit for Belamaf versus PomDex

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £36,000	NHB at £51,000
PomDex	[redacted]	[redacted]	-	-	-	-
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

B.3.11 Exploring uncertainty

Probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWSA) have been run and are presented in Section B.3.11.1 and B.3.11.2, respectively. Key areas of uncertainty tested in sensitivity analyses included the source of comparative effectiveness and subsequent treatment costs. Scenario analyses conducted in Section B.3.11.3 explore this uncertainty and show that there is little impact on the resulting ICERs.

B.3.11.1 Probabilistic sensitivity analysis

A PSA was conducted to estimate the uncertainties in the key model parameters. The analysis involved varying the inputs by randomly assigning a parameter value from predefined uncertainty distributions.

This was performed for each parameter simultaneously over multiple iterations, and the resulting incremental cost and QALY predictions were recorded. Based on the convergence plots (see Appendix P), showing incremental costs, QALYs and the ICER stabilising in the first few hundred runs, it was decided to run 1,000 iterations of PSA.

Table 90 presents the uncertainty distributions that were drawn from for each variable, along with the uncertainty data reported as standard errors/standard deviations. For event rates and utilities, a beta distribution was used to restrict draws between 0 and 1. For costs and resource use estimates a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed.

The results of the PSA including mean total costs, QALYs and the ICER for Belamaf versus PomDex are presented in Table 94. The incremental cost-effectiveness plane (ICEP) scatter plot, cost-effectiveness acceptability curve (CEAC), and cost-effectiveness acceptability frontier (CEAF) were produced to graphically illustrate the level of variability and uncertainty in the results, as shown in Figure 47, Figure 48 and Figure 49, respectively.

In the probabilistic base-case analysis, on average Belamaf generates [redacted] incremental QALYs with cost savings of £[redacted] over a 25-year time horizon compared with PomDex, dominating PomDex. (Table 94).

The ICEP (Figure 47) shows that [redacted]% of results are in the southeast quadrant (i.e. Belamaf is less costly and more effective) and [redacted]% are in the northeast quadrant (i.e. Belamaf is more costly and more effective).

The CEAC and CEAF show that at a WTP threshold of £51,000, Belamaf has a [redacted]% chance of being cost effective (Figure 48 and Figure 49).

Table 94. PSA base-case results for Belamaf versus PomDex

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
PomDex	[redacted]	[redacted]	[redacted]	-	-	-		
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

Figure 47. Incremental cost-effectiveness plane for Belamaf versus PomDex

Abbreviations: PSA, probability sensitivity analysis; QALYs, quality-adjusted life years

Figure 48. Cost-effectiveness acceptability curve Belamaf versus PomDex

Figure 49: Cost-effectiveness acceptability frontier Belamaf versus PomDex

B.3.11.2 Deterministic sensitivity analysis

A deterministic one-way sensitivity analysis (OWSA) was conducted to explore the key model parameters influencing the model results. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed. The OWSA involved varying one parameter at a time to upper and lower confidence intervals (CI; the low value is the lower bound of the 95% CI, the high value is the upper bound of the 95% CI). In the absence of CI data, the parameter was altered by +/- 20%. Table 90 presents the mean, standard error, upper bound and lower bound values for each variable.

A tornado diagram was developed to graphically present the parameters for all variables which have the greatest effect on the net monetary benefit (NMB), at a WTP threshold of £51,000 per QALY. The NMB was used as an alternative to the ICER in order to avoid negative ICERs within the OWSA (when Belamaf dominates PomDex).

A OWSA tornado diagram presenting the top 10 most sensitive parameters is given in Figure 50, with tabulated results presented in Table 95. The model was most sensitive to the RDI for pomalidomide and Belamaf, followed by OS and TTD for both Belamaf and PomDex

Figure 50. OWSA tornado diagram for Belamaf versus PomDex

Abbreviations: NMB, net monetary benefit; OS, overall survival; PD, progressed disease; PFS, progression-free survival; TTD, time to discontinuation, tx, treatment

Table 95. Tabulated OWSA results for Belamaf versus PomDex

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Pomalidomide relative dose intensity	[redacted]	[redacted]	[redacted]
Belamaf relative dose intensity	[redacted]	[redacted]	[redacted]
Belamaf - OS	[redacted]	[redacted]	[redacted]
PomDex - OS	[redacted]	[redacted]	[redacted]
PomDex - TTD	[redacted]	[redacted]	[redacted]
Belamaf - TTD	[redacted]	[redacted]	[redacted]
Utility: PD	[redacted]	[redacted]	[redacted]
PomDex concomitant therapies/supportive additional cost per cycle	[redacted]	[redacted]	[redacted]
PomDex - PFS	[redacted]	[redacted]	[redacted]
PomDex adverse event total cost	[redacted]	[redacted]	[redacted]

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis, OS, overall survival; PD, progressed disease; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.11.3 Scenario analysis

A number of scenarios were explored to investigate the impact of using alternative assumptions, values, and data sources for model inputs. These are summarised in .

Table 96 and the results are presented in Table 97.

Table 96. Scenarios explored in the cost-effectiveness analysis

#	Category	Base-case	Scenario	
		Value	**Value**	**Rationale**
1, 2	Time horizon	25 years	(1) 10 years and (2) 15 years	25 years represents lifetime horizon (see Table 91). Scenarios are explored to test the impact of shorter time horizons.
3	Annual discount rate for costs and QALYs	3.5%	1.5%	As per NICE guidelines.[91]
4	Number of health states	Four (PF on-tx, PF off-tx, PD, death)	Three (PF, PD, Death)	Four health states represent the time spent off-treatment by DREAMM-2 patients while progression-free which also aligned with previous NICE TAs[66,30] (see Table 91). Three health state scenario performed to test structural uncertainty.
5, 6, 7	Efficacy	• Naïve comparison • PFS capped at 0% at 2 years for PomDex • PFS, OS and TTD: Weibull	• (5) MAIC • (6) PomDex PFS uncapped • (7) PFS, OS: Exponential; TTD: Generalised Gamma	• (5) Naïve comparison used in base-case due to substantial limitations of the MAIC approach (Section B.2.8.2.4). MAIC results presented to show impact of attempt to partially adjust for differences in patient population. • (6) Applied cap to align with clinical opinion (see Table 91). Scenario included to test the impact of not applying this cap and using the Weibull curve to the end of the time horizon instead. • (7) Base-case and scenario analysis models selected following guidance in TSD 14 (see Section B.3.3.3). Alternative next best fitting curves tested in a scenario.

#	Category	Base-case	Scenario	
		Value	Value	Rationale
8	Progression-free health state utility values	Split by on- and off-treatment [PF on-tx = [redacted] (DREAMM-2), PF off-txt = [redacted] (DREAMM-2)]	Apply on treatment utility values to both on- and off-treatment progression-free health states [PF on-tx = PF off-tx = [redacted] (DREAMM-2)]	In absence of the HRQoL utility analysis performed based on an indicator for treatment discontinuation, response was assumed to be an acceptable proxy for determining the utility of patients on- and off-treatment. An alternative approach is considered in a scenario analysis by applying the same utility for PF for the on- and off-treatment health states.
9, 10	Treatment-specific utility values	Treatment-independent utility values, sourced from DREAMM-2 for both Belamaf and PomDex	Treatment-specific utility values, sourced from DREAMM-2 for Belamaf and: • (9) TA427 for PomDex*, or • (10) TA658 for PomDex	Since DREAMM-2 did not include a comparator arm, there is no head-to-head evidence for the HRQoL impact of Belamaf versus comparators. Therefore, treatment-independent utilities were used in the base-case. Scenarios test this by keeping DREAMM-2 utilities for Belamaf and using two alternate data sources for PomDex utilities.
11	AE disutilities	Include	Exclude	Scenario analysis explores the impact of excluding AE disutilities.
12	Age-adjusted utilities	Include	Exclude	The impact of removing age-related utility decrements was explored as a scenario analysis.
13	Wastage	No wastage; all administrations use vial sharing	50% of administrations use vial sharing	Vial sharing is expected to be prevalent in clinical practice during Belamaf administration. To test this assumption, a scenario explores the impact that vial sharing is only applicable in 50% of Belamaf administrations.
14	Subsequent treatment costs	Distribution of subsequent treatments received informed by DREAMM-2 and NCRAS	Distribution of subsequent treatments received informed by clinical opinion	Due to the paucity of evidence for interventions in 5L and 6L TCR MM, the treatment regimens for subsequent treatments are uncertain. Consequently, there remains uncertainty surrounding subsequent treatment costs for which a scenario has been explored using different resource use estimates based on clinical opinion.

Abbreviations: 5L, fifth line; 6L, sixth line; AE: adverse events HRQoL, health-related quality of life; MAIC, matching adjusted indirect comparison; MM, multiple myeloma; NCRAS, National Cancer Registration and Analysis Service, OS: overall survival; PD, progressed disease: PF, progression-free: PFS, progression-free survival; QALY, quality-adjusted life year; SE, standard error; TA, technology appraisal; TCR, triple class refractory; TSD, technical support document; TTD, time to treatment discontinuation; Tx, treatment. *Varied by 10% in absence of SE data.

Table 97. Results for scenario analyses

#	Category	Base-case	Scenario	Deterministic				Probabilistic
				Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£)	ICER (£)
1	Time horizon	25 years	10 years	[redacted]	[redacted]	[redacted]	Dominating	Dominating
2			15 years	[redacted]	[redacted]	[redacted]	Dominating	Dominating
3	Discounting	3.5%	1.5%	[redacted]	[redacted]	[redacted]	Dominating	Dominating
4	Number of health states	Four	Three	[redacted]	[redacted]	[redacted]	Dominating	Dominating
5	Efficacy	Naïve comparison with capped PFS	Unanchored MAIC	[redacted]	[redacted]	[redacted]	Dominating	Dominating
6	Efficacy	Naïve comparison with capped PFS	Naïve comparison without PFS cap	[redacted]	[redacted]	[redacted]	Dominating	Dominating
7	Survival curves	PFS, OS and TTD: Weibull	PFS, OS: Exponential; TTD: Generalised Gamma	[redacted]	[redacted]	[redacted]	Dominating	Dominating
8	Progression-free health state utilities	Progression-free utility values split by on- and off-treatment	Pooled progression-free health state utility values	[redacted]	[redacted]	[redacted]	Dominating	Dominating
9	Treatment-specific utilities	DREAMM-2	DREAMM-2 and TA427	[redacted]	[redacted]	[redacted]	Dominating	Dominating
10		DREAMM-2	DREAMM-2 and TA658	[redacted]	[redacted]	[redacted]	Dominating	Dominating
11	AE disutilities	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominating	Dominating
12	Age-adjusted utilities	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominating	Dominating
13	Wastage	No wastage	50% wastage	[redacted]	[redacted]	[redacted]	Dominating	Dominating
14	Subsequent treatment costs	Distribution from NCRAS	Distribution informed by clinical opinion	[redacted]	[redacted]	[redacted]	Dominating	Dominating

Abbreviations: AE: adverse events ICER, incremental cost-effectiveness ratio; LY, life year, MAIC, matching adjusted indirect comparison; NCRAS, National Cancer Registration and Analysis Service, OS: overall survival; PD, Progressed disease: PF, Progression-free: QALY, quality-adjusted life year; TTD, time to treatment discontinuation; TTNT, time to next treatment; Tx, treatment.

The results from the scenario analyses show that the cost-effectiveness results are robust to changes in model structure and inputs, with Belamaf continuing to dominate PomDex in all scenarios.

The scenarios with the greatest impact on incremental results are estimating survival using the MAIC, alternative survival curves and using treatment-specific utilities. However, in all scenarios Belamaf continues to dominate PomDex.

The probabilistic results from the scenario analysis were aligned with the deterministic results, showing that the scenarios were robust to probabilistic uncertainty.

B.3.12 Subgroup analysis

Subgroup analysis was not performed as part of this submission.

B.3.13 Benefits not captured in the QALY calculation

The most significant uncaptured benefit results from the introduction of a new mechanism of action in the MM treatment paradigm for a population that is triple class refractory. Hence, Belamaf as the first NICE-approved anti-BCMA option for MM patients would improve patients' QoL by bringing hope to a group who otherwise are left with poor treatment options which may negatively impact their and their family's mental health. It is important to highlight that with PIs, IMiDs, and anti-CD38 antibodies, BCMA-targeted agents have emerged as the fourth pillar of myeloma treatment.

Moreover, the burden on caregivers and impact on their HRQoL as described in Section B.1.3.1.4 is not reflected in the QALY calculations. Specifically, caregivers for patients with MM reported a lower quality of life compared with those for patients with other cancers.[48] A study on HRQoL of MM patient caregivers noted a lower quality of life was associated with financial and emotional unmet needs, and psychological morbidity.[49] In addition, the limited effective treatment options in this setting may have a detrimental psychological impact on patients, leaving them feeling hopeless.[21] The introduction of Belamaf offers an alternative effective treatment with a manageable side effect profile which may help to reduce some of the emotional burden by providing hope to both patients and their relatives in the 5L+ TCR MM setting.

Belamaf is easy to deliver on an outpatient basis and [redacted]. It is an "off the shelf" BCMA-targeted therapy, meaning that treatment can be initiated immediately, without the need for a waiting period[132] which may improve outcomes and may have a positive psychological benefit not captured in the QALY.

Given the relapsing and refractory nature of MM, the availability of interventions with new mechanism of action in later lines would give clinicians an increased flexibility to use regimens currently available while mitigating the risk of running out of options in later lines.

Finally, Belamaf is an innovative medicine, being both the only antibody drug conjugate and the only anti-BCMA treatment in MM, but innovation is not captured in the model.

Secondly, the assumed QALY benefits for Belamaf is likely conservative as patients who enter the post-progression state are assumed to report the same health state utility regardless of their disease history. Therefore, any potential durability of effect of Belamaf is not captured.

B.3.14 Validation

B.3.14.1.1 Validation of cost-effectiveness analysis

The model was developed by a team of independent health economists (FIECON) and has been through rigorous internal and external validation (FIECON and The Company).

A series of clinical interviews were conducted to ensure all modelling inputs and assumptions were reflective of the decision problem and were clinically valid and plausible, particularly in the absence of relevant data identified in the literature. UK clinical experts were selected as detailed in Appendix Q.

The clinical experts provided feedback on various model inputs including the choice of the parametric curves used to model clinical outcomes, treatment effect modifiers and prognostic factors relevant to the MAIC, the resource use associated with keratopathy management, concomitant therapy and subsequent treatments.

Model outputs have been compared to, and are in alignment with, outcomes from DREAMM-2 and NCRAS, presented in Appendix J. Comparison of model outputs with other HTA submissions has also been conducted and due to the population in the current decision problem being in a worse state of health to begin with, results are different to those in previous appraisals.

B.3.15 Interpretation and conclusions of economic evidence

B.3.15.1.1 Summary of cost-effectiveness analysis

In the deterministic base-case CEA, Belamaf was dominating when compared to PomDex over a lifetime time horizon with [redacted] additional QALYs and cost savings of [redacted], including the confidential PAS discount for Belamaf.

The mean PSA results were consistent with the deterministic base-case results and the probability of Belamaf being cost-effective at a WTP of £51,000 per QALY was [redacted]%, using the WTP threshold outlined in Section B.3.6. In the deterministic OWSA, the parameters with the greatest impact on the base-case ICERs were the RDI for pomalidomide and Belamaf, followed by OS and TTD for both Belamaf and PomDex.

The validity of the base-case analysis results was further supported by the scenario analyses results which indicated that Belamaf continued to dominate PomDex across all scenarios.

Overall, these results demonstrate that Belamaf would be a valuable and cost-effective addition to the treatment pathway for patients with 5L+ TCR MM in the UK.

B.3.15.1.2 Strengths

Finally, the model structure and other key assumptions (see Section B.3.2.2) were consistent with previous appraisals in late-stage MM.[97, 90]

Given the paucity of evidence available in the literature for the 5L+ TCR MM population, the NCRAS study and the DREAMM-2 trial represent the best sources of evidence to inform the efficacy of PomDex and Belamaf providing relevant efficacy data for the patient population considered in the CEA.

In addition, the CEA meets most aspects of the NICE reference case, including the selection of a cost-utility analysis, adopting an NHS/PSS perspective, the assessment of HRQoL using the EQ-5D-3L instrument, and the choice of a lifetime horizon and a 3.5% discounting of costs and benefits.

Where required, assumptions related to the clinical outcomes, utility, costs and resource use were validated with UK haematology experts with experience using Belamaf in clinical practice [redacted] to ensure that the economic analysis was as closely aligned to UK clinical practice as feasible.

B.3.15.1.3 Limitations

Whilst the economic analysis has many strengths, some limitations persist and are described below.

Firstly, the main challenge of the CEA relates to the selection of the source to inform the relative efficacy of Belamaf versus PomDex as described in Section B.3.7. Two options were considered, a naïve comparison of the NCRAS study and DREAMM-2 trial and an unanchored MAIC (see Section B.2.8.2). Due to the considerable differences in baseline characteristics, adjusting for treatment effect modifiers significantly reduced the sample sizes to the extent that the results produced were deemed too uncertain to be used in the CEA and unsuitable for decision making. Instead, the naïve comparison was selected as it allows the model to use all the data available in this population. In light of the population differences, it is reasonable to assume that the Belamaf population has a poorer prognosis than the PomDex cohort, meaning that the CEA likely reflects a conservative estimate of the clinical benefits that could be observed with Belamaf in a UK 5L+ TCR MM population. Nonetheless, the CEA results were consistent in both the base-case using the naïve comparison and in the scenario analysis using the unanchored MAIC suggesting that Belamaf is cost-effective versus PomDex.

Another limitation relates to the use of TTNT as a proxy for PFS in the economic model which was necessary given the absence of PFS reported in the NCRAS study and is in line with previous studies conducted using real-world datasets in multiple myeloma such as the SACT dataset in England.[30] While a comparison of NCRAS TTNT to DREAMM-2 PFS could have been considered (using TTNT as a proxy for PFS in the ITC) differences between the two outcomes as observed in DREAMM-2 (median TTNT [redacted] months versus median PFS [redacted] months) and confirmed by clinical experts indicated that this comparison would not be fair and would bias the results in favour of the PomDex arm. Therefore, TTNT was considered for both treatment arms and was used to inform the proportion of patients in the PFS health state for both treatment arms.

Furthermore, due to the paucity of evidence for interventions in 6L TCR MM, the distribution of subsequent treatments is uncertain. A scenario has been explored using different resource use estimates under which Belamaf continued to dominate PomDex.

In addition, safety data was not collected in the NCRAS study and sourced from MM-010[94] instead, assuming the populations from NCRAS and MM-010 are comparable. However, AE costs and disutilities are applied as a one-off cost and during the first four weeks on treatment, respectively, such that it has limited impact on the model results.

B.3.15.1.4 Conclusions

Belamaf is the only BCMA targeted therapy licensed in 5L+ TCR MM patients in Great Britain. These patients currently face a very poor prognosis, with limited treatment options and a lack of treatment guidelines.

The results of the economic analysis demonstrate that Belamaf is an effective and cost-saving use of NHS resources when compared to PomDex and considering a WTP threshold of £51,000 per QALY gained. The results of sensitivity and scenario analyses support the robustness of the conclusions and indicate a [redacted] % probability of being cost-effective at the £51,000 per QALY gained threshold.

For patients with 5L+ TCR MM, Belamaf represents a step change in the clinical management of this condition and this analysis demonstrates that Belamaf is a cost-effective use of NHS resources for these patients who are currently left to feel abandoned and to face an extremely poor prognosis.

B.4 References

1. BLENREP 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/12545/smpc#gref>

2. Friedman KM, Garrett TE, Evans JW, *et al.* Effective Targeting of Multiple B-Cell Maturation Antigen–Expressing Hematological Malignances by Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor T Cells. *Human Gene Therapy* 2018. 29: 585–601.

3. Cho S-F, Anderson KC & Tai Y-T. Targeting B Cell Maturation Antigen (BCMA) in Multiple Myeloma: Potential Uses of BCMA-Based Immunotherapy. *Frontiers in Immunology* 2018. 9:

4. O'Connor BP, Raman VS, Erickson LD, *et al.* BCMA Is Essential for the Survival of Long-lived Bone Marrow Plasma Cells. *Journal of Experimental Medicine* 2004. 199: 91–98.

5. Benson MJ, Dillon SR, Castigli E, *et al.* Cutting Edge: The Dependence of Plasma Cells and Independence of Memory B Cells on BAFF and APRIL. *J Immunol* 2008. 180: 3655–3659.

6. Yang M, Hase H, Legarda-Addison D, *et al.* B Cell Maturation Antigen, the Receptor for a Proliferation-Inducing Ligand and B Cell-Activating Factor of the TNF Family, Induces Antigen Presentation in B Cells. *J Immunol* 2005. 175: 2814–2824.

7. Avery DT, Kalled SL, Ellyard JI, *et al.* BAFF selectively enhances the survival of plasmablasts generated from human memory B cells. *J Clin Invest* 2003. 112: 286–297.

8. Lee L, Draper B, Chaplin N, *et al.* An APRIL-based chimeric antigen receptor for dual targeting of BCMA and TACI in multiple myeloma. *Blood* 2018. 131: 746–758.

9. Tai Y-T, Mayes PA, Acharya C, *et al.* Novel anti–B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood* 2014. 123: 3128–3138.

10. European Medicines Agency 2020. CHMP summary of positive opinion for Blenrep. at <https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-blenrep_en.pdf>

11. EMA. European Public Assessment Report for blenrep. 2020.

12. Medicinal forms | Belantamab mafodotin | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/belantamab-mafodotin/medicinal-forms/>

13. Kyle RA & Rajkumar S V. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia* 2009. 23: 3–9.

14. Myeloma statistics. *Cancer Research UK* 2022. at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma>

15. HMRN - Factsheets. at <https://hmrn.org/factsheets#myeloma>

16. Ferlay J, Colombet M, Soerjomataram I, *et al.* Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International Journal of Cancer* 2019. 144: 1941–1953.

17. Anderson KC, Kyle RA, Rajkumar S V, *et al.* Clinically relevant end points and new drug approvals for myeloma. *Leukemia* 2008. 22: 231–239.

18. Pieter Sonneveld & Annemiek Broijl. Treatment of relapsed and refractory multiple myeloma. *Haematologica* 2016. 101: 396–406.

19. Unplanned admissions for patients with myeloma in the UK_ Low frequency but high costs | Elsevier Enhanced Reader. doi:10.1016/j.jbo.2019.100243

20. National Institute for Health and Care Excellence. Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]: Response to stakeholder organisation comments on the draft remit and draft scope. 2022. at <https://www.nice.org.uk/guidance/gid-ta10568/documents/scope-consultation-comments-and-responses-2>

21. 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: 417–426.

22. Michels TC & Petersen KE. Multiple Myeloma: Diagnosis and Treatment. *American family physician* 2017. 95: 373–383.

23. Kumar SK, Therneau TM, Gertz MA, *et al.* Clinical Course of Patients With Relapsed Multiple Myeloma. *Mayo Clinic Proceedings* 2004. 79: 867–874.

24. Kurtin S & Faiman B. The Changing Landscape of Multiple Myeloma: Implications for Oncology Nurses. *Clinical Journal of Oncology Nursing* 2013. 17: 7–11.

25. Da Vià MC, Zicchеddu B, Maeda A, *et al.* A Journey Through Myeloma Evolution: From the Normal Plasma Cell to Disease Complexity. *Hemasphere* 2020. 4: e502.

26. Yong K, Delforge M, Driessen C, *et al.* Multiple myeloma: patient outcomes in real-world practice. *British Journal of Haematology* 2016. 175: 252–264.

27. Jagannath S, Roy A, Kish J, *et al.* Real-world treatment patterns and associated progression-free survival in relapsed/refractory multiple myeloma among US community oncology practices. *Expert Rev Hematol* 2016. 9: 707–717.

28. Kumar SK, Lee JH, Lahuerta JJ, *et al.* Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. *Leukemia* 2012. 26: 149–157.

29. Gandhi UH, Cornell RF, Lakshman A, *et al.* Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019. 33: 2266–2275.

30. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510)| Guidance | NICE. at <https://www.nice.org.uk/guidance/ta783>

31. Cancer Research UK. Myeloma incidence statistics. at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence>

32. HMRN - Survival. at <https://hmrn.org/statistics/survival>

33. Hari P, Romanus D, Luptakova K, *et al.* The impact of age and comorbidities on practice patterns and outcomes in patients with relapsed/refractory multiple myeloma in the era of novel therapies. *Journal of Geriatric Oncology* 2018. 9: 138–144.

34. Gerecke C, Fuhrmann S, Strifler S, *et al.* The Diagnosis and Treatment of Multiple Myeloma. *Deutsches Ärzteblatt international* 2016. doi:10.3238/arztebl.2016.0470

35. Talamo G, Farooq U, Zangari M, *et al.* Beyond the CRAB symptoms: a study of presenting clinical manifestations of multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2010. 10: 464–468.

36. Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. *American Journal of Hematology* 2016. 91: 719–734.

37. Moysés-Neto M, Guimarães FM, Ayoub FH, *et al.* Acute Renal Failure and Hypercalcemia. *Renal Failure* 2006. 28: 153–159.

38. Ramsenthaler C, Kane P, Gao W, *et al.* Prevalence of symptoms in patients with multiple myeloma: a systematic review and meta-analysis. *Eur J Haematol* 2016. 97: 416–429.

39. Baz R, Lin HM, Hui A-M, *et al.* Development of a conceptual model to illustrate the impact of multiple myeloma and its treatment on health-related quality of life. *Support Care Cancer* 2015. 23: 2789–2797.

40. Ludwig H, Pönisch W, Knop S, *et al.* PS1509 QUALITY OF LIFE IN PATIENTS WITH RRMM DURING IXA-THAL-DEX INDUCTION AND IXAZOMIB MAINTENANCE THERAPY IN COMPARISON TO THE GENERAL POPULATION. *HemaSphere* 2019. 3: 695–696.

41. 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. *Clinical Lymphoma Myeloma and Leukemia* 2019. 19: e13–e28.

42. Bennink C, van der Klift M, Scheurer H, *et al.* Perspectives on returning to work of multiple myeloma patients: A qualitative interview study. *European Journal of Cancer Care* 2021. 30: e13481.

43. Myeloma UK. Fatigue and myeloma. Symptoms and complications Infoguide. 2018. at <https://www.myeloma.org.uk/wp-content/uploads/2018/03/Myeloma-UK-Fatigue-Infoguide.pdf>

44. Beattie S & Lebel S. The experience of caregivers of hematological cancer patients undergoing a hematopoietic stem cell transplant: a comprehensive literature review. *Psycho-Oncology* 2011. 20: 1137–1150.

45. Quiñoa-Salanova C, Porta-Sales J, Monforte-Royo C, *et al.* The experiences and needs of primary family caregivers of patients with multiple myeloma: A qualitative analysis. *Palliat Med* 2019. 33: 500–509.

46. Stenberg U, Ruland CM & Miaskowski C. Review of the literature on the effects of caring for a patient with cancer. *Psychooncology* 2010. 19: 1013–1025.

47. Kurtin S, Lilleby K & Spong J. Caregivers of multiple myeloma survivors. *Clin J Oncol Nurs* 2013. 17 Suppl: 25–32.

48. Deniz H & Inci F. The burden of care and quality of life of caregivers of leukemia and lymphoma patients following peripheric stem cell transplantation. *J Psychosoc Oncol* 2015. 33: 250–262.

49. Pereira MG, Vilaça M, Pinheiro M, *et al.* Quality of life in caregivers of patients with multiple myeloma. *Aging & Mental Health* 2020. 24: 1402–1410.

50. Gonzalez-McQuire S, Yong K, Leleu H, *et al.* Healthcare resource utilization among patients with relapsed multiple myeloma in the UK, France, and Italy. *Journal of Medical Economics* 2018. 21: 450–467.

51. Roy A, Kish JK, Bloudek L, *et al.* Estimating the Costs of Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma: A Model Framework. *Am Health Drug Benefits* 2015. 8: 204–215.

52. Rajan AM & Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. *Blood Cancer Journal* 2015. 5: e365–e365.

53. Bladé J, Beksac M, Caers J, *et al.* Extramedullary disease in multiple myeloma: a systematic literature review. *Blood Cancer J* 2022. 12: 45.

54. SEER Cancer Statistics Review, 1975-2016. *SEER* at <https://seer.cancer.gov/csr/1975_2016/index.html>

55. HMRN - QuickStats. at <https://hmrn.org/statistics/quickstats>

56. Bal S, Malek E, Kansagra A, *et al.* Treatment outcomes of triple class refractory multiple myeloma: a benchmark for new therapies. *Leukemia* 2022. 36: 877–880.

57. Mateos M-V, Weisel K, De Stefano V, *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: 1371–1376.

58. Zanwar S, Ho M, Kapoor P, *et al.* Outcomes of triple class (proteasome inhibitor, IMiDs and monoclonal antibody) refractory patients with multiple myeloma. *Leukemia* 2022. 36: 873–876.

59. 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. 117–120.

60. National Disease Registration Service. National Cancer Registration and Analysis Service Study Protocol.

61. Sive J, Cuthill K, Hunter H, *et al.* Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. *Br J Haematol* 2021. 193: 245–268.

62. Su CT & Ye JC. Emerging therapies for relapsed/refractory multiple myeloma: CAR-T and beyond. *Journal of Hematology & Oncology* 2021. 14: 115.

63. Recommendations | Myeloma: diagnosis and management | Guidance | NICE. at <https://www.nice.org.uk/guidance/ng35/chapter/Recommendations#managing-relapsed-myeloma>

64. Overview | Panobinostat for treating multiple myeloma after at least 2 previous treatments | Guidance | NICE. at <https://www.nice.org.uk/Guidance/TA380>

65. Overview | Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta427>

66. Bird S, Pawlyn C, Nallamilli S, *et al.* A real-world study of panobinostat, weekly bortezomib and dexamethasone in a very heavily pretreated population of multiple-myeloma patients. *British Journal of Haematology* 2020. 191: 927–930.

67. Maouche N, Kishore B, Bhatti Z, *et al.* Panobinostat in combination with bortezomib and dexamethasone in multiply relapsed and refractory myeloma; UK routine care cohort. *PLoS ONE* 2022. 17:

68. NHS England » Bendamustine for relapsed multiple myeloma (all ages). at <https://www.england.nhs.uk/publication/bendamustine-for-relapsed-multiple-myeloma-all-ages/>

69. Lonial S, Lee HC, Badros A, *et al.* Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *The Lancet Oncology* 2020. 21: 207–221.

70. Dimopoulos MA, Moreau P, Terpos E, *et al.* Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology* 2021. 32: 309–322.

71. NCCN Guidelines for Patients Multiple Myeloma. *Multiple Myeloma* 2022. 72.

72. GSK. Trial Protocol for DREAMM-2.

73. GSK. Reporting and Analysis Plan for A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses of the Antibody Drug Conjugate GSK2857916 in Participants with Multiple Myeloma Who Had 3 or More Prior Lines of Treatment, Are Refractory to a Proteasome Inhibitor and an Immunomodulatory Agent and Have Failed an Anti-CD38 Antibody (DREAMM 2).

74. Lonial S, Lee HC, Badros A, *et al.* Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer* 2021. 127: 4198–4212.

75. About NCIN. at <http://www.ncin.org.uk/about_ncin/>

76. GSK. Clinical Study Report for DREAMM-2 13-Month Follow-Up.

77. Rajkumar SV, Dimopoulos MA, Palumbo A, *et al.* International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* 2014. 15: e538–e548.

78. GSK. Clinical Study Report for DREAMM-2 Primary Analysis.

79. Elsada A, Zalin-Miller A, Knott C, *et al.* 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: 493–497.

80. Imnovid 3 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/3465/smpc#POSOLOGY>

81. Stalker ME & Mark TM. Clinical Management of Triple-Class Refractory Multiple Myeloma: A Review of Current Strategies and Emerging Therapies. *Curr Oncol* 2022. 29: 4464–4477.

82. Popat R, Lonial S, Voorhees P, *et al.* Patient-reported outcomes with belantamab mafodotin treatment in patients with triple-class refractory multiple myeloma. 2022.

83. Popat R, Lonial S, Voorhees P, *et al.* Supplementary material: Patient-reported outcomes with belantamab mafodotin treatment in patients with triple-class refractory multiple myeloma. 2022.

84. Population-adjusted indirect comparisons (MAIC and STC) | NICE Decision Support Unit | The University of Sheffield. at <https://www.sheffield.ac.uk/nice-dsu/tsds/population-adjusted>

85. Lonial S, Lee H, Badros A, *et al.* Supplementary Appendix: Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *The lancet Oncology* 2020. 21: 207-221.

86. Alain Bron A, Ananth Viswanathan, Thelen, *et al.* International vision requirements for driver licensing and disability pensions: using a milestone approach in characterization of progressive eye disease. *OPTH* 2010. 1361. doi:10.2147/OPTH.S15359

87. Farooq A, Degli Esposti S, Popat R, *et al.* Corneal Epithelial Findings in Patients with Multiple Myeloma Treated with Antibody–Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study. *Ophthalmology and therapy* 2020. doi:10.1007/s40123-020-00280-8

88. GlaxoSmithKline. *A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Single Agent Belantamab Mafodotin Compared to Pomalidomide Plus Lowdose Dexamethasone (Pom/Dex) in Participants With Relapsed/Refractory Multiple*

Myeloma (RRMM) (DREAMM 3). (clinicaltrials.gov, 2022). at <https://clinicaltrials.gov/ct2/show/NCT04162210>

89. EMA. Blenrep. *European Medicines Agency* 2020. at <https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep>

90. Woods B SE, Palmer S, Latimer N, Soares M. . National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 19. Partitioned Survival Analysis For Decision Modelling In Health Care: A Critical Review. Available at: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf [accessed 27 April 2021]. 2017.

91. 5 The reference case | Guide to the methods of technology appraisal 2013 | Guidance | NICE. at <https://www.nice.org.uk/process/pmg9/chapter/the-reference-case>

92. Overview | Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta427>

93. Overview | Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta658>

94. Dimopoulos MA, Palumbo A, Corradini P, *et al.* Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. *Blood* 2016. 128: 497–503.

95. 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.

96. Proskorovsky I, Lewis P, Williams CD, *et al.* Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes* 2014. 12: 35.

97. Nikolaou A, Ambavane A, Shah A, *et al.* Belantamab mafodotin for the treatment of relapsed/refractory multiple myeloma in heavily pretreated patients: a US cost-effectiveness analysis. *Expert Review of Hematology* 2021. 14: 1137–1145.

98. Overview | Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta369>

99. Millne RJ, Heaton-Brown KH & Hansen P. Quality-of-life valuations of advanced breast cancer by New Zealand women. *Pharacoeconomics* 2006. 24: 281–92.

100. Ara R & Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010. 13: 509–518.

101. NHS England » National Cost Collection for the NHS. at <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>

102. National Institute for Health and Care Excellence. NICE BNF. at <https://bnf.nice.org.uk/>

103. Unit Costs of Health and Social Care | PSSRU. at <https://www.pssru.ac.uk/project-pages/unit-costs/>

104. daratumumab (Darzalex). *Scottish Medicines Consortium* at <https://www.scottishmedicines.org.uk/medicines-advice/daratumumab-darzalex-resubmission-120517/>

105. Pomalidomide | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/pomalidomide/>

106. Dexamethasone | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/dexamethasone/>

107. Bortezomib | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/bortezomib/>

108. Belantamab mafodotin | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/belantamab-mafodotin/>

109. BLENREP 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/12545/smpc#gref>

110. Dexamethasone 20mg Soluble Tablets - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/13198/smpc#gref>

111. National Institute for Health and Care Excellence. NICE BNF - Hypromellose. at <https://bnf.nice.org.uk/drugs/hypromellose/medicinal-forms/>

112. 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).

113. Enoxaparin sodium | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/enoxaparin-sodium/>

114. Aspirin 75mg Tablets - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/2408/smpc#gref>

115. Inhixa 15,000 IU (150mg)/1 mL solution for injection - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/9855/smpc#gref>

116. Bortezomib | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/bortezomib/>

117. National Institute for Health and Care Excellence. NICE BNF - Pomalidomide. at <https://bnf.nice.org.uk/drugs/pomalidomide/medicinal-forms/>

118. Lenalidomide | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/lenalidomide/>

119. Thalidomide | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/thalidomide/>

120. Cyclophosphamide | Drugs | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/cyclophosphamide/>

121. Cyclophosphamide 500 mg Powder for Solution for Injection or Infusion - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/3526/smpc#gref>

122. National Institute for Health and Care Excellence. NICE BNF - Dexamethasone. at <https://bnf.nice.org.uk/drugs/dexamethasone/medicinal-forms/>

123. Bortezomib 1mg powder for solution for injection - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/10551/smpc#gref>

124. National Institute for Health and Care Excellence. NICE BNF - Panobinostat. at <https://bnf.nice.org.uk/drugs/panobinostat/medicinal-forms/>

125. Farydak 20mg hard capsules - Summary of Product Characteristics (SmPC) - (emc). at <https://www.medicines.org.uk/emc/product/12139/smpc#POSOLOGY>

126. Paul Schneider, Simon McNamara, James Love-Koh, Tim Doran, Nils Gutacker. QALY Shortfall Calculator. 2021.

127. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022. at <https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741>

128. National life tables: England - Office for National Statistics. at <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables>

129. NatCen Social Research & University College London DOE. HSEHealth Survey for England, 1991-Health Survey for England, 2018. 2022. doi:10.5255/UKDA-SN-8649-2

130. Hernández-Alava M & Pudney S. Mapping between EQ-5D-3L and EQ-5D-5L: A survey experiment on the validity of multi-instrument data. *Health Economics* 2022. 31: 923–939.

131. National Institute for Health and Care Excellence. NICE TA658: Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. at <https://www.nice.org.uk/guidance/ta658/documents/committee-papers-2>

132. Shah N, Chari A, Scott E, *et al.* B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia* 2020. 34: 985–1005.

B.5 Appendices

The appendices included with this submission are as follows:

- Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
- 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 use 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: Belamaf comparison with PanoBorDex
- Appendix N: List price results
- Appendix O: Unanchored matching-adjusted indirect treatment comparison
- Appendix P: Supplementary economic modelling material
- Appendix Q: Clinical validation

NATIONAL INSTITUTE FOR HEALTH AN D CARE EXCELLENCE

Single technology appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Summary of Information for Patients (SIP)

October 2022

File name	Version	Contains confidential information	Date
ID2701 Belantamab mafodotin Summary of Information for Patients v1.0 06Oct2022.docx	V1.0	No	11th October, 2022

Summary of Information for Patients:

International template V.1

Introduction for patient organisations:

Background:

Understanding the experiences of patients, their families and carers, is becoming widely recognised as an important component in any Health Technology Assessment (HTA). Patients and patient organisations can help to provide this information through their engagement with the HTA process, and it is now becoming standard practice for HTA bodies to request input during the assessment process. It is therefore important that relevant patient representative have an informed and appropriate understanding of the medicine under review to optimise their input.

Why should I use a *Summary of Information for Patients*?

This *Summary of Information for Patients* is a supporting document that has been developed to provide you with relevant background information about the medicine under assessment. It aims to help you to structure a response to the HTA body, and comment on where you see the medicine adding most value to the patient community. The Summary has been prepared in response to patient organisations requesting this information. However, using it is optional.

The information within this Summary has been provided by the pharmaceutical company that is developing the medicine, and sent to you by the HTA body assessing the medicine. The information has been reviewed by the HTA body to ensure that the content is not commercial in any way. **(NOTE TO HTA: Please delete last sentence if HTA body is not reviewing the industry content for accuracy and balance).**

The Summary is intended to be used as background reading to inform and support your input into the HTA. Patient organisations are requested to not copy statements directly into their responses when providing input into the HTA review.

The Summary has four sections:

- **SECTION 1: Submission summary.** This includes a summary about the medicine, the pharmaceutical company that makes it and the HTA body undertaking the assessment of the medicine.

- **SECTION 2: Current landscape.** This section has details about the condition, how it is diagnosed and currently treated. Patient-based evidence about the condition may be included here to help set the scene as to where the medicine will potentially fit in and provide benefit to patients.

- **SECTION 3: The medicine.** This is where all of the details about the medicine can be found, such as how it works, how it is given or taken, and its key attributes.

- **SECTION 4: Further information, glossary and references.**

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the guidance included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers.

1a) Executive summary: In only a few sentences please provide a top-level summary to describe the medicine. Please outline the main patient population it is proposed to treat:

Belantamab Mafodotin ('Belamaf') is a new treatment for multiple myeloma, a cancer arising from plasma cells, a type of white blood cell that is made in the bone marrow. In myeloma, plasma cells which form part of the immune system (a complex group of cells and organs that protect the body against infection and disease) become abnormal and multiply uncontrollably.[1] MM symptoms are typically bone pain, fatigue, anaemia, recurring infections, and kidney damage. The clinical course of the disease, although variable, typically includes periods of treatment and remission separated by inevitable relapses (referred to as relapsed/refractory MM).
The main therapeutic goals are to control the growth of the myeloma, maximise the depth and duration of response to treatment, to improve overall survival (OS) and quality of life (QoL), as well as to alleviate symptoms, while minimising toxicity[2].

The NICE pathway for the treatment of MM is complex and characterised by the build-up of resistance to different classes of therapies as the disease progresses, referred to as 'refractory'. MM patients who are refractory to an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody (mAb) are referred to as triple class refractory (TCR). Belamaf is intended to treat patients who are triple class refractory and who have received at least four previous lines of therapy (5L+ TCR).

Belamaf is a type of drug known as an antibody-drug conjugate (ADC). ADCs consist of two parts joined together: a monoclonal antibody and a chemotherapy drug (a drug intended to kill cancer cells). The monoclonal antibody (belantamab) recognises a protein on the surface of myeloma cells called B-cell maturation antigen (BCMA). Myeloma cells have a lot of BCMA on their surface, while healthy cells have very little. This means that the belantamab can effectively target myeloma cells, and the effects on healthy cells are minimised. The chemotherapy drug linked to the belantamab is called mafodotin. It works by stopping normal cell processes in actively dividing cells and causing cell death. Mafodotin is too toxic to be given on its own – the linker attaching it to the belantamab stops it being released in the body until it is inside a myeloma cell. Once the belentamab has recognised the BCMA on the surface of a myeloma cell and attached to it, the belantamab mafodotin is absorbed into the myeloma cell, and the mafodotin is then released and acts to kill the cell. The belantamab attached to the BCMA on the cell surface also triggers an immune response against the myeloma cells[3].

1b) Name of the medicine (generic and brand name):

Belantamab Mafodotin (which is abbreviated in this submission to 'Belamaf') is sold under the brand name BLENREP.

1c) Authorisation: Please provide marketing authorisation information and link to the regulatory agency approval:

The Medicines and Healthcare Regulatory Agency (MHRA) and European Medicines Agency (EMA) granted a conditional marketing authorisation for Belamaf on 1st January 2021 and 25th August 2020 respectively [4, 5].

A 'conditional marketing authorisation' is a method of fast-tracking medicines which address significant unmet need. Manufacturers who receive a 'conditional marketing authorisation' must agree to certain conditions such as collecting more data on the medicine before they are allowed to give it to patients.

1d) Name, address and contact details of Summary author at the pharmaceutical company making the submission. Please provide this for patients/patient groups should they require additional information. In some countries, this section may be removed depending on local compliance regulations:

GSK
980 Great West Road
Brentford
TW8 9GS

Representative name and title: Katy Leonard – Patient Advocacy Lead, UK Oncology
Representative contact details (email/phone): katy.x.leonard@gsk.com / +4407376056322

1e) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Myeloma UK have engaged with GSK on a number of issues of importance to patients. In all cases they were paid for their time at a fair market rate for a virtual remote engagement:

- March 2022 spoke at an internal GSK event to raise awareness of the symptoms of Myeloma to GSK employees and share the work they do to support people affected by this disease.
- May 2022 shared their experiences in working with expert patient during the HTA process with other patient organisations at a GSK-sponsored workshop.
- June 2022 a representative from Myeloma UK attended a GSK Advisory board meeting with leading myeloma clinicians to ensure the needs and views of the myeloma patient community were represented in the discussions.
- September 2022 provided guidance on the design and content of patient support information.

Section 1f to be completed by the HTA organisation

1f) Health Technology Assessment (HTA) organisation:

- HTA organisation name and address:
  - National Institute for Health and Care Excellence (NICE)
  - 2 Redman Place, London E20
- Representative name and title:
  - XXXXXXX NICE TO COMPLETE XXXXX
- Representative contact details (email/phone):

- XXXXXXX NICE TO COMPLETE XXXXX
- Submission date:
  - 06/10/22
- If known, please also include an indication of the overall timelines for this health technology assessment:
  - Although dates are not certain, it is expected the first public committee meeting will be in March 23, with a decision published in May 23

SECTION 2: Current landscape

Note to authors: This Summary is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation may wish to add country-level information where needed to provide local country-level context.

Please focus this submission on the **target indication** rather than sub-groups, as this could distract from the focus of the Summary and the HTA review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition

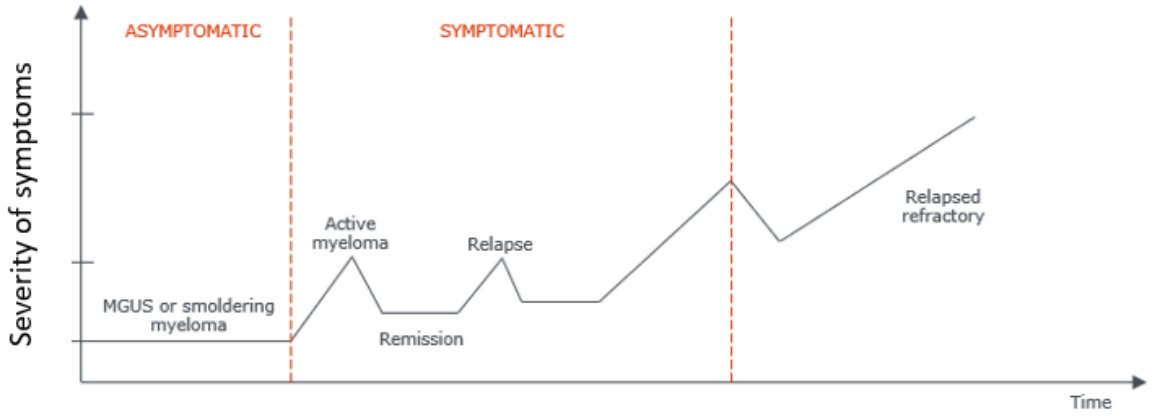
Please provide a few sentences to describe the main condition that the medicine is planned to treat. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available.
Myeloma is a type of cancer arising from plasma cells that are normally found in the bone marrow. Unlike many other cancers, myeloma can affect the body in several ways causing several symptoms and complications. This is due to the myeloma cells acting directly on the tissues of the body and releasing a variety of proteins and other chemicals into the bone marrow and bloodstream. ***Myeloma bone disease***[6] • Myeloma cells can interfere with the normal process of bone maintenance, a complication known as myeloma bone disease, which affects the majority of myeloma patients. It can cause areas of thinning in the bone (lytic lesions), which can lead to a variety of other complications. • Bone pain: Pain can be a symptom of bone disease. The middle or lower back, the rib cage and the hips are the most frequently affected areas. This pain is often persistent, dull and aching and is usually made worse by movement. • Bone fractures: The bones that most commonly fracture due to myeloma bone disease are the spine and the ribs. Breaks can sometimes occur with only minor pressure or injury. Fractures of the bones of the spine can lead to collapse of the spine with associated height loss and, occasionally, spinal cord compression. • Hypercalcaemia: This is a condition in which the level of calcium in the blood is too high. It can occur in myeloma patients as bone disease causes too much calcium to be released from the affected bones. The symptoms of hypercalcaemia are thirst, nausea, vomiting, confusion and constipation. ***Low blood cell count***[6] • Myeloma cells crowd out the bone marrow, preventing the normal number of blood cells from being produced. This can lead to further complications and symptoms. Treatment for myeloma can also cause a low blood cell count. • Fatigue: persistent fatigue (an overwhelming tiredness) is a common symptom of myeloma and its complications. It can also be a side effect of the treatment given. It can be caused by anaemia stemming from a reduced red blood cell count but there may also be a number of other factors causing it. • Anaemia: this is a drop in the number of red blood cells or the oxygen-carrying haemoglobin they contain. It can occur as a result of the myeloma or as a side effect of treatment and can cause fatigue, weakness or breathlessness.

- Infection: this is common in myeloma patients because myeloma and its treatments can interfere with the immune system, reducing the while blood cell count, making patients more susceptible to infection.

Kidney damage[6]

- This can occur in myeloma patients for a variety of reasons. The abnormal protein produced by myeloma cells can damage the kidneys, as can hypercalcaemia. In addition, some of the drugs used to treat myeloma can sometimes cause kidney damage.

Unfortunately, there is no cure for multiple myeloma. There are multiple effective treatment options, but the malignant (cancerous) cells will inevitably mutate and change to become resistant to these treatments over time[2]. Consequently, management of multiple myeloma is concentrated around managing 'relapse', which is the period between the disease mutating and a new effective treatment being found[7]. Throughout the submission and this summary, reference to 'fifth line' or 'fourth line' and so on is made – this counts the number of different treatments which have been tried, and each treatment usually ends in a 'relapse' once the disease has become 'refractory' (unmanageable / resistant) to that treatment. In some circumstances it is possible to try a new line of treatment without a relapse (for example if a patient experiences severe side effects to a particular treatment). See the figure below for an illustration of the usual pattern of progression for myeloma.



Source: Adapted from Kurtin et al. 2013[7].

Treatment for multiple myeloma is therefore very complicated, with the options available to patients depending on the treatments they have already tried and relapsed on. Belamaf is expected to be used in 'fifth-line-plus, triple-class-refractory' patients, meaning it will be used by patients who have tried at least four prior lines of therapy and have found that three key kinds of treatment will no longer help manage their condition. These three treatments are:

1. Immunomodulatory Drugs (IMiDs), which are most commonly taken early in the treatment pathway. The most common IMiD is lenalidomide, although other options for patients are pomalidomide and thalidomide.
2. Proteasome inhibitors (PIs), which are taken throughout the treatment pathway and come in different forms. The most common PI is bortezomib, but some patients might take carfilzomib in the second line if their clinician thinks it is more appropriate. Ixazomib is another option in this area which is available to some patients from the third line onwards as part of the Cancer Drugs Fund.
3. Anti-CD38 monoclonal antibodies, which include daratumumab and isatuximab. This class of drugs is available at multiple points in the treatment pathway (sometimes as

part of the Cancer Drugs Fund) but many patients will first encounter anti-CD38s in the second line setting as part of the daratumumab, bortezomib and dexamethasone triplet, although this is currently only available through the Cancer Drugs Fund.

Belamaf is potentially appropriate for a small number of patients within the NICE treatment pathway (those with triple-class refractory myeloma at fifth-line-plus). However, in these patients Belamaf is one of only a limited number of treatments with a chance of working, and therefore potentially of high importance to these patients.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

If relevant to the medicine submission, please briefly explain how the condition is diagnosed and how this impacts patients:

Evidence shows that myeloma patients experience some of the longest delays to diagnosis of all cancer patients, and this remains the case despite national referral guidelines for suspected cancer. This is in part due to the vague and non-specific nature of symptoms.

In general, a blood or urine test can be used to identify myeloma. This is because myeloma cells produce a large amount of a certain type of protein (commonly called a 'paraprotein' or 'M protein') which serves no useful function[1]. Therefore, finding paraprotein in the blood or urine is suggestive that myeloma cells are present in the body.

There are benign (non-cancerous) conditions which cause paraprotein to be produced, such as Monoclonal Gammopathy of Undetermined Significance (MGUS)[8]. MGUS can turn into multiple myeloma, but this is rare[8]. Therefore, often doctors will perform another test to determine whether the paraprotein is caused by myeloma (and needs treatment) or a benign condition like MGUS (which doesn't typically require treatment). This test will sometimes be an x-ray to look for bone damage (which is common in myeloma but very rare in MGUS) or taking a sample of bone marrow and looking at it under the microscope to look for evidence of myeloma cells. However, these are not the only tests that may be offered, and in addition to diagnosing myeloma, patients may be offered tests to identify what the most appropriate treatment may be.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is considered the standard of care for this condition? Please give emphasis to the specific setting and condition being considered by the HTA body in this review
- Please also consider:
    - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are
    - What are the short- and long-term implications of using current medicines?
- Please reference current treatment guidelines where needed
- Please conclude by stating how you feel the medicine will potentially address the unmet needs of patients

Treatment for MM is complex and the options available to patients depend on which options they have previously received.

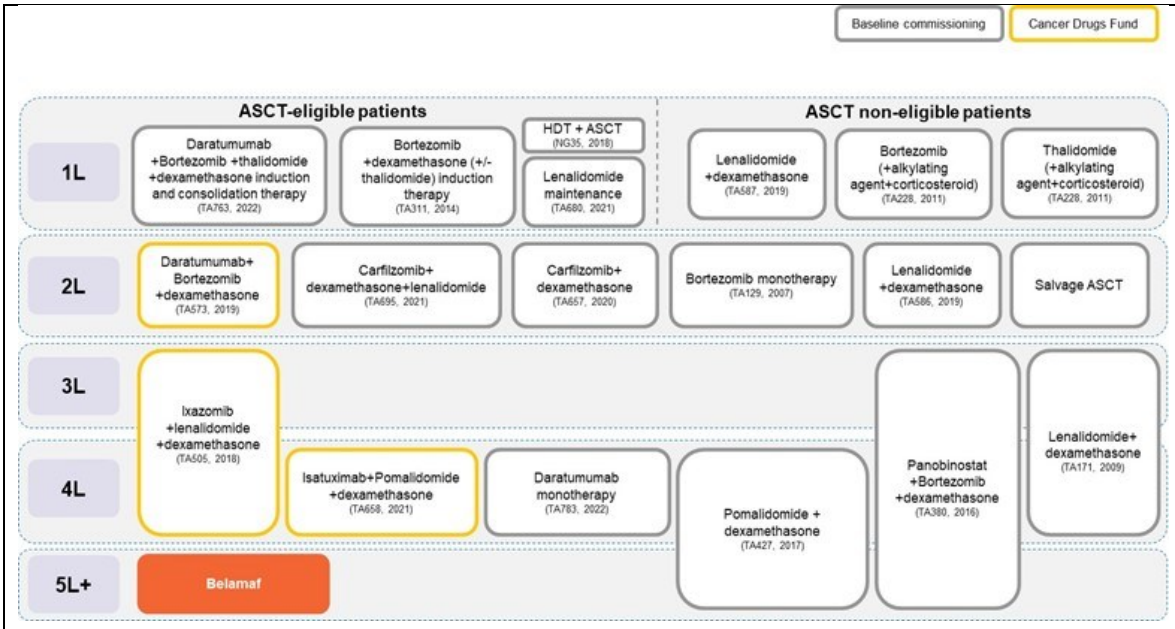
Treatment options from diagnosis to 5L

- Upon diagnosis, immediate treatment may not always be required and the results from various tests and investigations, together with symptoms will help determine when treatment should be initiated.
- When an immediate treatment is not required, regular monitoring for signs of progression and vigilance for any changes in symptoms and general health will be observed.
- Initial treatment for MM is almost always with a combination of drugs. After an initial course of treatment (induction therapy) often consisting of daratumumab, bortezomib, thalidomide and dexamethasone, patients may be suitable to receive a more intensive treatment called high-dose therapy and stem cell transplantation (HDT-SCT). Subsequently, maintenance therapy may be considered to maximise remission (lenalidomide maintenance therapy).
- If a patient is not suitable for a bone marrow transplant, they will often have lenalidomide in combination with dexamethasone (LenDex) although for high-risk patients bortezomib-based triplets may be considered.
- Upon progression, patients usually receive a subsequent line of therapy (second line [2L]). The two main options at 2L are daratumumab + bortezomib + dexamethasone or carfilzomib, lenalidomide and dexamethasone.
- Following a second relapse (3L), three treatment options are approved by NICE in 3L and beyond (3L+), panobinostat, bortezomib and dexamethasone (PanoBorDex), LenDex and ixazomib, lenalidomide and dexamethasone (IxaLenDex, available via the Cancer Drug Fund [CDF] in 3L and 4L).
- In the fourth line setting (4L), options available in the 3L+ setting may also be considered for patients if they are eligible. Other options include: pomalidomide and dexamethasone (PomDex recommended for 4L+), daratumumab (available at 4L) and isatuximab, pomalidamide and dexamethasone (IsaPomDex, available via the Cancer Drug Fund [CDF] for 3L and 4L).

Current treatment options in 5L+ TCR

- For patients at fifth line and beyond (5L+) who are refractory to a PI, an IMiD and an anti-CD38 two treatments are currently available in the UK, PomDex and PanoBorDex.
- An England-based real-world evidence study performed by the company indicated that while some use of PanoBorDex is observed, the majority of 5L+ TCR MM patients receive PomDex which is therefore considered as the most relevant comparator in this appraisal.
- If no alternative options are suitable in this setting, therapy may be received via a clinical trial and/or compassionate use scheme. Chemotherapy based palliation may also be considered.

The diagram below depicts the treatment pathway for patients with RRMM and includes the anticipated positioning of Belamaf in the 5L+ TCR MM setting.



The considerations described above highlight the high unmet need for treatment options with a new mechanism of action for patients who are in the 5L+ setting and are refractory to the three main pillars of MM management (PIs, IMiDs and anti-CD38).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might include outputs from patient preference studies, when conducted in order to show what matters most to patients and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE evidence that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Any such evidence included in the Summary should be formally referenced wherever possible.

MM and its treatment can bring many changes to the daily life of patients and their carers including a physical and emotional burden.

Compared to people without myeloma, patients report that having the disease significantly impacts physical functioning and social activities [9]. The symptoms of myeloma can negatively impact a person's ability to work [10] resulting in financial worry about needing to discontinue employment or reduce their earning capabilities [10, 11].

Furthermore, difficulty in processing the diagnosis of MM or relapses throughout the course of the disease can affect mental health and generate anxiety [10]. Furthermore, it is not only the physical symptoms that pose challenges; mental difficulty in accepting their diagnosis and/or relapse can lead patients to have low mood and a lack of motivation [10, 11].

In addition to patients themselves, their caregivers' HRQoL can also be negatively affected. Caregivers are often a close member of the family which can further impact the emotional burden a person may feel regarding the possibility of death and suffering [12]. The burden of caring for

someone with myeloma may restrict the caregiver's daily activities, leading to isolation and a lack of social support [13].

SECTION 3: The medicine

3a) How does the medicine work?

What are the important features of this medicine?

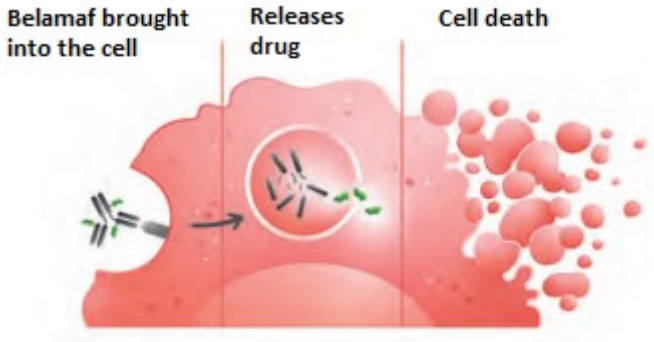
Please outline as clearly as possible important details relating to the mechanism of action and how the medicine interacts with the body that you consider relevant to patient groups.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

Belamaf is a type of drug known as an antibody-drug conjugate (ADC). ADCs consist of two parts joined together: a monoclonal antibody and a chemotherapy drug (a drug intended to kill cancer cells). The monoclonal antibody (Belamaf) recognises a protein on the surface of myeloma cells called B-cell maturation antigen (BCMA). Myeloma cells have a lot of BCMA on their surface, while healthy cells have very little. This means that the belantamab can effectively target myeloma cells, and the effects on healthy cells are minimised. The chemotherapy drug linked to the belantamab is called mafodotin. It works by stopping normal cell processes in actively dividing cells and causing cell death. Mafodotin is too toxic to be given on its own – the linker attaching it to the belantamab stops it being released in the body until it is inside a myeloma cell[3].

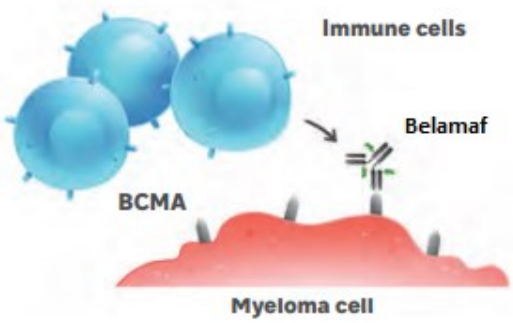
Belamaf works in two ways[3]:

1. Once the belantamab has recognised the BCMA on the surface of a myeloma cell and attached to it, the belantamab mafodotin is absorbed into the myeloma cell, and the mafodotin is then released and acts to kill the cell.



Source: GSK internal

2. The belantamab attached to the BCMA on the cell surface also triggers an immune response against the myeloma cells.



Source: GSK internal

The use of an ADC is innovative (Belamaf is the only such drug approved for MM) and Belamaf is currently the only licensed therapy in Great Britain that targets the B-cell maturation antigen. Other treatments target different pathways, and that means that when the disease mutates to become refractory to other treatments it may not also be refractory to Belamaf. This means that patients may receive treatment for more relapses (and hence hopefully live longer in a better quality of life) because no other NICE-approved drug can recognise cells expressing B-cell maturation antigen.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes? / No? If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination medicine, please ensure the sections on efficacy (3d), QoL (3e) and safety/side effects (3f) focus on data that relate to the combination, rather than the individual medicine.**
Belamaf is used in monotherapy (not taken in combination with any other medicines)[4].

3c) Administration and dosing

How and where is the medicine given or taken? Please include the amount and how often the medicine should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Belamaf is given as a 30-min infusion once every three weeks, in the absence of no infusion related reactions. Typically, Belamaf will be given until the myeloma cells start to grow again and become resistant to this treatment. However, some patients will experience side effects that may lead to a discontinuation and may then be offered a different treatment. Side effects can also be managed by dose modifications such as dose reductions or dose delays, as described in Summary of Product Characteristics for the drug [4]. As described above, the patient group who will be eligible for Belamaf have a great need for treatments with a new mechanism of action. Given the short infusion time and since patients usually attend frequent hospital visits for disease monitoring, the administration route of Belamaf is not expected to negatively impact patients QoL.

3d) Efficacy

Efficacy is the measure of how well a medicine works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the medicine is at treating the main condition outlined in section 2a. If there are data available, please also describe how it is different to other medicines available outlined in section 2c?

DREAMM-2 trial

The efficacy and safety of Belamaf was demonstrated in a non-comparative open-label dosing study called DREAMM-2. In the study, 97 patients in line with the licensed dose of 2.5 mg/kg were treated with Belamaf, and their clinical progress recorded. The numbers below refer to progress recorded at 13 months, which is the most recent data that the Company has published.

Overall, clinically meaningful (overall responses achieved by 32% of patients) and deep (58% of responders with a ≥VGPR) responses with single-agent belamaf 2.5 mg/kg were sustained at the 13-month follow up in the DREAMM-2 study. The median estimated OS was 13.7 months in the 13-month analysis, which is substantially longer than that reported in a similar population[14]. The median estimated DoR in the 2.5 mg/kg group was 11 months. In the overall population, the median PFS was 2.8 months; in patients who had an sCR or a CR, the median PFS was not reached. Furthermore, in patients who had a ≥VGPR, the median PFS was 14 months. In patients with deep responses (≥VGPR) who were tested for MRD status, 5 of 13 (38%) achieved MRD negativity at the 13-month analysis.

Comparative evidence vs PomDex

In the absence of direct comparative evidence for the main comparator in the 5L+ TCR MM population PomDex, a real world evidence study using the England's National Cancer Registration and Analysis Service (NCRAS) database, was performed by the Company.

The results of this study were then used to assess how Belamaf is likely to perform compared to PomDex via a direct (naïve) comparison of the outcomes and an indirect treatment comparison aiming to adjust for differences observed between the population baseline characteristics.

Despite the challenges arising from the population differences between the DREAMM-2 trial and the NCRAS study, the results suggests that Belamaf offers benefits in terms of OS and PFS when indirectly compared to PomDex.

3e) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand the trade-offs and willingness to accept benefit/risk by patients. Please include all references as required.

HRQoL in the DREAMM-2 trial

Patients in the DREAMM-2 trial were asked to complete a questionnaire about their quality of life, called the EORTC-QLQ-C30. This is a commonly used quality of life survey that isn't specific to any particular disease, and includes questions about multiple topics which contribute to quality of life. For example, it asks about 'Physical Functioning', which measures ability to do essential tasks (such as walking up the stairs, carrying groceries, etc.) and 'Fatigue' (weakness in arms or legs,

becoming easily tired, lacking energy). In general, quality of life in every category was the same at the start and end of treatment.

Patients were also asked to complete a second questionnaire, the EORTC-QLQ-MY20. This is a myeloma-specific survey and similar results were consistent with EORTC-QLQ-C30 questionnaire.

Patients satisfaction interviews

In addition to the evidence from the DREAMM-2 trial, a group of 104 patients were interviewed at some point during their treatment with Belamaf, with 26 interviewed throughout the entire treatment process. Despite ocular symptoms, overall, patients reported high satisfaction while on treatment and a desire to remain on treatment, particularly in responders. [15]

A potentially important area looked at in the group discussions was weighing up the benefits and risks of the side effects of Belamaf, especially the side effects relating to vision. All patients agreed that they anticipated the effects on their vision they experienced, and although six patients (23%) considered stopping treatment because of these symptoms, only three patients (11.5%) actually did. Some comments made by participants about these symptoms are reproduced below:

- *"Aside from the eyes I had no other side effects, and I don't know if the eyes will recur or if they won't but even if they do, that's okay. I'd rather be alive."*
- *"There are side effects to absolutely any treatment you have and some of the treatments I've had have had much worse"*
- *"I thought seriously about not continuing, and if there had been another drug for me at this point, approved and ready for me to get it, I might have stopped it, but there is not... so I just decided that I would just put up with not being able to see"*

3f) Safety of the medicine and side effects

When a regulatory or HTA body makes a decision about a medicine, it will pay close attention to the benefits of the medicine in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this medicine, and include benefit/risk assessment details where possible. This will support patient group reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen and how they could potentially be managed. Where appropriate and relevant to patients, please also highlight risk reduction comparisons with other treatments.

Where it will add value or context for patient readers please included references to the Summary of Product Characteristics from regulatory agencies etc.

As of the 13-month analysis, no new safety signals were identified relative to the primary analysis. The occurrence of AEs was comparable in subgroups of patients with high-risk cytogenetics and renal impairment. As previously described, thrombocytopenia was common but was considered self-limited; Infusion-related reactions (IRRs) occurred early in treatment and were mainly grade 1 and 2. The low rates of grade ≥3 hematologic AEs (thrombocytopenia, 21 of 95 patients [22%]; anemia, 20 of 95 patients [21%]; and neutropenia, 10 of 95 patients [11%]) and IRRs of any grade (20 of 95 patients; 21%), coupled with the short outpatient administration time and no mandatory requirement for premedication, make belamaf an attractive treatment option[16].

Although keratopathy was frequently observed on eye examination, fewer patients experienced symptoms, most did not experience a clinically meaningful best corrected visual acuity (BCVA) decline, and events rarely led to treatment discontinuation[16].

Changes in BCVA were manageable with dose modifications and resolved around the time of the next eye examination (conducted approximately every 21 days). No permanent complete loss of vision has been reported to date. Corneal events associated with belamaf may be adequately managed by close liaison with eye care professionals, according to the keratopathy and visual acuity (KVA) scale guidelines[16].

3g) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the medicine. Please provide a top-level summary for each, such as title, location, patient group size, completion dates etc.

There are multiple ongoing clinical trials of Belamaf. Four of these trials are likely to be of particular interest to UK patient groups:

DREAMM-3 (NCT04162210)

The phase 3, multicentre, randomised, open-label DREAMM-3 study is planned to randomise 320 participants (2:1) to receive either belantamab mafodotin or pomalidomide plus dexamethasone. Patients treated with ≥2 prior lines of therapy, including ≥2 consecutive cycles of both lenalidomide and a proteasome inhibitor, and refractory to the last line of treatment, will be eligible for inclusion. The primary endpoint is PFS, and overall survival is a key secondary endpoint.

DREAMM-7 (NCT04246047)

DREAMM-7 is an ongoing, randomised, open-label, global, multicentre, phase 3, two-arm study in patients with measurable RRMM who had received ≥1 prior therapy with documented disease progression. Patients aged ≥18 years with Eastern Cooperative Oncology Group Performance Status 0-2, adequate organ system function will be eligible. Patients intolerant/refractory to daratumumab or bortezomib, or with prior exposure to anti-BCMA therapy, will be excluded. Approximately 478 patients will be randomised (1:1) to Arm A (belantamab mafodotin + bortezomib + dexamethasone) or Arm B (daratumumab + bortezomib + dexamethasone). The primary endpoint is progression-free survival (PFS; time from randomisation to the earliest date of documented disease progression or death [any cause]). The key secondary endpoint is minimal residual disease negativity rate, as assessed by next-generation sequencing.

DREAMM-8 (NCT04484623)

This phase 3, two-arm, randomised, open-label, multicentre study will include patients with measurable RRMM who have received ≥1 prior line of therapy (including lenalidomide), with documented disease progression. Patients aged ≥18 years with Eastern Cooperative Oncology Group Performance Status 0-2, adequate organ system function will be eligible. Patients with prior exposure to BCMA-targeted therapies or pomalidomide and those intolerant/refractory to bortezomib will be excluded. Approximately 450 patients will be randomised (1:1) to Arm A (belantamab mafodotin + pomalidomide + dexamethasone) or Arm B (bortezomib + pomalidomide + dexamethasone). No more than 50% of participants with two or more prior lines of treatment will be enrolled. The primary endpoint is progression-free survival (PFS; time from randomisation to the earliest date of documented disease progression or death [any cause]). Minimal residual disease negativity rate is a key secondary endpoint.

3h) Summary of key benefits to patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the medicine for patients, caregivers and their communities when compared with current medicines
- Please outline any data from the clinical trials listed above that support this
- This should inform any relevant cost or value considerations in the following section (3j)

The key benefits of Belamaf to 5L+ MM patients, carers and society include:

- Belamaf is a monotherapy with a high efficacy demonstrated by deep and durable responses and a manageable, well-characterised safety profile in patients with 5L+ TCR MM treated in the DREAMM-2 trial.
- Belamaf represents the addition of a new mechanism of action into the NICE MM treatment paradigm to further improve patients' survival by delaying the stage at which patients require palliative care. This may also help to reduce some of the emotional burden by providing hope to both patients and their relatives in the 5L+ TCR MM setting.
- Belamaf is easy to deliver on an outpatient basis, and it is an "off the shelf" BCMA-targeted therapy, meaning that treatment can be initiated immediately, without the need for a waiting period. Furthermore, Belamaf represents a steroid-free option in the 5L+ TCR setting which may improve QoL by preventing the side-effects associated with steroids.

3i) Value and economic considerations (this section may be considered as not relevant in some countries or HTA assessments and can be deleted by the HTA body in those cases)

Introduction for patient groups:

Health services want to get the most value from their budget and therefore needs to decide whether a new medicine provides good value compared with other medicines. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the medicines already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the HTA appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant endpoints, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or adverse events of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g. travel costs, time-off work)?

Instructions to manufacturer: This is intended as a single-page summary for patient groups and needs to be completed in non-technical language. Focus should be on a summary of the key costs/drivers used in any models, the value afforded by the medicine, and any financial implications that may be of relevance to patients/patient groups, rather than a detailed health economic justification (cost/QALY, for example).

- What were the important improvements in health from the medicine compared with the medicines already in use that support its value offering (e.g. longer survival times or reduction in severity or frequency of symptoms)? Were there important side effect differences between the medicines that support the value of the medicine?
- Would the medicine lead to any cost implications (positive or negative) for the health service (e.g. number of days in hospital)?
- Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g. where it is given or the monitoring that is needed)?

Belamaf a step change in the clinical management of 5L+ TCR MM patients who are currently left to feel abandoned and to face an extremely poor prognosis.

Whilst associated with uncertainty, the relative efficacy of Belamaf vs PomDex suggests that Belamaf has the potential to further improve survival outcomes for a 5L+ TCR population.

The company performed an economic analysis to assess the cost-effectiveness of Belamaf vs PomDex in a population of patients with 5L+ TCR MM. The results of this analysis confirmed that Belamaf represents good value for money for the NHS particularly when reflecting the severity of disease in the determination of the willingness to pay threshold of £36,000 to £51,000 per QALY gained.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patient groups would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the HTA assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Response:

Further information on multiple myeloma and getting involved with a patient group:

- NHS website for multiple myeloma: https://www.nhs.uk/conditions/multiple-myeloma/
- NICE guideline for multiple myeloma: https://www.nice.org.uk/guidance/ng35
- Myeloma UK's website: https://www.myeloma.org.uk/
- Information on understanding multiple myeloma generally: https://www.myeloma.org.uk/understanding-myeloma/what-is-myeloma/
- Information on Belamaf specifically: https://www.myeloma.org.uk/documents/belantamab-mafodotin-horizons-infosheet/

Further information on HTA and the role of patient groups**:**

- EUPATI guidance on patient involvement in HTA: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

ADC	Antibody-drug conjugate
BCMA	B-cell maturation antigen

BCVA	Best corrected visual acuity
Belamaf	Belantamab mafodotin
IMiD	Immunomodulatory drug
IRR	Infusion-related reaction
IxaLenDex	Ixazomib, lenalidomide and dexamethasone
KVA	Keratopathy and visual acuity
LenDex	Lenalidomide and dexamethasone
mAb	Monoclonal antibody
MM	Multiple myeloma
NCRAS	National Cancer Registration and Analysis Service
OS	Overall survival
PanoBorDex	Panobinostat, bortezomib and dexamethasone
PI	Proteasome inhibitor
QoL	Quality of life
TCR	Triple class refractory

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Kyle R, Rajkumar SVJL. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. 2009;23(1):3-9.
2. Sive J, Cuthill K, Hunter H, Kazmi M, Pratt G, Smith D, et al. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. 2021;193(2):245-68.
3. Myeloma UK. Belantamab mafodotin Horizons Infosheet 2018 [Available from: .
7. Kurtin SJND. The Changing Landscape of Multiple Myeloma. 1969;17(6):7-11.
8. Kyle R, Durie B, Rajkumar SV, Landgren O, Bladé J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. 2010;24(6):1121-7.
9. Ludwig H, Pönisch W, Knop S, Egle A, Hinke A, Schreder M, et al. PS1509 QUALITY OF LIFE IN PATIENTS WITH RRMM DURING IXA-THAL-DEX INDUCTION AND IXAZOMIB MAINTENANCE THERAPY IN COMPARISON TO THE GENERAL POPULATION. 2019;3(S1):695-6.
10. Bennink C, van Der Klift M, Scheurer H, Sonneveld P, Duijts SFJEJoCC. Perspectives on returning to work of multiple myeloma patients: A qualitative interview study. 2021;30(6):e13481.
11. Myeloma UK. Fatigue and myeloma. Symptoms and complications Infoguide 2018 [Available from: .
12. Beattie S, Lebel SJPo. The experience of caregivers of hematological cancer patients undergoing a hematopoietic stem cell transplant: a comprehensive literature review. 2011;20(11):1137-50.
13. Kurtin SJND. Caregivers of multiple myeloma survivors. 1969;17(6):25-32.
14. 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. 2019;33(9):2266-75.
15. Eliason L, Correll J, Martin M, Cardellino A, Opalinska J, Piontek T, et al. Patient-Reported Experiences During and Following Treatment With Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study. 2020;136:1.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Addendum to the Company submission

GSK confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

February 2023

File name	Version	Contains confidential information	Date
[ID2701] Belantamab Mafodotin Addendum to Company evidence submission 14Feb2023 AIC_CIC_redacted	**v1.0**	**Yes**	**14th February, 2023**

1 Background and summary

The original company evidence submission submitted on 6th October 2022 was based on the data from the final analysis of the DREAMM-2 trial and from the results of a study of the NCRAS dataset. This addendum to the submission includes additional evidence generated from the [redacted] ([redacted]) study and from a [redacted] subset of 5L+ TCR MM patients included in the DREAMM-3 trial.

No changes have been made on the decision problem considered in the original submission.

The additional evidence from a UK RWE study demonstrates that Belamaf is a highly efficacious option for UK patients with 5L+ TCR MM. Clinically meaningful (overall responses achieved by [redacted] of patients) and deep ([redacted] of responders with ≥VGPR) responses with single agent Belamaf were achieved in this cohort of [redacted] heavily pre-treated patients. The median OS was [redacted] months which is broadly consistent with the corresponding value derived from the DREAMM-2 trial (median OS was [redacted] months), and the median PFS was [redacted] months which is substantially longer than that reported in the DREAMM-2 trial (median PFS was [redacted] months).

The company revised base case uses the most comparable sources to inform the efficacy of Belamaf vs PomDex, and as such provide the most robust demonstration of the cost-effectiveness of Belamaf vs PomDex in the UK. Nonetheless, the Company's original base case using clinical and safety data from the DREAMM-2 trial, despite limitations due to the paucity of data for the comparator, also confirms that Belamaf represents a cost-effective use of NHS resources when compared with PomDex.

In the new base case using the efficacy data from the [redacted] study, the outcomes of the economic model suggest that a higher proportion of patients are alive and in the progression-free health state which translates into a higher level of QALYs while incurring lower costs over the lifetime horizon. As such, Belamaf was found to be dominant in the model when compared to PomDex and represents a cost-effective use of NHS resources.

In conclusion, the evidence presented in this addendum suggests that Belamaf not only can increase the range of effective treatment options available to treat a population where there is exquisitely high unmet need, but it also represents an efficacious treatment option for patients with 5L+ TCR MM and is a cost-effective use of NHS resources.

2 Summary of methodology of the relevant clinical effectiveness evidence

2.1 Belamaf ([redacted] study)

2.1.1 Summary of study methodology

Background and objectives

[redacted]. This is the same population as the current license and that evaluated in this appraisal. As of the end of Jan 2023, [redacted] patients have been treated with Belamaf within the UK [redacted] showing the high unmet need for Belamaf in the 5L+ TCR setting (Figure 1A). Experience has been gained in over [redacted] sites across the UK demonstrating the broad applicability of Belamaf as a BCMA-targeted therapy (as of the end of August 2022 and inclusive of both large university and small district general hospitals; Figure 1B).

Figure 1: (A) Belamaf [redacted] – UK cumulative patients treated; (B) Geographical distribution of [redacted] experience in the UK

[redacted]

An abstract for a RWE study describing outcome data collected from the Belamaf UK [redacted] has been submitted for publication to British Society for Haematology (BSH) 2023.[1] The aim of this study is to evaluate the efficacy and tolerability from the routine care of single agent Belamaf in the treatment of 5L+ TCR. This study is a retrospective national analysis of the [redacted], and is independent of the Company (i.e.,

the Company have not been involved in its design or management). The project lead of this study shared the abstract in confidence with the Company in Jan 2023 and provided their consent for the Company to incorporate this data within this appraisal. The following sections summarise the [redacted] study methodology.

Study design

The [redacted] study is a non-interventional retrospective multi-centre evaluation of relapsed MM patients who have received [redacted] single agent Belamaf in the UK, in line with its licensed indication for patients with 5L+ TCR MM. The aim of the project was to evaluate the efficacy and tolerability of Belamaf.

Data on baseline characteristics and key efficacy outcomes (overall response rate [ORR], event-free survival [EFS], overall survival [OS]) and safety outcomes are reported in the BSH 2023 abstract.[1] Study protocol[2] and additional data on outcomes have been obtained by the Company upon request from the study author. This data has allowed the Company to explore the feasibility of an indirect treatment comparison (ITC) comparing Belamaf within this data source to the PomDex patients within the Company's analysis of the NCRAS dataset presented in the original submission.

Inclusion and exclusion criteria to identify patients with 5L+ TCR MM

Patients were eligible for inclusion into the analysis of the [redacted] study, which will be referred to as the [redacted] dataset throughout, if they received Belamaf at fifth line or later and were TCR. This is the same population as the current license and represents the cohort of patients relevant to the decision problem evaluated in this appraisal.

TCR was pre-coded in the data received by the company – where individuals were classed as refractory to all three treatment classes of PI, IMiD, anti-CD38 mAb.

The clinical outcomes sought in the [redacted] dataset are presented in Table 1.

The full methodology of the [redacted] study is presented in the study protocol.[2]

Table 1. [redacted] outcome measures definition

Measure	Description
TTNT	Defined as the time from the start of the first dose to the date of first dose of the next line of therapy or death from any cause
OS	Defined as the time from the start of the first dose to the date of death
TTD	Defined as time from the start of the first dose until discontinuation
PFS	Defined as the time from the start of the first dose of belantamab to the date of first documentation of disease progression or death from any cause
ORR	According to IMWG definition: complete response, stringent complete response, very good partial response, partial response, minor response/stable disease, and progressive disease

Abbreviations: IMWG, International Myeloma Working Group; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation; TTNT, time to next treatment

Study outcomes

Patients were included from [redacted] myeloma centres across the UK.* From the cohort of [redacted] patients in the [redacted] study that received Belamaf, [redacted] were TCR and of these, [redacted] were 5L+ TCR. For the [redacted] patients in the 5L+ TCR subgroup, median follow-up was [redacted] months† (IQR [redacted] months) and the median number of cycles of Belamaf received was [redacted] (IQR [redacted] months).

2.1.2 Statistical analysis

The statistical analysis undertaken in the [redacted] study is presented in Table 2.

Table 2. [redacted] study statistical analysis

Outcome populations	The ITT population from the [redacted] study
Statistical analysis	**Summary statistics** Continuous variables were summarised by means and medians. Frequencies and percentages were presented for categorical data. Subjects were described in terms of their baseline demographic and clinical characteristics. **Missing data** The proportion of missing data was displayed. No imputations were carried out.

Abbreviations: ITT, intention-to-treat; [redacted], [redacted]

* Note that 1 patient from the Republic of Ireland (ROI) was included in the study.
† Note that median follow-up is lower than median PFS due to right-censoring in the dataset for PFS.

2.1.3 Critical appraisal of the [redacted] study

A complete quality assessment for the [redacted] study is provided below using the Downs and Black checklist (Table 3).[3]

Table 3. Downs and Black checklist for the [redacted] study

Criteria	Critique
Is the hypothesis/ aim/ objective of the study clearly described?	Unable to determine
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Unable to determine
Are the characteristics of the patients included in the study clearly described?	Yes
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Not applicable – groups of subjects were not compared in this study
Are the main findings of the study clearly described?	Unable to determine – only descriptive data has been provided
Does the study provide estimates of the random variability in the data for the main outcomes?	No
Have all important adverse events that may be a consequence of the intervention been reported?	No – data on adverse events are not available
Have the characteristics of patients lost to follow-up been described?	No
Have actual probability values been reported?	No
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Not applicable
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Not applicable
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine
Was an attempt made to blind study subjects to the intervention they have received?	No – not a blinded study/ comparison

Was an attempt made to blind those measuring the main outcomes of the intervention?	No – not a blinded study/ comparison
If any of the results of the study were based on 'data dredging', was this made clear?	Not applicable – no results were based on data dredging
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes – Kaplan-Meier survival analyses account for length of follow-up
Were the statistical tests used to assess the main outcomes appropriate?	Not applicable – no statistical hypothesis tests were performed and only descriptive results are provided
Was compliance with the intervention/s reliable?	Unable to determine
Were the main outcome measures used accurate (valid and reliable)?	Partial – mortality endpoints are valid and reliable. TTNT and TTD were based on algorithms applied to routine data so are as valid and reliable as possible in the absence of explicitly collected data.
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Not applicable – there were no intervention groups but all data is drawn from national data sources.
Were study subjects randomised to intervention groups?	Not applicable – there were no intervention groups
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Not applicable – there were no intervention groups
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Not applicable – only descriptive analysis was performed
Were losses of patients to follow-up taken into account?	Yes – Kaplan-Meier analysis accounts for loss to follow-up
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Not applicable – no treatment effect was assessed as it was a descriptive study only

2.2 Belamaf and PomDex (DREAMM-3)

2.2.1 Summary of trial methodology

DREAMM-3 (NCT04162210) is an ongoing phase 3, open-label, randomised multi-centre study to evaluate the efficacy and safety of single agent Belamaf compared with PomDex in patients with relapsed/refractory multiple myeloma (RRMM) who received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and an PI (given separately or in combination), and who have failed their last line of treatment. The study is being conducted in 19 countries in 184 sites, including 10 UK sites. There is a [redacted] 5L+ TCR population included with the DREAMM-3 population, which consists of [redacted] PomDex patients and [redacted] Belamaf patients. It should be noted that this was not a pre-specified subgroup and the DREAMM-3 trial was not powered to report on this subgroup.

In the ITT population, a total of 325 participants were randomised in a 2:1 ratio to receive either single agent Belamaf administered or PomDex. Participants were stratified based on the following: previous treatment with antiCD38 (Y/N), stage (International Staging System [ISS]) (I/II or III), and number of prior lines of therapy (≤3 vs >3).

Belamaf dosage was 2.5 mg/kg IV Q3W and PomDex dosage was pomalidomide 4 mg orally daily on Days 1 to 21 Q4W (28-day cycle) with dexamethasone 40 mg once weekly (Days 1, 8, 15, and 22) Q4W (28-day cycle). For participants >75 years old, the dose of dexamethasone was 20 mg once weekly (Days 1, 8, 15, and 22) Q4W (28-day cycle). The primary efficacy endpoint for the ITT population was PFS, defined as the time from the date of randomisation until the earliest date of documented disease progression (according to International Myeloma Working Group [IMWG] Response Criteria) or death due to any cause.

Other outcomes for the ITT population included:

- Key secondary endpoint: OS
- Secondary endpoints: ORR, clinical benefit rate (CBR), duration of response (DoR), time to response (TTR), and time to progression (TTP)

- Selected additional endpoint for the cost-effectiveness analysis: Time to treatment discontinuation (TTD)

The data presented in this addendum corresponds to the primary analysis of DREAMM-3. The primary analysis was conducted at the time of observing approximately 151 PFS events and the first 320 randomised subjects have been followed for a minimum of 4 months, as per the Statistical Analysis Plan.[4]

The median duration of follow-up for the ITT population (3L+ Len and PI exposed) for the primary analysis is [redacted] months for the PomDex arm and [redacted] months for the Belamaf arm.

A summary of the study methodology is reported in Table 4, with the definition of the efficacy outcome measures in Table 5. Full methodology is presented in the study protocol.[5][redacted]

Table 4. DREAMM-3 methodology

Study	DREAMM-3 study protocol and unpublished analysis
Trial design	Phase 3, open-label, randomised, two-arm multi-centre study

Eligibility criteria	**Inclusion criteria:**
	• Age 18 or older
	• ECOG performance status of 0-2
	• Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG criteria[7], and
	  ○ Has undergone a SCT or is considered transplant ineligible
	  ○ Has received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and a proteasome inhibitor (given separately or in combination), and must have documented disease progression on, or within 60 days of, completion of the last treatment as defined by IMWG
	• Has measurable disease with at least one of the following:
	a. Serum M-protein ≥0.5 g/dL (≥5 g/L)
	b. Urine M-protein ≥200 mg/24h
	c. Serum free light chain (FLC) assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
	• Patients with a history of autologous stem cell transplant were eligible for study participation provided the following eligibility criteria were met:
	a. Transplant was >100 days prior to study enrolment
	b. No active infection(s)

	c. Patient met the remainder of the eligibility criteria outlined in the protocol • Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies • Adequate organ system functions (including sufficient renal function as measured by estimated glomerular filtration rate ≥30 mL/min per 1.73 m²) • All prior treatment related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0 2017, must be ≤Grade 1 at the time of enrolment except for alopecia and Grade 2 peripheral neuropathy **Exclusion criteria:** The main exclusion criteria were: • Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' syndrome, active plasma cell leukaemia at the time of screening. • Systemic anti-myeloma therapy or use of an investigational drug within <14 days or five half-lives, whichever is shorter, before the first dose of study intervention • Prior treatment with an anti-MM monoclonal antibody within 30 days prior to receiving the first dose of study intervention • Prior BCMA-targeted therapy or prior pomalidomide treatment. • Plasmapheresis within 7 days prior to the first dose of study intervention • Prior allogeneic SCT • Any major surgery within the last four weeks • Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect patients' safety) • Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including laboratory abnormalities) that could interfere with patient's safety, obtaining formal consent or compliance to the study procedures • History of (non-infectious) pneumonitis that required steroids, or current pneumonitis • Evidence of active mucosal or internal bleeding • Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis • Patients with previous or concurrent malignancies other than MM are excluded, unless the second malignancy has been considered medically stable for at least 2 years. The patient must not be receiving active therapy, other than hormonal therapy for this disease. NOTE – patients with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction. • Pregnant or lactating female

Settings and where data were collected	The study is being conducted in 19 countries in 184 sites, including 10 UK sites
Trial drugs and concomitant medications	The trial drugs were Belamaf and PomDex. Belamaf dosage was 2.5 mg/kg IV Q3W. PomDex dosage was pomalidomide 4 mg orally daily on Days 1 to 21 Q4W (28-day cycle)/dexamethasone 40 mg once weekly (Days 1, 8, 15, and 22) Q4W (28-day cycle). For participants >75 years old, dexamethasone 20 mg once weekly (Days 1, 8, 15, and 22) Q4W (28-day cycle). Patients received full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheal, and analgesics, as appropriate. Concomitant therapy with bisphosphonates was allowed. Patients were permitted to receive local irradiation for pain or stability control.

Outcomes used in the economic model or specified in the scope, including primary outcome	**Efficacy outcomes**
	• Primary efficacy endpoint:
	  • PFS
	• Secondary efficacy endpoints:
	  • OS
	  • ORR
	  • CBR
	  • DoR
	  • TTR
	  • TTP
	  • MRD negativity
	  • Patient reported outcomes: EORTC-QLQ-C30, EORTC QLQ-IL52, EORTC QLQ-MY20 and the PRO-CTCAE
	• Exploratory outcomes:
	  • Time to best response (TTBR)
	  • PFS2
	• Patient reported outcomes:
	  • EQ-5D-3L
	  • FACT GP5
	• All efficacy outcomes are defined in Table 5.
	• Additional endpoints:
	  • TTD
	Safety outcomes
	• Adverse events
	• Serious adverse events

Abbreviations: BCMA, B-cell maturation antigen; CBR, clinical benefit rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; FACT, Functional Assessment of Cancer Therapy; FLC, free light chain; HRQoL, health-related quality of life; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IRC, independent review committee; ITT, intention-to-treat; MM, multiple myeloma; MRD, minimal residual disease; NCI-CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PRO-CTCAE, Patient-Reported Outcomes

version of the Common Terminology Criteria for Adverse Events; Q3W, once every 3 weeks; Q4W, once every 4 weeks; SCT, stem cell transplant; TTBR, time to best response; TTD, time to treatment discontinuation; TTP, time to progression; TTR, time to response
Source: DREAMM-3 study protocol[5]

Table 5. DREAMM-3 efficacy outcome measures definitions

Endpoint type	Measure	Description
Primary	PFS	Defined as the time from the date of randomisation until the earliest date of documented disease progression (according to IMWG Response Criteria) or death due to any cause
Secondary	OS	Defined as the time from randomisation until death due to any cause
	ORR	Defined as the percentage of participants with a confirmed PR or better per IMWG
	CBR	Defined as the percentage of participants with a confirmed minimal response or better per IMWG
	DoR	Defined as the time from first documented evidence of PR or better until PD per IMWG or death due to PD among participants who achieve confirmed PR or better
	TTR	Defined as the time between the date of randomisation and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better
	TTP	Defined as the time from the date of randomisation until the earliest date of documented PD (per IMWG Response Criteria) or death due to PD
	MRD negativity	MRD negativity rate, defined as; the percentage of participants who are MRD negative by NGS method
	Patient reported outcomes	Health-related QOL as measured by EORTC QLQC30 and EORTC IL52 (Disease Symptoms domain of EORTC QLQ-MY20). Symptomatic adverse effects as measured by the PRO-CTCAE
Exploratory	TTBR	Defined as the interval of time between the date of randomisation and the earliest date of achieving best response among participants with a confirmed PR or better as derived per IMWG
	PFS2	Defined as time from randomisation to disease progression after initiation of new anticancer therapy or death from any cause, whichever is earlier. If disease progression after new anti-cancer therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anticancer therapy, or death from any cause, whichever is earlier
Patient reported outcomes	EQ-5D-3L	A two-part self-assessment questionnaire consisting of five items covering mobility, self-care, usual activities, pain/discomfort, and anxiety-depression, and a visual analogue scale that has

		endpoints labelled 'best imaginable health state' and 'worst imaginable health state' anchored at 100 and 0 respectively
	FACT GP5	A 27-item compilation of general questions divided into 4 primary QoL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being
Additional	Time to discontinuation (TTD)	Defined as time on the treatment until discontinued

Abbreviations: CBR, clinical benefit rate; CR, complete response; DoR, duration of response; EORTC, European Organisation for Research and Treatment; FACT, Functional Assessment of Cancer Therapy; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; NGS, next generation sequencing; ORR, overall response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PR, partial response; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QoL, quality of life; sCR, stringent complete response; TTBR, time to best response; TTD, time to treatment discontinuation; TTP, time to progression; TTR, time to response
Source: DREAMM-3 study protocol[5]

Please note that for the 5L+ TCR subgroup, only PFS, OS, ORR, DoR, and TTD were available at the time of submission of this addendum.

2.2.2 Statistical analysis

The statistical analysis undertaken in the DREAMM-3 trial is presented in Table 6.

Table 6. DREAMM-3 statistical analysis

Trial number (acronym)	DREAMM-3, NCT04162210
Hypothesis objective	The primary study objective was to compare the efficacy of Belamaf vs pomalidomide plus low dose dexamethasone (PomDex) in participants with relapsed/refractory multiple myeloma (RRMM). Based on available data from literature, the median PFS in the PomDex arm was expected to be around 4 months.[8] It was expected that treatment with Belamaf would result in a 43% reduction in the hazard rate for PFS, i.e. an expected HR of 0.57 (corresponding to an increase in median PFS from 4 months to 7 months under the exponential model assumption).
Sample size, power calculation	The final PFS analysis was conducted at the time of observing approximately 151 events and the first 320 randomised subjects had been followed for a minimum of 4 months. With 151 events, the study had a power of 90% to detect a hazard ratio of 0.57 at 1-sided alpha of 0.025 (corresponding to a critical value of 0.713 for the hazard ratio). This calculation assumed participants randomized to the two treatment arms in a 2:1 ratio. Assuming that enrolment would continue for approximately 20 months at a uniform rate of 16 participants per month, a total of 320 participants would be randomised in a 2:1 ratio to receive single agent Belamaf or PomDex. It was estimated that the targeted 151 PFS events would be observed approximately 23 months after the first participant was randomised based on a lognormal cure rate model.
Outcome populations	The analyses for the 5L+ TCR subgroup were not pre-specified.

Statistical analysis	The analysis for the key efficacy endpoints is reported in Section 3.2 **Primary endpoint** – PFS The non-parametric Kaplan-Meier method was used to estimate the survival curves for PFS. Kaplan-Meier plots of PFS were presented by treatment arm. Kaplan-Meier estimates for the median PFS, the first and third quartiles, and 6-month PFS rate were presented, along with 95% CIs. CIs for quartiles were estimated using BrookmeyerCrowley method.[9] The treatment difference in PFS was compared by the stratified log-rank test at one-sided alpha level of 0.025. The stratified log-rank test (stratified by randomization factors) was only be performed for the primary analysis of primary estimand of PFS (i.e. based on investigator-assessed response and primary event and censoring rules) based on ITT Analysis Set. [redacted]Hazard ratio (HR) and its corresponding 95% CI were estimated from Cox proportional hazard model stratified by randomization factors with treatment arm as the sole explanatory variable. The Cox models were fitted using SAS PROC PHREG with the Efron method to control for ties. Hazard ratio (HR) and its corresponding 95% CI were also estimated from unstratified Cox proportional hazard model with treatment arm as the sole explanatory variable. The Cox models were fitted using SAS PROC PHREG with the Efron method to control for ties. Stratification factors entered for randomization were used in the primary analysis. If there was any mis-stratification, supplementary analyses were performed using the stratification data based on the clinical database. **Secondary endpoints** The secondary endpoints were assessed using the ITT population. OS, ORR, DoR and TTD were also assessed using the 5L+ TCR subgroup of patients. Analyses conducted were as follows: • OS – analysed in the same way as PFS • ORR – the number and percentage of participants with the best confirmed response in the following response categories were summarised by treatment arm: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding exact 95% CI for ORR was also provided. Participants with unknown or missing responses were treated as non-responders, i.e., these participants were included in the denominator when calculating percentages of response. The exact 95% CI for the difference was calculated. • DoR – distribution of DoR was summarised using the Kaplan-Meier method by treatment arm. The median, 25th and 75th percentiles of DoR were estimated and corresponding 95% confidence intervals were estimated using the BrookmeyerCrowley method.[9] • Additional endpoint TTD – analysed in a supplementary post-hoc analysis **Safety** All safety analyses were performed on the safety analysis set. An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, Grade 3 and 4 AEs, Grade 3 and 4 AEs related to study intervention, AEs

	leading to permanent discontinuation of study intervention, study intervention related AEs leading to permanent discontinuation of study intervention, AE leading to dose reductions, AEs leading to dose delays, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention were produced. **Belamaf:** • The number of cycles administered by study treatment were summarised with mean, median, standard deviation, minimum, and maximum. • Dose intensity, duration of exposure to treatment, dose reductions, dose delays, and dose modifications were summarised. **PomDex:** • Descriptive statistics of cumulative dose, dose exposure, average daily doses, dose intensity and relative dose intensity were summarised by cycle and by pomalidomide and dexamethasone, separately. The overall summary across cycles was also be provided. Duration of treatment by drug and overall treatment duration was summarised by descriptive statistics. The dose modifications (dose reductions, dose interruptions) were summarised by study drug and listed. **Health outcomes** The EORTC QLQ-C30 (version 3.0), EORTC QLQ-IL52 (disease symptom domain of EORTC QLQ-MY20), EORTC QLQ-MY20 and the PRO-CTCAE are three oncology specific Health-Related Quality-of-Life (HRQoL) assessments that were analysed in this study as supportive secondary endpoints. EORTC QLQ-IL52 was included in the EORTC QLQ-MY20 analyses. The analysis of EORTC QLQ-C30 and EORTC QLQ-MY20 (including EORTC QLQIL52) was based on the ITT Analysis Set; while the analysis of PRO-CTCAE was based on the Safety Analysis Set.
Data management and patient withdrawals	Not available at the time of submission of this addendum.
Interim analyses	Interim analyses (IA) including one futility interim for PFS, one efficacy interim for PFS, and up to two efficacy interims for OS were planned, and reviewed by an Independent Data Monitoring Committee (IDMC).

Abbreviations: AE, adverse event; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; HRQoL, health-related quality of life; IA, interim analysis; IDMC, Independent Data Monitoring Committee; IRC, Independent Response Committee; ITT, intention-to-treat; mAb, monoclonal antibody; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RRMM, relapsed/ refractory multiple myeloma; SAE, serious adverse event; TTD, time to death
Source: DREAMM-3 SAP[4], DREAMM-3 study protocol[5]

2.2.3 Critical appraisal of the DREAMM-3 trial

The critical appraisal of the DREAMM-3 trial is presented in

Table **7**, using the Cochrane Risk of Bias tool for randomised trials.[18]

Table 7. Risk of bias assessment of DREAMM-3 trial using Cochrane Risk of Bias tool

Criteria	Assessment	Comment
Random sequence generation	Low risk of bias	Patients were randomly assigned in a 2:1 ratio to Belamaf or PomDex, through the supply of unique numbers to each site and participants who were eligible for enrolment were assigned a unique participant number by the site. All participants were centrally randomised using central Interactive Response Technology. The unique participant number remained for the duration of the study.
Allocation concealment	Low risk of bias	Upon completion of all the required screening assessments, eligible participants were registered via an Interactive Response Technology, allowing sites to register and randomise participants. Randomisation was done centrally using a randomisation schedule, assigning patients to a 2:1 ratio of Belamaf to PomDex.
Blinding of participants and personnel	Some concerns	As this trial was open-label, the trial coordinators had access to the patient-level data throughout the study. However, trial integrity was ensured through steps taken to restrict access to key information whilst the study was ongoing and present data aggregation except for where specified in the protocol. This included PFS and OS interims, with the purposes of futility, efficacy, and superiority.
Blinding of outcome assessment	Unclear risk of bias	As this trial was open-label, the trial coordinators had access to the patient-level data throughout the study, it is not clear if outcome assessors were blinded to the treatment assigned.
Incomplete outcome data	Low risk of bias	Missing data have been imputed using appropriate methods, however data for the outcomes were available for most if not all of the participants.
Selective reporting	Low risk of bias	Data were analysed in accordance with a pre-specified analysis plan that was finalised ahead of when the unblinded outcome data were available for analysis – as specified in the protocol.
Other sources of bias	Low risk of bias	No other type of bias specified.

3 Clinical effectiveness results

3.1 Belamaf – Efficacy outcomes ([redacted] dataset)

In the BSH abstract[1], data was presented for a population broader than the scope of this appraisal. Additional data for this population were provided upon request to the study author and the 5L+ TCR cohort was selected. The next sections detail the methodology and outcomes generated from the analysis of the 5L+ TCR cohort.

3.1.1 Patient demographics and clinical characteristics

The demographics and clinical characteristics available are presented in Table 8.

Table 8. Patient characteristics in the [redacted] dataset

	[redacted] – Belamaf 5L+ TCR (N=[redacted])
Sex, n (%)	
Male	[redacted]
Age (years), n	
Mean	[redacted]
R-ISS staging system, n (%)	
I II III Unknown Not applicable	[redacted]
ECOG performance status, n (%)	
0-2 3-4 5-6 Unknown	[redacted]
Extramedullary disease, n (%)	
Yes No Unknown	[redacted]
Prior lines of therapy, median	[redacted]
Cytogenetic risk, n (%)	
Standard High Unknown Not applicable	[redacted]
Prior ASCT, n (%)	
Yes No Unknown	[redacted]

Abbreviations: ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; R-ISS, Revised International Staging System; TCR, triple class refractory; 5L+, fifth line and beyond

3.1.2 Statistical analysis

The statistical analysis performed on the [redacted] dataset is presented in Table 9.

Table 9. [redacted] dataset statistical analysis

Outcome populations	Outcomes are presented using the Belamaf population for the 5L+ TCR cohort
Statistical analysis	**Summary statistics** Continuous variables were summarised by means and medians. Frequencies and percentages were presented for categorical data. Subjects were described in terms of their baseline demographic and clinical characteristics. **Survival analyses** The Kaplan-Meier (KM) method were used to summarise time-to-event variables (OS, PFS, TTNT and TTD). Survival analyses, clinical data and KM data were generated for OS, PFS, TTNT and TTD. KM estimates (and their corresponding two-sided 95% CIs) were reported for patients at various time points following the index date. Estimates were presented alongside associated summary statistics, including the median survival time. Survival curves were presented graphically. **Missing data** The proportion of missing data was displayed. No imputations were carried out. Patients who experienced an event or were censored at time 0 were removed from the analyses.

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TCR, tiple-class refractory; TTD, time to treatment discontinuation; TTNT, time to next treatment

3.1.3 Overall Survival (OS)

In the cohort of 5L+ TCR patients included in the [redacted] dataset, median OS with Belamaf was [redacted] months (95% CI: [redacted]), with a survival probability of [redacted] at 12 months (95% CI: [redacted]) (

Table 10, Figure 2).

Table 10. [redacted] 5L+ TCR cohort - overall survival for Belamaf

Belamaf			**N=[redacted]**	
Number of events			[redacted]	
Number censored			[redacted]	
Median (95% CI) survival; months			[redacted]	[redacted]
Months from Line start	N at risk	Survival probability	Lower 95% CI	Upper 95% CI
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]			

Abbreviations: CI, confidence interval; n, number; NA, not available

Figure 2. [redacted] 5L+ TCR overall survival, Belamaf (Kaplan-Meier analysis)

Abbreviations: OS, overall survival

3.1.4 Progression-free survival (PFS)

Median PFS with Belamaf was [redacted] months (95% CI: [redacted]) with a probability of being progression-free at 12 months of [redacted] (95% CI: [redacted]) (Table 11, Figure 3).

Table 11. [redacted] 5L+ TCR cohort - progression-free survival for Belamaf

Belamaf	**N=[redacted]**

Number of events			[redacted]	
Number censored			[redacted]	
Median (95% CI) survival; months			[redacted]	[redacted]
Months from Line start	N at risk	Progression-free survival probability	Lower 95% CI	Upper 95% CI
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]			

Abbreviations: CI, confidence interval; n, number; NA, not available

Figure 3. [redacted] 5L+ TCR progression-free survival Belamaf (Kaplan-Meier analysis)

Abbreviations: PFS, progression-free survival

3.1.5 Time to next treatment (TTNT)

Median TTNT with Belamaf was [redacted] months (95% CI: [redacted]), with a probability of receiving the next treatment at 12 months of [redacted] (95% CI: [redacted]) (Table 12, Figure 4).

Within the [redacted] dataset, [redacted] patients ([redacted]) had a record of receiving a subsequent therapy within the follow-up time. Due to the number of missing data, the TTNT analysis produces implausible results and therefore are not reliable.

Table 12. [redacted] 5L+ TCR time to next treatment for Belamaf

Belamaf		**N=[redacted]***		
Number of events		[redacted]		
Number censored		[redacted]		
Median (95% CI) survival; months		[redacted]		[redacted]
Months from Line start	N at risk	Time to Next Treatment probability	Lower 95% CI	Upper 95% CI
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]			
18	[redacted]			

Abbreviations: CI, confidence interval; n, number; NA, not available
*1 patient experienced an event at time 0 and was removed from the analysis.

Figure 4. [redacted] 5L+ TCR time to next treatment, Belamaf (Kaplan-Meier analysis)

Abbreviations: TTNT, time to next treatment

3.1.6 Time to treatment discontinuation or death (TTD)

Median TTD with Belamaf was [redacted] months (95% CI: [redacted]), with a discontinuation probability at 12 months of [redacted] (95% CI: [redacted]) (Table 13, Figure 5).

Table 13. [redacted] 5L+ TCR time to treatment discontinuation or death for Belamaf

Belamaf			**N=[redacted]***	
Number of events			[redacted]	
Number censored			[redacted]	
Median (95% CI) survival; months			[redacted]	[redacted]
Months from Line start	N at risk	Time to Treatment Discontinuation probability	Lower 95% CI	Upper 95% CI
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]			

Abbreviations: CI, confidence interval; n, number; NA, not available
*1 patient experienced an event at time 0 and was removed from the analysis.

Figure 5. [redacted] 5L+ TCR time to treatment discontinuation or death, Belamaf (Kaplan-Meier analysis)

Abbreviations: TTD, time to treatment discontinuation

3.1.7 Overall response rate (ORR)

ORR for the [redacted] 5L+ TCR cohort was [redacted]% with [redacted]% obtaining very good partial response or better, and [redacted]% a partial response; [redacted]% saw a best response of stable disease and [redacted]% progressive disease ([redacted]% not evaluable) (Table 14).

Table 14. Overall response rate

	Belamaf ([redacted])
Best Response, n (%)	
Stringent complete response (sCR)	[redacted]
Complete response (CR)	[redacted]
Very good partial response (VGPR)	[redacted]
Partial response (PR)	[redacted]
Stable disease (SD)	[redacted]
Progressive disease (PD)	[redacted]
Not evaluable (NE)	[redacted]
Overall Response Rate, n (%)	
sCR+CR+VGPR+PR	[redacted]

Abbreviations: CR, complete response; n, number; NE, not evaluable; NR, not reported; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

3.2 Belamaf and PomDex – Efficacy outcomes (DREAMM-3)

3.2.1 Overview of the efficacy results in the DREAMM-3 ITT population

On 7th November 2022, and after the Company's original submission on 6th October 2022, GSK announced that DREAMM-3 did not meet its primary endpoint of PFS for the ITT population (3L+ Len and PI exposed).[10]

In the DREAMM-3 trial, the primary endpoint of PFS demonstrated a hazard ratio (HR) of 1.03 (95% CI: 0.72 1.47). The observed mPFS was longer for Belamaf vs PomDex (11.2 months vs 7 months). Secondary endpoints include ORR, DoR and OS. The ORR was 41% for Belamaf and 36% for PomDex. Belamaf demonstrated a deeper response rate when compared with PomDex (25% VGPR or better with Belamaf compared to 8% with PomDex). The median follow-up was 11.5 months for Belamaf and 10.8 months for PomDex; the mDoR was not reached for Belamaf (95% CI: 17.9, -) vs 8.5 months (95% CI: 7.6, -) for PomDex; DoR rates at 12 months were 76.8% and 48.4% for Belamaf and PomDex respectively.

At the time of the primary analysis, the OS data had only achieved 37.5% overall maturity. The mOS was 21.2 and 21.1 months for Belamaf and PomDex, respectively, with an HR of 1.14 (95% CI: 0.77, 1.68).[10]

The following sections detail baseline demographics and outcomes for the 5L+ TCR subgroup, the population under evaluation in this appraisal, within the ITT population of DREAMM-3 (3L+ lenalidomide [LEN] and proteasome inhibitor [PI] exposed).

3.2.2 Patient demographics and baseline characteristics of the 5L+ TCR subgroup in DREAMM-3

A summary of baseline characteristics in the 5L+ TCR subgroup within DREAMM-3 is reported in Table 15**Error! Reference source not found.**.

Table 15. Baseline characteristics for the 5L+ TCR subgroup in DREAMM-3

Parameter	**PomDex ( )**	**Belamaf ( )**
Sex, n (%)		
Male		
Age (years), n		
Mean (SD)		
Median (range)		
Age Group (years), n (%)		
<65		
≥65 to <75		
≥75		
Race Detail, n (%)		
Asian – East Asian Heritage		
Asian – Japanese Heritage		
Black or African American		
White – White/Caucasian/European Heritage		
Weight (kg), n		
Mean (SD)		
Median (range)		
ISS disease stage at screening, n (%)		
I		
II		
III		
Unknown		
Type of multiple myeloma, n (%)		
Non-secretory		
Secretory		
Myeloma light chain, n (%)		

Parameter	PomDex ([redacted])	Belamaf ([redacted])
Kappa light chain	[redacted]	[redacted]
Lambda light chain	[redacted]	[redacted]
Myeloma immunoglobulin, n (%)		
IgA	[redacted]	[redacted]
IgD	[redacted]	[redacted]
IgE	[redacted]	[redacted]
IgG	[redacted]	[redacted]
IgM	[redacted]	[redacted]
Extramedullary disease, n (%)		
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Lytic bone lesions, n (%)		
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Lines of therapy completed prior to screening, n (%)		
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
More than 10	[redacted]	[redacted]
High risk cytogenetics n (%)		
Yes	[redacted]	[redacted]
Other (non-high risk, negative, not evaluable, not done)	[redacted]	[redacted]

Abbreviations: ISS, International Staging System; n, number; SD, standard deviation

The following sections describe efficacy outcomes for the 5L+ TCR subgroup within DREAMM-3. It is important to note that due to the very small number of PomDex patients in this group ([redacted]), no interpretations can be made regarding the efficacy of PomDex and the comparative efficacy of Belamaf vs PomDex. The uncertainty is evidenced by the large confidence intervals associated with medians and hazard rations and non-significant p values.

3.2.3 Progression free survival (PFS)

A summary of PFS data in the 5L+ TCR subgroup within DREAMM-3 is reported in (Table 16, Figure 6).

Table 16. Progression-free survival

	PomDex ([redacted])	**Belamaf ([redacted])**
Number of patients, n (%) Progressed or died (event) Censored, follow-up ended Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%) Disease progression Death	[redacted]	[redacted]
Estimates for time variable (months) 1st quartile 95% CI Median 95% CI 3rd quartile 95% CI	[redacted]	[redacted]
Progression-free survival probability Time-to-event endpoint at 6 months 95% CI	[redacted]	[redacted]
Stratified HR 95%CI p value	[redacted]	

Abbreviations: CI, confidence interval; n, number

Figure 6. Kaplan-Meier analysis of PFS

3.2.4 Duration of response (DoR)

A summary of DoR data in the 5L+ TCR subgroup within DREAMM-3 is reported in (Table 17, Figure 7).

Table 17. Duration of response

	PomDex ([redacted])	Belamaf ([redacted])
Number of patients, n (%)	[redacted]	[redacted]
Progressed or died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary		
Disease progression	[redacted]	[redacted]
Death due to PD	[redacted]	[redacted]
Death not due to PD	[redacted]	[redacted]
Estimates for time variable (months) – Disease progression + PD deaths		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile		
95% CI		
Estimates for time variable (months) – Disease progression + all deaths		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile		
95% CI		

Abbreviations: CI, confidence interval; n, number; PD, progressed disease

Figure 7. Kaplan-Meier analysis of DoR

3.2.5 Overall response rate (ORR)

A summary of ORR data in the 5L+ TCR subgroup within DREAMM-3 is reported in (Table 18).

Table 18. Overall response rate

	PomDex ([redacted])	Belamaf ([redacted])
Best Response, n (%)		
Stringent complete response (sCR)	[redacted]	[redacted]
Complete response (CR)	[redacted]	[redacted]
Very good partial response (VGPR)	[redacted]	[redacted]
Partial response (PR)	[redacted]	[redacted]
Minimal response (MR)	[redacted]	[redacted]
Stable disease (SD)	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]
Not evaluable (NE)	[redacted]	[redacted]
Overall Response Rate, n (%)		
sCR+CR+VGPR+PR	[redacted]	[redacted]
95% confidence interval		
97.5% confidence interval	[redacted]	[redacted]
Clinical Benefit Rate, n (%)		
sCR+CR+VGPR+PR+MR	[redacted]	[redacted]
95% confidence interval		
97.5% confidence interval	[redacted]	[redacted]

Abbreviations: CR, complete response; n, number; NE, not evaluable; NR, not reported; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

3.2.6 Overall survival (OS)

A summary of OS data in the 5L+ TCR subgroup within DREAMM-3 is reported in (Table 19, Figure 8).

Table 19. Overall survival

	PomDex ([redacted])	Belamaf ([redacted])
Number of patients, n (%) Died (event) Censored, follow-up ended Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%) Death	[redacted]	[redacted]
Estimates for time variable (months) 1st quartile 95% CI Median 95% CI 3rd quartile 95% CI	[redacted]	[redacted]
Survival probability Time-to-event endpoint at 6 months 95% CI Time-to-event endpoint at 12 months 95% CI Time-to-event endpoint at 18 months 95% CI	[redacted]	[redacted]
Stratified HR 95%CI p value	[redacted]	

Abbreviations: CI, confidence interval; n, number

Figure 8. Kaplan-Meier analysis of OS

3.2.7 Time to treatment discontinuation (TTD)

A summary of TTD data in the 5L+ TCR subgroup within DREAMM-3 is reported in (Figure 9, **Table 20**).

Table 20. Time to treatment discontinuation

	PomDex ( )	Belamaf ( )
Number of patients, n (%)		
Treatment discontinued (event)		
Censored		
Not treated		
Estimates for time variable (months)		
1st quartile		
95% CI		
Median		
95% CI		
3rd quartile		
95% CI		
Time to Treatment Discontinuation probability still on treatment		
Time-to-event endpoint at 6 months		
95% CI		
Time-to-event endpoint at 12 months		
95% CI		

Abbreviations: CI, confidence interval; n, number

Figure 9. Kaplan-Meier analysis of TTD

3.3 Indirect and mixed treatment comparisons

3.3.1 Feasibility assessment for an unanchored matching-adjusted indirect comparison (MAIC)

The suitability of the [redacted] and the NCRAS datasets for inclusion in an unanchored matching-adjusted indirect comparison (MAIC) was determined by assessing whether they were sufficiently homogenous in terms of study setting, outcomes and baseline characteristics. The Cochrane Handbook for Systematic Reviews of Interventions was used to assess the level of heterogeneity across studies by comparing study designs, baseline characteristics, treatment arms and outcomes.[11] As outlined in NICE Decision Support Unit (DSU) Technical Support Document 1 the synthesis of evidence from clinically heterogeneous populations can increase the risk of statistical heterogeneity and inconsistency.[12] In addition, it often requires highly implausible assumptions which can limit the validity of the results. Cross-study heterogeneity in study population, inclusion/exclusion criteria, study setting, sample sizes, and outcome definitions and assessments between the [redacted] study and NCRAS study were evaluated to assess the feasibility of an unanchored MAIC.

Assessing heterogeneity between datasets should take account the key features of the studies such as those listed in Table 21. These elements have been adapted slightly to structure our own assessment of RRMM and the real-world evidence.

Table 21. Example of factors that might cause heterogeneity

Category	Factor
Different quality or methods of studies	Design Duration of follow up Loss to follow up Inclusion and exclusion criteria
Confounding factors in relation to participant population	Age Sex Ethnicity Severity of disease (Eastern Cooperative Oncology Group (ECOG) score) Number of prior lines of therapy Refractory to a PI, an IMiD, and an anti-CD38 Revised-ISS stage Cytogenetic profile Comorbidities Extramedullary disease
Confounding factors in relation to circumstances	Health systems Geography Setting in hospital or ambulatory care Date of study
Different treatment	Treatment exposure Dose Duration Timing Stopping or continuation criteria
Different outcome measures and methods of statistical analysis	Definition of outcome(s) Rating instrument Frequency of measurement Start point of measurement against duration or progression of disease or treatment, especially in time to event analyses Availability of data

Abbreviations: BCMA, B-cell maturation antigen; ECOG, Eastern Cooperative Oncology Group; ImiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor

The following sections evaluate the heterogeneity between the two datasets for the factors listed in Table 21 and assess the feasibility of an unanchored MAIC between the [redacted] and NCRAS datasets.

3.3.1.1 Methodology

3.3.1.1.1 Defining model outcomes and covariates

Comparison of study setting

The first step of the feasibility assessment was to compare the study and patient characteristics observed in each dataset.

The unanchored MAIC cannot account for differences between elements of study setting which differ between the two datasets and cannot be adjusted for. Hence, it is important to identify any differences between the two study settings. The patient population in the two datasets, along with their inclusion and exclusion criteria, were compared to confirm the dataset overlap.

Assessment of outcomes

In order for an unanchored MAIC of Belamaf ([redacted]) vs PomDex (NCRAS) to be conducted, data sourced from both datasets must:

- Report data for a common outcome
- Report sufficient data (including measure of variability) for comparisons to be made across the sources

A summary of outcome definitions from the [redacted] and NCRAS datasets is presented in Table 22 and demonstrate the comparability of definitions across both datasets.

Table 22. Definition of outcomes in the [redacted] and NCRAS datasets

	[redacted]	NCRAS
OS	Defined in protocol as the time from the start of the first dose to the date of death. Censoring is not defined in the protocol but was defined in the additional data analysis as patients still alive at the end of the study period will be censored.	Defined as the time from initiation of the first cohort-eligible line of therapy until failure (all-cause death). Patients lost to follow-up or still alive at the end of the study period will be censored.
PFS	Defined in protocol as the time from the start of the first dose to the date of first documentation of disease progression or death from any cause.	Not recorded.
TTNT	Defined in protocol as the time from the start of the first dose to the date of first dose of the next line of therapy or death from any cause.	Defined as the time from the start of the first cohort-eligible line of therapy until failure (the earliest of all-cause death or the start of a new line of treatment). Patients lost to follow-up or still in same line of treatment at the end of the study period will be censored.
TTD	Not defined in study protocol; defined in the data analysis as the time from the start of the first dose to the discontinuation of the intervention or death from any cause.	Defined as the earliest of: last administration plus 1 cycle length; start of a new line minus 1 day; death during follow-up. Those alive at follow-up end with no subsequent line and last administration date of the index line within a cycle length of administrative follow-up end were treated as censored.

Assessment of baseline characteristics and covariate selection

In order to perform an unanchored MAIC, the '*conditional constancy of absolute effects*' assumption must be met. This assumption states that the differences between absolute outcomes that would be observed in each trial are entirely explained by imbalances in prognostic variables and effect modifiers with respect to the chosen scale. As such, the assumption requires all effect modifiers and prognostic variables to be available.

The following effect modifiers and prognostic variables in relation to OS, PFS/TTNT and TTD were identified through targeted literature searches and validated with UK clinical experts as detailed in the Company's original submission.

- Age
- ECOG performance status
- Renal impairment
- Revised international staging system (R-ISS) stage
- High risk cytogenetics
- Lytic bone lesions
- Extramedullary disease
- Number of prior lines of therapy
- Median time from diagnosis
- Refractory status to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38

This list was used to assess and compare the cohorts from the [redacted] and NCRAS datasets for the available baseline characteristics. Since individual patient data (IPD) were available for the [redacted] dataset, the populations which could be assessed were restricted by the aggregate data available for the NCRAS dataset. Moreover, since there were missing data in the [redacted] (see Section 3.1.5), the populations to be assessed were further limited to those with data available.

3.3.1.2 Results

3.3.1.2.1 Study settings

Table 23 presents the study settings for both the [redacted] study and the NCRAS study for comparison.

Table 23. [redacted] study settings compared against NCRAS study

Characteristic	[redacted] study	NCRAS study	Deviations
Design	Descriptive, retrospective, non-interventional	Descriptive, retrospective, non-interventional	None

Adequate concealment of randomisation	Non-randomised	Non-randomised	None
Loss to follow-up	One patient was lost to follow-up	Unknown, patients are censored at this time	Unknown given lack of data from NCRAS
Cross-over	NR	NR	Unknown as NR
Locations	UK*	England	Though the NCRAS geographical location is smaller, it overlaps with the [redacted] locations, so similar treatment guidelines, baseline characteristics, etc can be expected. Consulted clinical experts also noted the England-based NCRAS dataset to be applicable to Scotland.
Relevant intervention/treatment	Belamaf	PomDex, PanoBorDex	Not applicable

*Note that 1 patient from the ROI was included in the study.
Abbreviations: NCRAS – National Cancer Registration and Analysis Service; NR – not reported; US – United States.

Impact on feasibility assessment

The deviations of study settings between the [redacted] and NCRAS studies are not significant due to the similarity between the nature of the observational studies. The impact of the few deviations that apply would have limited effect on the feasibility of a MAIC.

3.3.1.2.2 Outcomes

The outcomes used to compare the NCRAS and [redacted] datasets are shown in Table 24. As described in Section 3.1.5, there was a paucity of available data for subsequent therapies at the time of analysing in the [redacted] dataset. Therefore, Belamaf TTNT data from the [redacted] was considered inappropriate to inform a comparison of Belamaf vs PomDex. Instead, PFS was used for Belamaf and compared to PomDex TTNT.

Table 24. Outcomes in NCRAS and [redacted]

Endpoints of interest in the cost-effectiveness model	Outcomes used from [redacted] (IPD)	Outcomes used from NCRAS (aggregate data)	Justification
OS	OS	OS	Collected in both NCRAS and [redacted], as defined in Table 22
PFS	PFS	TTNT	As PFS is not collected in the NCRAS dataset, a comparison using [redacted] TTNT data was considered instead
TTD	TTD	TTD	Collected in NCRAS and calculated in [redacted] using the same definition as NCRAS

Abbreviations: IPD: individual patient-level data; NCRAS, National Cancer Registration and Analysis Service; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation; TTNT, time to next therapy

Impact on feasibility assessment

Definition of OS and TTD outcomes are similar in the [redacted] and NCRAS datasets, therefore is not expected to impact on the feasibility assessment. It should be noted that, as previously described and as identified by the EAG (issue number 4 described in sections 3.5.1.1, 3.5.1.2 of the EAG report). TTNT may overestimate PFS and thus, the comparison of Belamaf PFS vs PomDex TTNT is likely to reflect a conservative estimate of Belamaf efficacy. Nonetheless, it was deemed more appropriate in light of the level of missing data in the analysis of Belamaf TTNT.

3.3.1.2.3 Baseline characteristics

The baseline characteristics of the [redacted] dataset and the NCRAS dataset are detailed in Table 25.

Table 25. [redacted] dataset baseline characteristics compared to the NCRAS dataset

Characteristic	[redacted], Belamaf (n=[redacted])	NCRAS, PomDex (n=[redacted])
Age (years), mean (SD)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Median prior LOT (min, max)	[redacted]	[redacted]
ISS stage, n (%)	[redacted]	[redacted]

Characteristic	[redacted], Belamaf (n=[redacted])	NCRAS, PomDex (n=[redacted])
Extramedullary disease, n (%)	[redacted]	[redacted]
Lytic bone lesions, n (%)	[redacted]	[redacted]
Refractory status, n (%)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
ECOG Performance Status, n (%)	[redacted]	[redacted]
Cytogenetic risk factor, n (%)	[redacted]	[redacted]
Renal impairment, n (%)	[redacted]	[redacted]

Impact on feasibility assessment[redacted]

The key differences in baseline characteristics between the [redacted] dataset and the NCRAS dataset are the number of prior lines of therapy, ECOG PS, extramedullary disease and ISS stage. All of these factors are expected to be prognostic variables/ treatment effect modifiers in the analyses.

In both datasets, the majority of patients has an ECOG performance status (PS) of 1 or 2 ([redacted]% and [redacted]% in [redacted] and NCRAS cohorts, respectively). However, ECOG PS was not available for [redacted]% of patients in the [redacted] dataset and [redacted]% of patients in the NCRAS dataset. Moreover, [redacted]% of patients in the [redacted] dataset had an ECOG PS of 5 or 6 while no data was reported for this score for the NCRAS dataset. Due to missing data and the limited overlap in this category, it is not possible to match all the patients in the [redacted] dataset to those in the NCRAS dataset on their ECOG PS. ECOG PS is an important prognostic factor, thus, this difference in baseline scores between the two cohorts may be a source of bias in the treatment comparison.

A median of [redacted] prior lines of therapy was reported for the patients in the [redacted] dataset while whereas in the NCRAS dataset patients had a median of [redacted] prior lines of therapy before receiving PomDex. Furthermore, while [redacted] patients in the NCRAS dataset had received four to six prior lines of therapy, [redacted]% of patients in

the [redacted] dataset had more than six prior lines of therapy thus attempting to adjust for prior lines would significantly reduce the effective sample size (ESS).

A large proportion of patients in both the [redacted] and NCRAS datasets have an unknown ISS stage ([redacted]% and [redacted]%, respectively). Upon matching, these patients would be removed from the analysis which would reduce the ESS dramatically in the MAIC, therefore reducing the reliability of the results due to reduced power in the sample size.

There is limited overlap for baseline extramedullary disease (EMD) between the [redacted] and NCRAS patient populations with over four times as many patients in the [redacted] dataset presenting extramedullary disease ([redacted]%) than the NCRAS dataset ([redacted]%). Similarly, a larger proportion of patients in the NCRAS dataset do not have extramedullary disease ([redacted]) than those in the [redacted] dataset ([redacted]%). However, the primary factor impacting the feasibility of matching for EMD is the number of 'unknown' values in the [redacted] dataset ([redacted]%), compared with no 'unknown' values in the NCRAS dataset. This would result in a reduction of the ESS and would affecting the reliability of the results due to reduced power in the sample size.

High cytogenetic risk and renal impairment at baseline were not reported in the NCRAS dataset and therefore any adjustment on those variables would not be feasible.

3.3.1.2.4 Conclusion

Considering the significant level of missing patient characteristics data in both the [redacted] and NCRAS datasets, a MAIC adjusting for the key identified prognostic factors and treatment effect modifiers is likely to result in a significantly reduced ESS.

Given the conclusions of the feasibility assessment, a MAIC was deemed unfeasible and thus, a naïve comparison of Belamaf ([redacted] dataset) vs PomDex (NCRAS dataset) was selected instead to inform the base-case in the cost-effectiveness model.

3.4 Adverse reactions

In the overall cohort from the [redacted] study (n=[redacted]), safety data was available for [redacted] patients and [redacted] ([redacted]%) experienced an adverse event. Ocular toxicity occurred in

[redacted] patients ([redacted]%), median grade [redacted] and caused a dose delay in [redacted]([redacted]%) and a dose reduction in [redacted]([redacted]%).[1]

In the DREAMM-3 ITT population (3L+ Len and PI exposed), the safety and tolerability profile of Belamaf was consistent with the known safety profile, and no new safety signals were identified. Overall rates of grade 3 keratopathy are consistent with prior reported data.[10]

3.5 Interpretation of clinical effectiveness and safety evidence

3.5.1 Principal findings from the clinical evidence base

3.5.1.1 Clinical effectiveness

UK RWE evidence from the [redacted] study

In a UK real-world cohort of [redacted] heavily pre-treated 5L+ TCR MM patients receiving Belamaf in the [redacted] data, clinically meaningful (overall responses achieved by [redacted] of patients) and deep ([redacted] of responders with ≥VGPR) responses with single agent Belamaf were achieved. The median OS was [redacted] months in this analysis, which is broadly consistent with the corresponding value derived from the final analysis of the DREAMM-2 trial (median OS was [redacted] months). The median PFS was [redacted] months which is substantially longer than that reported in the DREAMM-2 trial (median PFS was [redacted] months as of the final analysis).

DREAMM-3

In the DREAMM-3 study for the 5L+ TCR subgroup, [redacted] patients were treated with PomDex and [redacted] patients were treated with Belamaf, consistent with the 2:1 randomisation of the trial (Belamaf:PomDex respectively). For the patients in the Belamaf arm, overall responses were achieved by [redacted] of patients. The median PFS was [redacted] months, and the median OS was [redacted] months which are broadly consistent with the corresponding values derived from the final analysis of the DREAMM-2 trial (median PFS was [redacted] months, median OS was [redacted] months). Due to the very small number of PomDex patients in the 5L+ TCR subgroup of DREAMM-3 ([redacted]), no interpretations can be made regarding the efficacy of PomDex and the comparative

efficacy of Belamaf vs PomDex. The uncertainty is evidenced by the large confidence intervals associated with medians and hazard ratios and non-significant p values.

3.5.1.2 Safety

The new [redacted] and DREAMM-3 datasets further confirmed the manageable safety profile of Belamaf in patients with RRMM.

In the DREAMM-3 ITT population (3L+ Len and PI exposed), the safety and tolerability profile of Belamaf was consistent with the known safety profile, and no new safety signals were identified.[10]

In the overall cohort from the [redacted] study (N=[redacted]), [redacted]% of patients experienced an adverse event including. Ocular toxicity occurred in [redacted]% of patients leading to a dose delay or dose reduction in [redacted]% and [redacted]% of those patients, respectively.[1]

3.5.1.3 Comparative efficacy

The feasibility of an unanchored MAIC comparing efficacy outcomes from two RWE datasets was explored, namely the UK [redacted] dataset for Belamaf and the England-based NCRAS dataset for PomDex. However, due to some missing baseline characteristics, adjusting for key prognostic factors while maintaining an ESS sufficient to generate meaningful results was deemed unfeasible.

For the baseline characteristics available, the [redacted] and NCRAS populations were broadly comparable and therefore, a naïve comparison of OS, PFS ([redacted]) vs TTNT (NCRAS) and TTD outcomes was preferred to inform the base-case cost-effectiveness analysis (CEA).

The naïve comparison suggests that in the UK, patients with 5L+ TCR MM could experience a [redacted] OS, PFS/TTNT and TTD when treated with Belamaf than with PomDex ([redacted] months vs [redacted] months for OS, [redacted] months for Belamaf PFS vs [redacted] months for PomDex TTNT and [redacted] vs [redacted] months for TTD for Belamaf and PomDex, respectively).

3.5.2 Strengths and limitations of the clinical evidence base

3.5.2.1 Strengths of the clinical evidence base

[redacted] study

Since the original submission, an additional source of evidence reporting efficacy and safety data for Belamaf in patients treated as part of the UK [redacted] has become available. This study, described in Section 2.1, is the first and only UK RWE study reporting evidence for key efficacy outcomes for Belamaf used within a population of 5L+ TCR MM patients, in line with the current license and the population considered in this appraisal. As such, the [redacted] dataset provides the most robust demonstration of the clinical benefits of Belamaf in a population of 5L+ TCR MM patients in the UK. In addition, this study further confirms the manageable safety profile of Belamaf in UK RRMM patients.

Furthermore, this new source of evidence has the potential to address some of the limitations identified by the EAG. Indeed, in 'key issue n.4' the EAG questioned whether the healthcare systems across the centres included in the DREAMM-2 trial and the NCRAS dataset were comparable in terms of treatment pathways and availability of technologies. The comparison of Belamaf ([redacted] dataset) vs PomDex (NCRAS dataset) uses data collected from a UK RWE setting and thus, not only improves the homogeneity in terms of treatment pathway and subsequent treatments but also increases the generalisability of results to the UK population of patients with 5L+ TCR MM.

3.5.2.2 Limitations of the clinical evidence base

Comparative efficacy evidence ([redacted] and NCRAS datasets)

While both the NCRAS and [redacted] datasets are the most robust and most representative source of evidence demonstrating the efficacy of Belamaf and PomDex in a population of UK patients with 5L+ TCR MM, both are associated with some limitations. Indeed, in both datasets a proportion of baseline characteristics was unknown or missing which limits the comparability of the datasets. Consequently, a MAIC was deemed unfeasible, and a naïve comparison was selected instead to inform the base-case CEA. While some differences may exist between the two cohorts for the available and/or missing baseline characteristics, it is

difficult to assess and quantify the level and direction of any potential bias. Overall, the populations were broadly comparable across the two datasets and represent a UK population with 5L+ TCR MM.

In addition, as described in the original submission, no evidence was available for PFS in the NCRAS dataset and therefore a comparison of TTNT was considered and used as a proxy to inform PFS in the economic model to limit the risk of bias. A substantial amount of missing data for subsequent treatments recording was observed in the [redacted] dataset. Hence, it was not possible to generate robust and clinically plausible TTNT data for Belamaf from the [redacted] dataset. Instead, PFS was used and compared to PomDex TTNT in NCRAS. In light of the treatment gap that may exist between progression and the initiation of subsequent therapy to allow for the resolution of toxicities and/or for a decision to be made on the next intervention, comparing Belamaf PFS to PomDex TTNT is likely to overestimate the efficacy of PomDex and therefore this comparison can be considered as conservative.

DREAMM-3 5L+ TCR subgroup

While the DREAMM-3 trial includes a subset of patients with 5L+ TCR MM, it is important to highlight this was not a pre-specified subgroup within the trial and the sample size is very limited with [redacted] and [redacted] patients receiving PomDex and Belamaf, respectively. Consequently, results for key outcomes in this subgroup are not statistically significant, as evidenced by the large confidence intervals associated with the median and the stratified HRs. Thus, no interpretations can be made regarding the comparative efficacy of Belamaf vs PomDex due to the high degree of uncertainty.

3.5.3 Conclusion

The efficacy and safety of Belamaf in 5L+ TCR MM patients was demonstrated in the DREAMM-2 trial, a key source of evidence generalisable to the UK population, as evidenced in the original submission.

In addition, new RWE evidence from the [redacted] confirmed the high potential for Belamaf to provide significant clinical benefit for UK patients with 5L+ TCR MM as

evidenced with the ORR, PFS and OS data being superior to that of the registrational DREAMM-2 trial.

When comparing the unadjusted results of the [redacted] study and NCRAS study cohorts, a [redacted] OS, PFS/TTNT and TTD was observed with Belamaf compared to PomDex with a median OS of [redacted] months for Belamaf vs [redacted] months for PomDex, a PFS of [redacted] for Belamaf vs a TTNT of [redacted] months for PomDex and a TTD of [redacted] vs [redacted] months for Belamaf and PomDex, respectively). While the two cohorts presented some differences in baseline characteristics and a number of variables were not available, both cohorts are the most representative of UK patients with 5L+ TCR MM and provide a robust estimate of the efficacy of both interventions in a RWE setting. Hence, a naïve comparison was considered as the most appropriate source of comparative evidence to inform the base case CEA.

While DREAMM-3 is a head-to-head trial of Belamaf vs PomDex, the ITT population is broader than the that of this appraisal. The clinical evidence reported for the subset of 5L+ TCR MM patients within the trial is highly uncertain due to the small sample size (N=[redacted] and N=[redacted] patients for PomDex and Belamaf, respectively) and thus no interpretations can be made regarding the comparative efficacy of Belamaf vs PomDex.

Finally, there are extremely limited treatment options and exquisitely high unmet medical need for the population under evaluation in this appraisal. Belamaf (as the first and only licensed BCMA-targeting antibody-drug conjugate for patients with TCR MM) would provide hope for heavily pre-treated, TCR MM patients who currently face a poor prognosis. The new evidence submitted in this addendum confirms that Belamaf is a clinically effective novel treatment option for 5L+ TCR MM, and as such it has the potential to shift the NICE MM treatment paradigm and provide significant clinical benefit to UK patients.

4 Cost-effectiveness

4.1 Clinical parameters and variables

4.1.1 Data sources for survival endpoints

The key outcomes used in the economic model are OS, PFS and TTD.

As described in Section 3.5.2.2, PFS was not reported in NCRAS, therefore TTNT was selected as a proxy-PFS for PomDex. Both TTNT and PFS were available for Belamaf in the [redacted] dataset, however due to missing data for subsequent treatments it was not possible to generate robust and clinically plausible TTNT data; therefore, PFS was selected for Belamaf, as a conservative estimate of Belamaf efficacy. An unanchored MAIC comparing Belamaf from the [redacted] dataset to PomDex from the NCRAS dataset was explored, as described in Section 3.3, but was deemed unfeasible due to a significant level of missing data for baseline characteristics which would likely results in a reduced ESS. Instead, a naïve comparison of both datasets was selected to inform the base-case in the CEA. For PomDex, only aggregate data for OS, TTNT and TTD were available from NCRAS in the form of KM plots, and as such, these plots were digitised using WebPlotDigitizer software to generate reconstructed KM data. However, for Belamaf, IPD was available from the [redacted] dataset and was used to construct KM plots for OS, PFS and TTD.

Table 26 summarises the clinical efficacy input data used in the CEA base-case.

Table 26. Clinical input data for the base-case naïve (unadjusted) comparison of Belamaf ([redacted]) vs PomDex (NCRAS)

Endpoint	Source of clinical effectiveness	
	Belamaf	**PomDex**
OS	OS IPD collected in [redacted]	OS reconstructed KM from NCRAS
PFS	PFS IPD collected in [redacted]	TTNT reconstructed KM from NCRAS
TTD	TTD calculated in [redacted] from IPD	TTD reconstructed KM from NCRAS

Abbreviations: KM, Kaplan-Meier; NCRAS, national cancer registration and analysis service; OS, overall survival; IPD, individual patient data; PFS, progression-free survival; TTD, time to treatment discontinuation; TTNT, time to next treatment.

4.1.2 Parametric survival modelling

4.1.2.1 [redacted] vs NCRAS analysis

4.1.2.1.1 Overall Survival (OS)

The cumulative log-log plot, the Schoenfeld residual plot and the Cox-Snell plots for OS are presented in Figure 10 (A-C), respectively.

Figure 10. OS diagnostic plots

(A) Top left: Cumulative log-log plot [redacted]/NCRAS, (B) Top right: Schoenfeld plot [redacted]/NCRAS, (C) Bottom: Cox-Snell [redacted]/NCRAS

Abbreviations: 5L+, fifth line and beyond; NCRAS, National Cancer Registration and Analysis Service; [redacted]; MM, multiple myeloma; OS, overall survival; TCR, triple class refractory

Initial inspection of the log cumulative hazard plot (Figure 10 (A)) suggests the PH assumption can be rejected as the lines cross. In contrast, the Schoenfeld residual plot (Figure 10 (B)) shows an approximate 0 slope with a p-value of 0.2071 suggesting the PH assumption cannot be rejected. Additionally, the Cox-Snell plot Figure 10 (C) does not have a unit slope, signifying the PH assumption can again be rejected. Based on the violation of the PH assumption in at least one of the diagnostic plots reported, independent parametric models were fitted to both treatment arms.

Six parametric independent models were fitted to OS KM collected from [redacted]. The AIC/BIC goodness of fit for these six distributions are shown in Table 27. Extrapolations up to 100 months are presented in Figure 11. The corresponding landmark survival estimates are reported in Table 28.

Table 27. Base-case: AIC and BIC statistical goodness of fit data for Belamaf OS from [redacted] (independent models)

Goodness of fit statistics: Belamaf, OS		
Parametric survival model	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; OS, overall survival
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 11. Belamaf OS extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Table 28. Base-case: Belamaf survival landmark rates for OS

	Proportion of patients alive at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Proportion of patients alive at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS; overall survival

According to the AIC and BIC, the [redacted] and [redacted] are the best statistically fitting curves for Belamaf OS (**Table 27**Table 27). The [redacted] has the largest tail over time, potentially overestimating the survival for Belamaf.

The landmark survival rates estimate a 5-year survival probability of [redacted]% for the [redacted] curve. The [redacted] curve estimates a 5- and 10-year survival probability of [redacted]% and [redacted]% respectively. The [redacted] and [redacted] curves therefore provide similar estimates and are lower than what was validated in the original CS, so therefore may be underestimating the OS for Belamaf (Table 28).

PomDex overall survival

Please see the CS document B section B.3.3.3.2 for the full details of AIC/BIC and landmark survival rates for PomDex OS from the NCRAS study. These are consistent with those included in the updated base-case. Figure 12 shows the extrapolations using each model up to 70-months.

Figure 12. Base-case: PomDex OS extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; OS; overall survival

According to the AIC and BIC, the [redacted] distribution was the best statistically fitting model for PomDex OS (CS document B, Table 52). Despite this, the tail in the [redacted] distribution appears to potentially overestimate OS compared to clinical expert expectations (Figure 12).

Landmark survival estimates at 2-years show a variation from [redacted]% to [redacted]% of patients are expected to be alive based on the distribution selected (CS document B, Table 53). The conclusion from clinical opinion suggest that the [redacted] distribution produced the most clinically plausible results with [redacted]% of patients expected to be alive at 2-years and [redacted]% alive at 5-years.

Overall survival conclusions

Considering the visual fit, statistical fit and expert clinical opinion, the [redacted] curve was chosen as the base-case distribution for both treatment arms. Figure 13 shows the chosen base-case OS distribution for both treatments where OS is capped by general mortality i.e., OS is modelled to not exceed general population survival.

Figure 13. Belamaf and PomDex OS KM and [redacted] curves

Abbreviations: OS, overall survival

4.1.2.1.2 Progression-free survival (PFS)

The cumulative log-log plot, the Schoenfeld residual plot and the Cox-Snell plots for PFS are presented in Figure 14 (A-C), respectively.

Figure 14. PFS diagnostic plots

(A) Top left: Cumulative log-log plot [redacted]/NCRAS, (B) Top right: Schoenfeld plot [redacted]/NCRAS, (C) Bottom: Cox-Snell [redacted]/NCRAS

Abbreviations: 5L+, fifth line and beyond; NCRAS, National Cancer Registration and Analysis Service; [redacted]; MM, multiple myeloma; PFS, progression-free survival; TCR, triple class refractory

Initial inspection of the log cumulative hazard plot (Figure 14 (A)) suggests the PH assumption can be rejected as the lines cross. Contrastingly, the Schoenfeld residual plot (Figure 14 (B)) shows an approximate 0 slope with a p-value of 0.1772 suggesting the PH assumption cannot be rejected. Finally, the Cox-Snell plot (Figure 14 (C)) does not have a unit slope, signifying the PH assumption can again be rejected. Based on the rejection of the PH assumption in at least one of the diagnostic plots reported, independent parametric models were fitted to both treatment arms.

Belamaf PFS

Six parametric independent models were fitted to PFS KM collected from [redacted] however the [redacted] curve did not converge. The AIC/BIC statistical goodness of fit for the five distributions which converged are shown in Table 29**Error! Reference source not found.**. Extrapolations of PFS using each model is presented in Figure 15. **Belamaf PFS extrapolated dependent survival curvesError! Reference source not found.** to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility. The landmark survival estimates from each of the PFS extrapolations are presented in Table 30**Error! Reference source not found.**.

Table 29. Base-case: AIC and BIC statistical goodness of fit data for Belamaf PFS from [redacted] (independent models)

Goodness of fit statistics: Belamaf, PFS		
Parametric survival model	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; NA, not available; PFS, progression-free survival
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.
The [redacted] curve did not converge.

Figure 15. Belamaf PFS extrapolated dependent survival curves

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Table 30. Base-case: Belamaf landmark PFS rates

Distribution	Proportion of patients who are progression-free at:				
	6 months	1-year	2-years	5-years	10-years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not available. Note: The [redacted] curve did not converge.

According to the AIC and BIC, the [redacted] distribution appeared to provide the best statistically fitting model for Belamaf PFS. However landmark rates show the [redacted] curve estimates that [redacted]% and [redacted]% of patients are progression-free at 5-years and 10-years, respectively (Table 33). These estimates are not consistent with Belamaf OS estimated at [redacted]% and [redacted]% and 5-years and 10-years, respectively (Table 28), as per the base-case [redacted] distribution. The [redacted] and [redacted] PFS distributions are consistent with the base-case OS [redacted] distribution with [redacted]% and [redacted]% at 5-years and [redacted]% at 10-years, with the [redacted] distribution being the most conservative and selected for the base-case.

PomDex PFS

Please see the CS document B section B.3.3.3.1 for the full details of AIC/BIC and landmark survival rates for PomDex PFS from the NCRAS study. These are consistent with those included in the updated base-case Figure 16 shows the PFS extrapolations from each model up 60-months.

Figure 16. PomDex PFS extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

According to the AIC and BIC, the [redacted] distribution was the best statistically fitting model for PomDex PFS (CS document B, Table 48). The statistical fit data for Gompertz was not reported such that this aspect could not be assessed. The landmark survival rates from all six distributions show that, at 2-years, between [redacted]% and [redacted]% of patients are progression-free (CS document B, Table 49).

According to clinical expert opinion, all the landmark rates overestimate PomDex PFS from 2 years onwards as, in clinical practice, it is not expected that patients would be progression-free beyond this time point.

PFS survival conclusions

Considering the visual fit, statistical fit, clinical plausibility and clinical expert opinion the [redacted] curve represents the most appropriate distribution to extrapolate PFS and therefore was selected for both treatment arms in the base-case analysis. The [redacted] provides one of the lowest proportions of patients progression-free at 2 years across both Belamaf and PomDex at [redacted]% and [redacted]%, respectively.

Feedback from clinical experts indicated that no patients receiving PomDex and Belamaf would be expected to be progression-free beyond 2 years. Furthermore, based on the BSH 2023 abstract, median EFS was [redacted] months (IQR [redacted]) indicating the curve for Belamaf most likely overestimates PFS at 2 years. Accordingly, PFS was capped so that after 2-years, 0% of PomDex and Belamaf patients remain progression-free with a 50% waning applied after 1-year. In addition, PFS was capped by OS i.e., PFS modelled to not exceed OS.

Figure 17 shows the chosen base-case PFS distribution for both treatment arms, inclusive of the 2-year cap and waning, alongside the KM curves from the respective data sources.

Figure 17. Belamaf and PomDex PFS KM and [redacted] curve (base-case)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

4.1.2.1.3 Time to treatment discontinuation or death (TTD)

The cumulative log-log plot, the Schoenfeld residual plot and the Cox-Snell plots for TTD are presented in Figure 18 (A-C), respectively.

Figure 18. TTD diagnostic plots

[redacted]

(A) Top left: Cumulative log-log plot [redacted]/NCRAS, (B) Bottom left: Schoenfeld plot [redacted]/NCRAS, (C) Right: Cox-Snell [redacted]/NCRAS

Abbreviations: 5L+, fifth line and beyond; MM, multiple myeloma; NCRAS, National Cancer Registration and Analysis Service; [redacted], [redacted]; TCR, triple class refractory; TTD, time to treatment discontinuation

Initial inspection of the log cumulative hazard plot (Figure 18 (A)) suggests the PH assumption can be rejected as the lines cross. The Schoenfeld residual plot (Figure 18 (B)) shows a slightly declining slope however the p-value of 0.001 suggests the PH assumption can be rejected. Similarly, the Cox-Snell plot (Figure 18 (C)) does not have a unit slope, signifying the PH assumption can be rejected. Based on the violation of the PH assumption in all of the diagnostic plots reported, independent parametric models were fitted to both treatment arms.

Belamaf time to treatment discontinuation

In line with the approach for OS, six parametric independent models were fitted to the TTD KM collected from [redacted]. The AIC/BIC goodness of fit for these six distributions are shown in Table 31. Figure 19 presents the TTD extrapolations from each models up to 60-months and Table 32 summarises the TTD landmark estimates from each of the distributions up to a 10-year timepoint.

Table 31. Base-case: AIC and BIC statistical goodness of fit data for Belamaf TTD from [redacted] (independent models)

Goodness of fit statistics: Belamaf, TTD		
Parametric survival model	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; Bayesian information criterion; TTD, time to treatment discontinuation
Note: Parametric survival models with the best statistical fit (i.e., with the lowest AIC/BIC) are highlighted in bold.

Figure 19. Belamaf TTD extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

Table 32. Base-case: Belamaf landmark rates for TTD

	Proportion of patients who discontinued at:				
Distribution	**6 months**	**1-year**	**2-years**	**5-years**	**10-years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD, time to treatment discontinuation

According to the AIC and BIC, the [redacted] distribution provides the best statistically fitting curve for Belamaf TTD (Table 31) however does not converge from [redacted] months with extremely small estimates which are handled by Excel by rounding to zero. Subsequently, visually, the [redacted] distribution is the best fit (Figure 19).

Landmark rates indicate that [redacted]% and [redacted]% of patients remain on treatment at 10 years and 5 years respectively when [redacted] is chosen. This is consistent with the

landmark rates of the [redacted] distribution for PFS which suggests that [redacted]% are progression-free beyond 10-years (Table 32).

PomDex time to treatment discontinuation

Please see the CS document B section B.3.3.3.3 for the full details of AIC/BIC and landmark survival rates for PomDex TTD from the NCRAS study. These are consistent with those included in the updated base-case. Figure 20 shows the TTD extrapolations from each model up 60-months.

Figure 20. Base-case: PomDex TTD extrapolated independent survival curves

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

According to the AIC and BIC, the [redacted] distribution is best statistically fitting curve for PomDex TTD (CS document B, Table 56). Landmark rates (CS document B, Table 57) show that the [redacted] distribution estimates the lowest proportion of patients on treatment beyond 5 year and closest to the observed data.

Time to treatment discontinuation conclusions

Considering the visual fit, statistical fit, clinical plausibility and expert clinical opinion the [redacted] curve was deemed most appropriate to model both treatment arms and was chosen as the base-case. Figure 21 shows the chosen base-case TTD distribution for both treatments.

Figure 21. Belamaf and PomDex KM and [redacted] TTD curves (base-case)

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

4.2 Cost parameters

4.2.1 Drug acquisition costs for Belamaf

Belamaf is available as a 100 mg powder for concentration solution at a list price per vial of £5,707.83.[13] An updated confidential simple Patient Access Scheme (PAS) discount of [redacted]% is proposed by the Company. At a list price of £5,707.83 for 1 vial of 100 mg powder for concentration solution, this results in a PAS price of £[redacted].

4.2.2 Relative dose intensity (RDI) from [redacted] dataset

For the base-case, information on relative dose intensity (RDI) was sought from the [redacted] dataset. RDI is based on dose delays and dose reductions.

To calculate the impact of dose delays on RDI, the study start and end date for each patient in the [redacted] cohort was considered. The study start date was available for all patients, and the end date was available for [redacted] patients (the total number of patients from the BSH abstract (74) was considered here as it is assumed that dosing in the total cohort will be the same as that in the 5L+ TCR subgroup). From these dates, it is possible to calculate how many doses of Belamaf these patients should have received during this time frame and compare this figure to the number of doses actually received. Patients with no recorded end date were censored at the

date of last observation. Comparing actual versus expected Belamaf doses gives an RDI of [redacted]% prior to inclusion of dose reduction.

For dose reduction, the number of patients with a dose reduction is recorded within the [redacted] study, but when patients received the reduction and how much the dose was reduced by was not recorded. Given the lack of available data, the average dose from DREAMM-2 was applied to the [redacted] data, giving a final RDI of [redacted]%.

4.2.3 Subsequent treatments

Use of subsequent therapy data for Belamaf from the [redacted] dataset was attempted, however data were available for [redacted] patients only. Therefore, the NCRAS subsequent therapy data were assumed for Belamaf. The median number of prior lines is higher in the Belamaf cohort ([redacted] vs [redacted]) and the proportion of patients reaching 7L (after relapse on Belamaf at 6L) is expected to be lower than the proportion of patients reaching 6L (after relapse on PomDex at 5L) due a decreasing probability of survival as patients progress. Furthermore, the number of treatment options available decrease as patients progress in the 5L+ TCR setting and as such it is expected that a lower proportion of patients may be able to receive subsequent treatments after Belamaf than after PomDex in this context. Hence, this assumption is considered conservative and a scenario analysis exploring a 5% decrement of the proportion of patients receiving subsequent treatments was explored.

4.3 Summary of base-case analysis inputs and assumptions

4.3.1 Summary of base-case analysis inputs

A summary of the variables updated for the base-case and applied in the CEA is presented in Table 33.

Table 33. Summary of updates to base-case analysis inputs

Parameter	Value	OWSA			Within PSA varied by	Reference to location in submission
		SE	Lower bound	Upper bound		
Drug acquisition costs						
Belamaf cost per cycle (£)	[redacted]	-	-	-	-	TE addendum section 4.2.1 and 4.2.2
Belamaf relative dose intensity (%)	[redacted]	[redacted]	[redacted]	[redacted]	Beta	

Parameter	Value	OWSA			Within PSA varied by	Reference to location in submission
		SE	Lower bound	Upper bound		
Subsequent treatments						
Belamaf subsequent tx (% patients)	[redacted]	[redacted]	[redacted]	[redacted]	Beta	TE addendum section 4.2.3
Belamaf subsequent tx cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	Gamma	
Concomitant therapies*						
Belamaf concomitant therapies/supportive care one-off cost (£)	392.48	78.50	253.99	560.62	Gamma	Document B, section B.3.5.4.2
PomDex concomitant therapies/supportive care one-off cost (£)	1,136	227.18	735.11	1622.56	Gamma	
Routine monitoring costs**						
Belamaf routine monitoring PFS on-tx total cost (£)	46.97	9.39	30.40	67.09	Gamma	Document B, section B.3.5.2.1
Belamaf routine monitoring PFS off-tx total cost (£)	17.06	3.41	11.04	24.37	Gamma	
Belamaf routine monitoring PD total cost (£)	17.98	3.60	11.63	25.68	Gamma	
PomDex routine monitoring PFS on-tx total cost (£)	46.97	9.39	30.40	67.09	Gamma	
PomDex routine monitoring PFS off-tx total cost (£)	17.06	3.41	11.04	24.37	Gamma	
PomDex routine monitoring PD total cost (£)	17.98	3.60	11.63	25.68	Gamma	
Quality of life						
Utility: PFS on-tx	[redacted]	[redacted]	[redacted]	[redacted]	Beta	TE response document, Issue 3
Utility: PFS off tx	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Utility: PD	[redacted]	[redacted]	[redacted]	[redacted]	Beta	
Belamaf adverse event total disutility†	0.20	0.04	0.130	0.29	Beta	
Waning and curve capping						
Year 1-2 PomDex PFS waning (%)	50	-	-	-	-	TE addendum section 4.1.2.1.2
Year 1-2 Belamaf PFS waning (%)	50	-	-	-	-	
Belamaf PFS curve cap at 2 years (%)	0	-	-	-	-	

Parameter	Value	OWSA			Within PSA varied by	Reference to location in submission
		SE	Lower bound	Upper bound		
PomDex PFS curve cap at 2 years (%)	0	-	-	-	-	

Abbreviations: OWSA, one-way sensitivity analysis; PD, progressed disease; PFS, progression-free disease; PSA, probabilistic sensitivity analysis; SE, standard error; TE, Technical Engagement
* Concomitant therapy costs have changed from the original submission based on updates made at the Clarification Question stage
** Routine monitoring costs have changed due to updated survival curves in the base case
† AE disutility for Belamaf has changed from the original submission based on updates made at the Clarification Question stage

4.3.2 Assumptions

The summary of modelling assumptions was provided in Document B, section B.3.9.2, Table 91 of the original submission.

In addition to the key assumptions described in the original submission (section B.3.9.2, Table 91), additional assumptions were required when implementing new evidence into the cost-effectiveness model. These assumptions are detailed in Table 34. The updated base-case results and conclusions can be found in the main response document.

The updated base-case results and conclusions can be found in the main response document.

Table 34. List of assumptions for the base-case cost-effectiveness analysis

Category	Assumption	Justification
Clinical effectiveness	TTNT is used as a proxy for PomDex PFS in the economic analysis	PFS was not reported in NCRAS, and TTNT from the [redacted] dataset was subject to missing data. Therefore, PFS was used for Belamaf from the [redacted] dataset while TTNT was considered for PomDex as a proxy for PFS in the economic model. This approach is likely to underestimate the comparative effectiveness of Belamaf relative to PomDex.
	A naïve comparison was used to inform the efficacy for Belamaf ([redacted] dataset) to PomDex (NCRAS dataset)	Given the level of missing data for baseline characteristics in the [redacted] and NCRAS datasets, an unanchored MAIC was deemed unfeasible due to likely reduction in ESS and instead, a naïve comparison was selected as the most appropriate source of evidence in the base case cost-effectiveness analysis.
	PFS is capped at 2-years for PomDex and Belamaf	Clinical experts have indicated that in practice patients are unlikely to remain progression-free after 2-years when receiving treatment in the 5L+ TCR setting therefore the PFS curves for PomDex and Belamaf were capped at this timepoint.
	50% waning is applied to PFS after 1-year for Belamaf and PomDex	The proportion of patients in the progression-free survival state in the economic model seems to be higher than expected in clinical practice, based on clinical expert feedback. A 50% waning was applied to PFS to adjust the proportion of patients in PFS after 1-year in both arms.
	RDI is [redacted]% based on the [redacted] dataset	To reflect the updated base case using Belamaf efficacy data from the [redacted] dataset, RDI data from the [redacted] dataset are also used.
	The updated DREAMM-2 data utility values have been used	The utility values used in base case have been updated to the 40-month final analysis values of DREAMM-2 in order to provide the most up-to-date estimates for health state utilities.
Cost and resource use inputs	Subsequent treatments were informed by the NCRAS dataset for both Belamaf and PomDex	Given the high level of missing data for subsequent treatment in the [redacted] dataset, NCRAS was used as the next best available source to inform the proportion of patients receiving subsequent treatment for Belamaf. This is likely to be a conservative assumption as described in section 4.2.3 and a scenario analysis applying a 5% decrement in the proportion of patients receiving subsequent therapy.

5 References

1. BSH. Data on file. Abstract: Belantamab Mafodotin for Relapsed/ refractory Myeloma patients: A Retrospective Real-World, Multi-Centre UK & ROI Study. 2023.

2. NHS Foundation Trust. Efficacy and toxicity outcomes of belantamab mafodotin in relapsed/refractory myeloma: UK-wide real-world study of the compassionate use programme. Study Protocol. 2021.

3. 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.

4. GSK. Statistical Analysis Plan for DREAMM-3. 2022.

5. GSK. DREAMM-3 study protocol. 2019.

6. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. Cancer. 2021 Nov 15;127(22):4198–212.

7. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet Oncology. 2014 Nov;15(12):e538–48.

8. San Miguel JF, KC W, KW S. 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;100:1334–9.

9. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics. 1982;38(1):29–41.

10. GSK. GSK provides update on DREAMM-3 phase III trial for Blenrep in relapsed/refractory multiple myeloma [Internet]. 2022. Available from: https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-dreamm-3-phase-iii-trial-for-blenrep/

11. Collaboration C. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Available from: http://handbook.cochrane.org/.

12. Population-adjusted indirect comparisons (MAIC and STC) | NICE Decision Support Unit | The University of Sheffield [Internet]. [cited 2022 Sep 23]. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/population-adjusted

13. Belantamab mafodotin | Drugs | BNF content published by NICE [Internet]. [cited 2022 Aug 19]. Available from: https://bnf.nice.org.uk/drugs/belantamab-mafodotin/

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Clarification questions

November 2022

File name	Version	Contains confidential information	Date
ID2701 belantamab mafodotin clarification response v1.0 07Nov2022 AIC	1.0	Yes	7th November, 2022

Section A: Clarification on effectiveness data

Literature searching

A1. Appendix D, Figure 1 (PRISMA diagram, page 25)

a) **Please provide a list of the 752 publications excluded during full-text screening from the original clinical efficacy and safety SLR.**
b) **Please, provide a breakdown of 69 publications in a table with unique study in each row with its reference(s) and design (RCT, single-arm study, observational cohort study, etc.)**

Response: The requested lists are provided in Appendix B; the 752 studies excluded from the original clinical efficacy and safety systematic literature review (SLR) are shown in Table 1, while the 71 included studies from the original clinical efficacy and safety SLR are shown in Table 2.

A2. Appendix G, Figure 1 (PRISMA diagram, page 12): Please provide a list of the 238 publications excluded during full-text screening from the original economic SLR.

Response: The requested list is provided in Appendix B, Table 3.

A3. Appendix D, Figure 2 (PRISMA diagram, page 30): Of these 88 publications, 55 were clinical publications and 17 unique studies which are detailed in Table 13. Can the company explain if the 17 unique studies are represented in 55 clinical publications? And why the 17 unique studies are not included in the PRISMA chart (final box)? The numbers do not add up from 17 to 55 because most of the 17 unique studies represent a single publication.

Response: The 17 unique studies are not included in the PRISMA chart because there were 55 publications found that referred to these. The preference is to report n=55 as this is the actual number of publications found. A list of the 55 publications identified through the database searching and grey literature searches have been grouped by the 17 unique studies (Table 1).

Table 1. Publications identified through database searches (n=55)

Trial name, identifier	Author	Year	Title
DREAMM-2 NCT03525678 [1–27]	Lonial et al.	2021	Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study
	Lonial et al.	2021	Characterization of ocular adverse events in patients receiving Belantamab Mafadotin for ≥12 months: post-hoc analysis of DREAMM-2 study in relapsed/refractory Multiple Myeloma
	Popat et al.	2021	Can Patient-Reported Ocular Symptoms Guide Dose Modifications in Patients with Relapsed/Refractory Multiple Myeloma Receiving Belantamab Mafodotin?
	Terpos et al.	2021	Relationship between corneal exam findings, best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin (belamaf)
	Terpos et al.	2021	Relationship between corneal exam findings best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin
	Lonial et al.	2021	Recovery of ocular events with longer-term follow-up in the DREAMM-2 study of single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma
	Eliason et al.	2020	Patient-Reported Experiences during and Following Treatment with Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study
	Popat et al.	2021	DREAMM-2: Single-agent belantamab mafodotin (BELAMAF) effects on patient-reported outcome (PRO) measures in patients with relapsed/refractory multiple myeloma (RRMM)
	Trautmann-Grill et al.	2021	Characterization of ocular adverse events in patients receiving belantamab mafodotin (Belamaf) for ≥12 months: Post-hoc analysis of dreamm-2 study in relapsed/refractory multiple myeloma (RRMM)
	Nooka et al.	2020	Infusion-Related Reactions (IRRs) in the DREAMM-2 Study of Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)
	Popat et al.	2020	Ocular Health of Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Baseline Data from the DREAMM-2 Trial of Belantamab Mafodotin (Belamaf)
	Richardson et al.	2020	Single-agent belantamab mafodotin for relapsed/refractory multiple myeloma: analysis of the lyophilised presentation cohort from the pivotal DREAMM-2 study
	Lonial et al.	2020	MM-219: Pivotal DREAMM-2 Study: Single-Agent Belantamab Mafodotin (Belamaf; GSK2857916) in

Trial name, identifier	Author	Year	Title
			Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to Proteasome Inhibitors and Immunomodulatory Agents, and Refractory and/or Intolerant to Anti-CD38 Monoclonal Antibodies (mAbs), Including Subgroups with Renal Impairment (RI) and High-Risk (HR) Cytogenetics
	Lee et al.	2020	DREAMM-2: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) and renal impairment
	Lee et al.	2020	DREAMM-2: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) and renal impairment
	Lonial et al.	2020	DREAMM-2: Single-agent belantamab mafodotin in relapsed/refractory multiple myeloma refractory to proteasome inhibitors, immunomodulatory agents, and refractory and/or intolerant to anti-CD38 mABs
	Lonial et al.	2020	DREAMM-2: Single-agent belantamab mafodotin in patients with relapsed/refractory multiple myeloma (RRMM)-outcomes by prior therapies
	Richardson et al.	2020	DREAMM-2 pivotal study: Analysis of the lyophilized presentation cohort of single-agent belantamab mafodotin for relapsed/refractory multiple myeloma
	Lonial et al.	2021	MM-078: Characterization of Ocular Adverse Events in Patients Receiving Belantamab Mafodotin (Belamaf) for ≥12 Months: Post Hoc Analysis of DREAMM-2 Study in Relapsed/Refractory Multiple Myeloma (RRMM)
	Lonial et al.	2021	Characterization of ocular adverse events in patients receiving belantamab mafadotin for ≥12 months: post-hoc analysis of dreamm-2 study in relapsed/refractory multiple myeloma
	Baines et al.	2022	FDA Approval Summary: Belantamab Mafodotin for Patients with Relapsed or Refractory Multiple Myeloma
	Kortüm et al.	2021	Relationship between corneal exam findings, best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin (GSK2857916; belamaf; BLENREP)
	Terpos et al.	2021	MM-103: Relationship Between Corneal Exam Findings, Best-Corrected Visual Acuity (BCVA), and Ocular Symptoms in Patients with Relapsed or Refractory Multiple Myeloma (RRMM) Receiving Belantamab Mafodotin (GSK2857916; Belamaf)
	Eliason et al.	2021	Patient-reported experiences during and following treatment with belantamab mafodotin (BELAMAF) for relapsed/refractory multiple myeloma (RRMM) in the DREAMM-2 study
	Lonial et al.	2020	Pivotal DREAMM-2 study: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM)

Trial name, identifier	Author	Year	Title
			refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs)
	Cohen et al.	2020	DREAMM-2: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) and high-risk (HR) cytogenetics
	Lonial et al.	2020	Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study
PomDex RWE study Cerchione, C 2022 [28–35]	Cerchione et al.	2022	Domestic opportunity in heavily pretreated multiple myeloma not eligible to hospital-based treatment: Role of pomalidomide-dexamethasone
	Cerchione et al.	2021	Pomalidomide-Dexamethasone in the Management of Heavily Pretreated Multiple Myeloma
	Nappi et al.	2021	MM-415: Pomalidomide-Dexamethasone in the Management of Heavily Pretreated Multiple Myeloma
	Cerchione et al.	2021	Pomalidomide-dexamethasone in the management of relapsed/refractory multiple myeloma
	Cerchione et al.	2021	Pomalidomide-dexamethasone in the management of heavily pretreated multiple myeloma
	Cerchione et al.	2020	Pomalidomide-Dexamethasone in the Management of Heavily Pretreated Multiple Myeloma
	Cerchione et al.	2020	Pomalidomide-dexamethasone in the management of heavily pretreated multiple myeloma
	Cerchione et al.	2020	MM-389: Pomalidomide-Dexamethasone in the Management of Heavily Pre-Treated Multiple Myeloma
NIMBUS NCT01311687 [36,37]	NCT01311687	-	A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Pomalidomide in Combination With Low-Dose Dexamethasone Versus High-Dose Dexamethasone in Subjects With Refractory Multiple Myeloma or Relapsed and Refractory Multiple Myeloma and Companion Study (NIMBUS)
	van Beurden-Tan et al.	2022	Multinomial network meta-analysis using response rates: relapsed/refractory multiple myeloma treatment rankings differ depending on the choice of outcome
APOLLO NCT03180736 [38]	Dimopoulos et al.	2020	Apollo: phase 3 randomized study of subcutaneous daratumumab plus pomalidomide and dexamethasone (D-PD) versus pomalidomide and dexamethasone (PD) alone in patients (PTS) with relapsed/refractory multiple myeloma (RRMM)
ICARIA-MM NCT02990338 [39]	NCT02990338	2016	Multinational Clinical Study Comparing Isatuximab, Pomalidomide, and Dexamethasone to Pomalidomide and Dexamethasone in Refractory or Relapsed and Refractory Multiple Myeloma Patients

Trial name, identifier	Author	Year	Title
MM-011 NCT02011113 [40]	Ichinohe et al.	2016	A multicenter phase 2 study of pomalidomide plus dexamethasone in patients with relapsed and refractory multiple myeloma: the Japanese MM-011 trial
PANORAMA-1 Maouche, N 2022[41,42]	Maouche et al.	2022	Panobinostat in combination with bortezomib and dexamethasone in multiply relapsed and refractory myeloma; UK routine care cohort
	Maouche et al.	2020	Panobinostat in combination with bortezomib and dexamethasone for heavily pre-treated myeloma: A UK real-world multi-centre cohort
PANORAMA-1 Bird, S 2019 [43,44]	Bird et al.	2019	A 'real-world' study of panobinostat, bortezomib and dexamethasone in a very heavily pre-treated population of myeloma patients
	Bird et al.	2020	MM-296: A Real-World Study of Panobinostat, Weekly Bortezomib, and Dexamethasone in a Very Heavily Pre-Treated Population of Multiple Myeloma Patients
IFM2009-02 Leleu, X 2011 [45,46]	Leleu et al.	2011	Phase 2 randomised open label study of 2 modalities of pomalidomide (CC4047) plus low-dose dexamethasone in patients with multiple myeloma, refractory to both lenalidomide and bortezomib
	Leleu et al.	2013	Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: intergroupe Francophone du Myélome
Wester, R 2022 [47]	Wester et al.	2022	Pomalidomide in Patients With Relapsed and/or Refractory Multiple Myeloma: A Prospective Study Within the Nationwide Netherlands Cancer Registry
Park, H 2022 [48]	Park et al.	2022	Cyclophosphamide addition to pomalidomide/dexamethasone is not necessarily associated with universal benefits in RRMM
Abeykoon, P 2021 [49]	Abeykoon et al.	2021	Ocular toxicity of commercially available belantamab mafodotin in patients with advanced multiple myeloma
Del Giudice, ML 2021 [50]	Del Giudice et al.	2021	Real-Life Experience with Pomalidomide plus Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma: A Retrospective and Prospective Study
Shragai, T 2021 [51 52]	Shragai et al.	2021	Belantamab mafodotin treatment for patients with relapsed/refractory myeloma via GSK expanded access program: Real-world data
	Shragai et al.	2020	Real-world outcomes of belantamab mafodotin treatment for patients with relapsed/ refractory myeloma via GSK expanded access program
Becnel, M 2022 [53]	Becnel et al.	2022	Retrospective, single-center, real-world experience of belantamab mafodotin in relapsed/refractory multiple myeloma
Talbot, A 2022[54]	Talbot et al.	2022	P-276 Real-world study of the efficacy and safety of belantamab mafodotin (GSK2857916) in relapsed or refractory multiple myeloma based on data from the nominative ATU in France: IFM 2020-04 study

Trial name, identifier	Author	Year	Title
Pooled DREAMM-1 and DREAMM-2 Trudel, S 2020[55]	Trudel et al.	2020	Safety and tolerability of single-agent belantamab mafodotin in heavily pre-treated patients with relapsed/refractory multiple myeloma: Pooled data from DREAMM-1 and DREAMM-2

A4. Appendix H.2, SLR update (page 2-3): the SLR update for HRQoL/utilities included 18 publications, of which 9 reported utilities and are listed in Table 2. Please provide a list of the remaining 9 publications that did not report utilities (or a full list of all 18 included studies).

Response: The list of all 18 health-related quality of life (HRQoL) publications identified through the database searching and grey literature searches is provided in Table 2.

Table 2. Full list of HRQoL publications identified in the SLR update (n=18)

Author	Year	Title
Nikolaou et al.[56]	2021	Belantamab mafodotin for the treatment of relapsed/refractory multiple myeloma in heavily pretreated patients: a US cost-effectiveness analysis
Dimopoulos et al.[57]	2020	Health-related quality of life in heavily pretreated and renally impaired patients with relapsed/ refractory multiple myeloma receiving isatuximab plus pomalidomide and dexamethasone: ICARIA-MM study
Dimopoulos et al.[58]	2021	Treatment of patients with relapsed/ refractory multiple myeloma with pomalidomide and dexamethasone with or without subcutaneous daratumumab: patient-reported outcomes from Apollo
Delforge et al.[59]	2020	Health state utility valuation in patients with triple-class-exposed relapsed and refractory multiple myeloma treated with the bcma-directed car t cell therapy, idecabtagene vicleucel (IDE-Cel,BB2121): results from the Karmma trial
Tang et al.[60]	2021	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
Popat et al.[61]	2020	DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) Effects on Patient-Reported Outcome (PRO) Measures in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)
Oriol et al.[62]	2020	HORIZON (OP-106): Melflufen Plus Dexamethasone (dex) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM) - Health-Related Quality of Life (HRQoL) Analysis
Shah et al.[63]	2020	Secondary Quality-of-Life Domains in Patients with Relapsed and Refractory Multiple Myeloma Treated with the Bcma-Directed CAR T

		Cell Therapy Idecabtagene Vicleucel (ide-cel; bb2121): Results from the Karmma Clinical Trial
Martin et al.[64]	2020	Health-Related Quality of Life in the Cartitude-1 Study of Ciltacabtagene Autoleucel for Relapsed/Refractory Multiple Myeloma
Delforge et al.[65]	2020	Quality of life in patients with relapsed and refractory multiple myeloma treated with the BCMA targeted CAR T cell therapy idecabtagene vicleucel (IDE-CEL; BB2121): Results from the KarMMa trial
Popat et al.[66]	2020	DREAMM-2: Belantamab mafodotin effect on disease symptoms and health-related quality of life in patients with relapsed/refractory multiple myeloma (RRMM)
Engelhardt et al.[67]	2020	Health-related quality of life (HRQOL) reported by patients with multiple myeloma (MM) in Germany
Richardson et al.[68]	2019	The Burden of Relapsed/Refractory Multiple Myeloma: An Indirect Comparison of Health-Related Quality of Life Burden across Different Types of Advanced Cancers at Baseline and after Treatment Based on HORIZON (OP-106) Study of Melflufen Plus Dexamethasone
Delforge et al.[69]	2022	P-239 Health-related quality of life (HRQoL) in patients with relapsed/refractory multiple myeloma (RRMM) receiving real life standard of care (SOC) treatments: results from the LocoMMotion study
Wagner et al.[70]	2021	P-136 Health-Related Quality of Life (HRQL) Among Real-World Ide-Cel–Eligible Patients (pts) With Relapsed/Refractory Multiple Myeloma (RRMM): Results From the Connect® MM Registry
NICE TA510/ TA783[71,72]	2022	Daratumumab monotherapy for treating relapsed and refractory multiple myeloma
NICE TA658[73]	2020	Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma
NICE TA427[74]	2017	Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib

A5. When describing identified studied used to inform the CS (page 38), Becnel et al. 2022[83] reported RWE for the efficacy and safety of Belamaf in a population which was 95% TCR, most of the patients (69%) were ineligible for inclusion in DREAMM-2 and notably, 21% were refractory to a BCMA; an exclusion criteria for DREAMM-2. Given the patient population characteristics and limited data reported (abstract only) the study was not deemed relevant to the decision problem. However, Becnel et al. 2022[83] is not listed in Table 14, Appendix D. Will the Company explain why?

(NB. A full list of all studies excluded from the SLR update at second pass alongside reasons for exclusion are given in Table 14)

Response: The Company had included text to describe that DREAMM-2 and Becnel et al. 2022[53] were the only studies included in the clinical and safety SLR with triple-

class refractory (TCR) multiple myeloma (MM) patients which should be considered for the decision problem, however Becnel et al. 2022[53] was subsequently deemed not relevant to the decision problem and therefore not included in Section B.2 of the Company submission since most of the patients were ineligible for inclusion in DREAMM-2 (69%) and some were refractory to a B-cell maturation antigen (BCMA) (21%), as stated in the question. Becnel et al. 2022[53] was not included in Table 14 of Appendix D because it was not excluded at second pass, it was included (part of n=55 studies identified as per Question A3. Appendix D, Figure 2 (PRISMA diagram, page 30): Of these 88 publications, 55 were clinical publications and 17 unique studies which are detailed in Table 13. Can the company explain if the 17 unique studies are represented in 55 clinical publications? And why the 17 unique studies are not included in the PRISMA chart (final box)? The numbers do not add up from 17 to 55 because most of the 17 unique studies represent a single publication.) however was deemed not relevant to the decision problem upon subsequent exploration.

Clinical effectiveness

A6. In Section B.1.3.3.1 Treatment pathway in 5L+ TCR MM (page 20), the Company states that given NCRAS database, the use of PomDex in 5L + TCR MMRR population accounts for about [redacted], PanoBorDex [redacted], and chemotherapy [redacted], which accounts for a total of [redacted] of usage. Can the company specify what treatments account for the remaining [redacted] usage in the 5L + TCR MMRR population, according to NCRAS?

Response: A summary of the National Cancer Registration and Analysis Service (NCRAS) treatment distribution (5L+ TCR MM) is provided below:

- PomDex: n=[redacted] ([redacted])
- PanoBorDex: n=[redacted] ([redacted])
- Chemotherapy (see below paragraph): n=[redacted] ([redacted])
- Other: n=[redacted] ([redacted])
- Total 5L+ TCR cohort: n=[redacted] ([redacted]).

“Chemotherapy” was defined as chemotherapy with or without a steroid and with or without thalidomide as per NICE’s final scope.[75]

A breakdown of the ‘other’ group is given in Table 3.

Table 3. Treatment distribution among 'other' group

Regimen (see note 1 below)	Number of 5L+ TCR patients (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Notes: 1. Steroids may not be recorded in the NCRAS data set; 2. [redacted]

A7. In Section B.2.3.2 PomDex (NCRAS study) (page 37), Figure 7 the CS states CDF-excluded patients (N=[redacted]), Figure 7. Can the Company clarify who "CDF-excluded patients (N=[redacted])" are? and specify why they were excluded from 5L TCR MM group of patients.

Response: The guidelines for analyses using the NCRAS dataset require a censoring of patients who have received an intervention currently provided via the Cancer Drugs Fund (CDF). An embargo is in place as part of an agreement between NCRAS and NHS England, to prevent release of data relating to CDF evaluations prior to a decision from NICE as to whether a given drug/indication will go into routine commissioning. Consequently, a total of [redacted] patients receiving a CDF-funded treatment at any point of the pathway were excluded from the 5L+ TCR MM cohort.

A8. In Section B.2.5.1.2 Duration of response (DoR), page 41, Table 15 states Patients in 5L+ only (Belamaf 2.5 mg/kg): [redacted] Number of patients, n (%): [redacted] Progressed or died due to PD: [redacted] Censored, follow-up ended: [redacted] Censored, follow-up ongoing: [redacted]. DoR was measured in [redacted] patients with 5L+ (Belamaf 2.5 mg/kg), who achieved a response, of who subsequently [redacted] progressed and

[redacted] censored at end of follow-up (i.e., retained achieved response?). Who were the remaining [redacted] patients? (i.e., =[redacted]) Those who never achieved a response.

Response: DoR is defined in the protocol[77] as the time from first documented evidence of partial response (PR) or better until the earliest date of documented disease progression (PD) per International Myeloma Working Group (IMWG) criteria; or death due to PD occurring among participants who achieve an overall response of confirmed PR or better. The median DoR for the 2.5 mg/kg 5L+ cohort, with [redacted] of [redacted] responders later experiencing an event of PD, was [redacted] months as of the final analysis. The remaining [redacted] patients did not achieve a PR or better or their best response was not evaluable as shown in Table 4 below (Table 14 from Company Submission [CS] Document B.2.5.1.1, relevant data highlighted in **bold** for clarity).

Table 4. Best confirmed response based on IRC assessment (DREAMM-2) (Table 14 from CS Document B.2.5.1.1)

	Belamaf Q3W		
	13-Month follow-up (31Jan20)	**Final analysis (4May22)**	**Final analysis (4May22)**
	2.5 mg/kg (N=97) ITT	**2.5 mg/kg (N=97) ITT**	**2.5 mg/kg (N=[redacted]) Patients in 5L+ only**
Best Response, n (%)			
Stringent complete response (sCR)	2 (2)	[redacted]	[redacted]
Complete response (CR)	5 (5)	[redacted]	[redacted]
Very good partial response (VGPR)	11 (11)	[redacted]	[redacted]
Partial response (PR)	13 (13)	[redacted]	[redacted]
Minimal response (MR)	4 (4)	[redacted]	[redacted]
Stable disease (SD)	27 (28)	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]	[redacted]
Not evaluable (NE)	[redacted]	[redacted]	[redacted]
Primary endpoint: Overall Response Rate, n (%)			
sCR+CR+VGPR+PR	31 (32)	[redacted]	[redacted]
97.5% confidence interval	(21.7, 43.6)	[redacted]	[redacted]
Clinical Benefit Rate, n (%)			
sCR+CR+VGPR+PR+MR	35 (36)	[redacted]	[redacted]
97.5% confidence interval	(25.4, 47.9)	[redacted]	[redacted]

Abbreviations: CR, complete response; IRC, Independent Review Committee; ITT, intent-to-treat; n, number; NE, not evaluable; NR, not reported; PD, progressive disease; PR, partial response; Q3W, once every three weeks; sCR, stringent complete response; VGPR, very good partial response; 5L+, fifth line and beyond
Source: DREAMM-2 13-months follow-up clinical study report[78], Lonial et al. 2021[79]

A9. In Section B.2.5.1.9 Time to next treatment (TTNT), page 55, the CS states that to allow a comparison with PomDex TTNT data from the NCRAS study, was reconstructed by combining TTD to TSNT. Can the Company present this information graphically?

Response: The Company would like to clarify that TTNT was not generated as a combination of time to discontinuation or death (TTD) and time to start of next treatment (TSNT) but is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. Patients who did not start a follow-up treatment or who withdrew or were lost to follow-up were censored at the time of study discontinuation (EoS), withdrawal or lost to follow-up.

As such we believe the graphical representation of TTD and TSNT is redundant since the plots for TTNT representing the correct definition have been provided in the CS Document B.2.5.1.9 (Figures 19, 20).

A10. The company reported median times to OS, TTNT, and TTD in Document B (Table 20, 22-23; and Tables 25-27; pages 49-64) and Appendix M (Tables 1-3; pages 1-4), it is not clear what individual hazard rates (for DREAMM-2 arm and NCRAS arms [PomDex and PanoBorDex)]) were used for the calculation of hazard rate ratios of MAIC (in these two tables A and B below).

Please, populate the remaining empty cells in Tables A and B provided.

Table A.

Endpoint	DREAMM-2 IPD Belamaf (unadjusted) Hazard rate (95% CI)	DREAMM-2 IPD Belamaf (adjusted) Hazard rate (95% CI)	NCRAS AD Hazard rate (PomDex)	Unanchored MAIC Hazard ratio (95% CI)
OS				[redacted]
TTNT				[redacted]
TTD				[redacted]
AD=aggregate data; IPD=individual patient data; CI: confidence interval; OS=overall survival; TTD=time to treatment discontinuation; TTNT= time to next treatment				

Table B.

Endpoint	DREAMM-2 IPD Belamaf (unadjusted) Hazard rate (95% CI)	DREAMM-2 IPD Belamaf (adjusted) Hazard rate (95% CI)	NCRAS AD Hazard rate (PanoBorDex)	Unanchored MAIC Hazard ratio (95% CI)
OS				[redacted]

TTNT				[redacted]
TTD				[redacted]
AD=aggregate data; IPD=individual patient data; CI: confidence interval; OS=overall survival; TTD=time to treatment discontinuation; TTNT= time to next treatment				

Response: The standard Cox regression model was used to estimate the hazard ratios (HRs). The Cox model is a semi-parametric model that models the HR but does not model the hazard rate per arm (i.e. the baseline hazard function was not modelled). This approach was taken in TA427[80] and is used routinely in survival analysis. Therefore the Company is unable to populate the empty cells in Tables A and B provided.

PRIORITY QUESTION A11. Regarding the post hoc calculation in the CS Document B (Table 6 as below).

a) **Please explain in full detail how TSNT and TTD were "combined" to reconstruct TTNT, and please define TTD as used in this post-hoc calculation.**

Additional	Time to discontinuation (TTD)*	Defined as time on the treatment until discontinued. This is analysed from the safety population.
	Time to next treatment (TTNT)*	TTNT was not a pre-specified outcome. It was reconstructed by combining TTD to TSNT from discontinuation.

Response: As per Question A9. In Section B.2.5.1.9 Time to next treatment (TTNT), page 55, the CS states that to allow a comparison with PomDex TTNT data from the NCRAS study, was reconstructed by combining TTD to TSNT. Can the Company present this information graphically?, the Company would like to clarify that TTNT was not generated as a combination of TTD and TSNT but is defined as time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. Patients who did not start a follow-up treatment or who withdrew or were lost to follow-up were censored at the time of EoS, withdrawal or lost to follow-up. This definition was used to generate TTNT data from the DREAMM-2 trial.

TTD is defined as time from initiation until the date of discontinuation of study treatment or death due to any cause.

TSNT is defined as time from discontinuation of study treatment to initiation of follow-up anti-cancer treatment or death due to any cause.

A summary of outcome definitions from DREAMM-2 and NCRAS study is summarised in

Table ***5***.

Table 5. Definition of outcomes

	DREAMM-2	NCRAS
OS	Defined as the time from first dose until death due to any cause.	Defined as the time from initiation of the first cohort-eligible line of therapy until failure (all-cause death). Patients lost to follow-up or still alive at the end of the study period will be censored.
PFS	Defined as the time from first dose until the earliest date of documented disease progression (PD) per IMWG, or death due to any cause.	Not available
TTNT	Defined as the time from randomization until the date of start of follow-up anti-cancer treatment or death due to any cause. Patients who did not start a follow-up treatment or who withdraw or are lost to follow-up will be censored at the time of study discontinuation (EoS), withdrawal or lost to follow-up.	Defined as the time from the start of the first cohort-eligible line of therapy until failure (the earliest of all-cause death or the start of a new line of treatment). Patients lost to follow-up or still in same line of treatment at the end of the study period will be censored.
TSNT	Defined as time from discontinuation of study treatment to initiation of follow-up anti-cancer treatment or death due to any cause.	Not available
TTD	Defined as time from initiation until the date of discontinuation of study treatment or death due to any cause	Defined as the earliest of: last administration plus 1 cycle length; start of a new line minus 1 day; death during follow-up. Those alive at follow-up end with no subsequent line and last administration date of the index line within a cycle length of administrative follow-up end were treated as censored

c) **Regarding the post hoc calculation in CS Document B Table 8 (page 34), the CS states *TSNT – analysed in a post-hoc analysis (analysed from the ITT population)*. However, Table 22 reports TTD for the "safety" population. Since these are "combined" to generate TTNT it appears that slightly different populations were being combined. Please explain the rationale for this procedure.**

Response: TTD is defined as time from study treatment initiation to discontinuation or death and therefore is based on the population who initiated study treatment (the safety population, N=95). The two patients who were randomised but did not initiate the study treatment were not accounted for.

As per Question A9. In Section B.2.5.1.9 Time to next treatment (TTNT), page 55, the CS states that to allow a comparison with PomDex TTNT data from the NCRAS study, was reconstructed by combining TTD to TSNT. Can the Company present this information graphically? and PRIORITY QUESTION A11. Regarding the post hoc calculation in the CS Document B (Table 6 as below)., the Company would like to clarify that TTNT was not generated as a combination of TTD and TSNT. TTNT is defined as time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. Therefore, the intention-to-treat (ITT) population (N=97) considering all randomised patients (regardless of whether they have initiated treatment) was selected.

A12. CS Document B Table 7 describes baseline characteristics of the ITT population. Median is reported as 65 ([redacted]). Please supply:

a) **the IQR range around the median;**

b) **the number of patients aged ≤ 60 yrs;**

c) **the number of patients aged ≤ 50 yrs;**

d) **the number of patients aged ≥ 70 years.**

Response: The following baseline characteristics is presented in Table 6. Age groups and Median age (IQR)

Table 6. Age groups and Median age (IQR) (DREAMM-2 final analysis, ITT population)

	2.5 mg/kg (N=97) ITT
Age (years), n	
Mean (SD)	[redacted]
Median (range)	65.0 [redacted]
Median (IQR)	65.0 (60 to 70)
Age Group (years), n (%)	
≤ 50	[redacted]
≤ 60	[redacted]
>60 to <70	[redacted]
≥ 70	[redacted]

A14. Please clarify if "next treatment" used in calculating TSNT and TTNT needed to be within 60 days of TTD to be counted. If this is the case:

a) **please explain the rational for use of 60 day cut-off, and**

b) **please supply analyses in which all next treatments (including those beyond 60 days) are included.**

Response: In the submission, a 60-days cut-off is applied in the definition of refractoriness, as follows:

- In the NCRAS study, individuals were classed as refractory to a treatment class (proteasome inhibitor [PI], immunomodulatory drug [IMiD], anti-CD38) where a new line is initiated within 60 days of completion of the PI, IMiD or anti-CD38-containing line.

- In the DREAMM-2 trial, refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of PD while on therapy. This definition is consistent with the IMWG criteria.

a) In the DREAMM-2 trial, TTNT is defined as time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. TSNT is defined as time from discontinuation of study treatment to initiation of follow-up anti-cancer treatment or death due to any cause. Thus, no cut-off at 60 days from the time of discontinuation has been applied to these outcomes.

b) Not applicable.

A15. CS Document B Table 24, the last row refers to *Time from study treatment discontinuation to start of subsequent anti-cancer therapy (days).* Please clarify: does this refer to *Time from study treatment discontinuation to start of next subsequent anti-cancer therapy (days).*

Response: Time from study treatment discontinuation to start of subsequent anti-cancer therapy (days) refers to the time from the discontinuation of the study treatment that is, Belamaf 2.5 mg/kg to the initiation of the first subsequent therapy.

A16. CS Document B Table 24 lists single drugs that were received as next therapies in BELAMAF ITT population. Please present the numbers of patients receiving specified drug combinations and single drug only and identify those next therapies that have at some time been supported by the CDF.

Response: The number of patients receiving subsequent therapies as combination are not reported in the DREAMM-2 trial. Instead, only the individual agents received as subsequent therapy are recorded and have been provided in Table 24 of the CS Document B.2.5.1.9.

Thus, it is not possible to identify the next therapies that have at some time been supported by the CDF.

A17. CS Document B Table 23. Please explain why deaths were counted as events rather than as censorings.

Response: Deaths are counted as an event in the TTNT analysis as a conservative and consistent approach to time to event analysis.

In the NCRAS study, Death was treated as a ‘failure’ in the TTNT analysis and is therefore also counted as an event in the TTNT analysis.

A summary of outcomes definitions is presented in PRIORITY QUESTION A11. Regarding the post hoc calculation in the CS Document B (Table 6 as below).

A18. Time to next treatment and time to start of next treatment are based on data from 58 MM centres across multiple domains. It seems possible the delay to next treatment may vary between centres and or countries.

Pease provide the distribution of the times TSNT and TTNT for the UK centres (all UK participants combined) and compare these distributions with those from other jurisdictions.

Response: In the 2.5 mg/kg arm of the DREAMM-2 trial, there are N=[redacted] UK patients. Given the small sample size, it is not feasible to generate an estimate of TSNT and TTNT for those three UK patients combined and to protect patients' confidentiality, individual patient data (IPD) data cannot be provided.

A19. CS Document B Figure 7 summarises patients included in the NCRAS study. [redacted] patients is reduced to [redacted]; the EAG is unclear whether this is on the basis that [redacted] received CDF supported treatments rather than POM DEX or that they received CDF treatments as next treatment after POM DEX or before POM DEX.

Of the remaining [redacted] only [redacted] received POM DEX and this is the population analysed. It is unclear to the EAG how many of the [redacted] patients received POM DEX. Please supply this number and provide KM plots for OS, TTD and TTNT for this larger population (i.e. similar to Figs 26, 27 and 28, but including POM DEX recipients that may have received CDF supported treatment. Please do not include PANOVD).

Response: As described in response to Question A7. In Section B.2.3.2 PomDex (NCRAS study) (page 37), Figure 7 the CS states CDF-excluded patients (N=[redacted]), Figure 7. Can the Company clarify who "CDF-excluded patients (N=[redacted])" are? and specify why they were excluded from 5L TCR MM group of patients., the exclusion criterion is applied to the N=266 patients who have received a therapy currently funded by the CDF at any point in their entire treatment history. For instance, if a patient had received PomDex at 5L+ but also received an intervention currently funded via CDF in their entire treatment history, they would be excluded. For further clarity, 65 TCR patients received PomDex at 5L+ who did not receive a CDF currently funded option in their entire treatment history, these patients are included in the NCRAS study (see Figure 7 in CS Document B.2.3.2).

Unfortunately, given the required CDF embargo, only limited baseline characteristics were provided to the Company about these patients, therefore it is not feasible to provide the number of patients who have received PomDex at 5L among the overall 5L+ TCR MM cohort (N=[redacted]) and similarly, no Kaplan-Meier (KM) plots for overall survival (OS), TTD and TTNT for this larger population can be provided.

PRIORITY QUESTION A20. In the CS, the ITT population used for base case had [redacted] patients who received BELAMAF as 4th line therapy. Please confirm.

a) **For each of these individuals and for each of OS, TTD, PFS, and TTNT please list time to event or time to censoring as appropriate.**

b) **Please report how many of the 4th line patients were among the [redacted] ITT that received next therapy.**

Response:

a) To maintain the confidentiality of IPD, OS, TTD, progression-free survival (PFS) and TTNT for each of these individuals cannot be provided. However, the OS, TTD, PFS and TTNT results for the ITT and the 5L+ only (excluding the N=[redacted] patients at 4L) have been provided in the CS, Document B.2.5.1 Figures 12, 15, 18 and 20.

b) As shown in Table ***7*** below (and Table 23 from CS Document B.2.5.1.9), concerning time to next treatment (DREAMM-2, post-hoc analysis, 4May2022) for the 2.5 mg/kg ITT and 5L+ cohorts, [redacted] and [redacted] patients respectively received follow-up treatment (relevant data highlighted in **bold** for clarity).

   Therefore, [redacted] 4th line patients in the ITT cohort received a follow-up treatment.

Table 7. Time to next treatment (DREAMM-2, post-hoc analysis, 4May2022)

	Belamaf Q3W	
	Post-hoc analysis (4May2022)	
	2.5 mg/kg (N=97) ITT	2.5 mg/kg (N=[redacted]) 5L+ subgroup
Number of patients, n (%)		
Follow-up treatment received or Died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Event summary, n (%)		
Follow-up treatment received	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for time variable (months)		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time to Next Treatment probability		
Time-to-event endpoint at 6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 12 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intent-to-treat; n, number; Q3W, once every three weeks; 5L+, fifth line and beyond

MAIC

A21. In Section B.2.8.1.2 Choice of ITC, page 67, the CS presents an unanchored MAIC of Belamaf 2.5 mg/kg versus PomDex based on the DREAMM-2 trial and the NCRAS study including 3 covariates for OS, TTNT and TTD. The feasibility assessment and methodology for the unanchored MAIC are presented in Appendix O and summarised in Section B.2.8.2. Can the company clarify if "covariates" should be replaced with "endpoints/outcomes"

Response: The treatment effect modifiers and prognostic factors adjusted for in the matched adjusted indirect comparison (MAIC), also referred to as "covariates" are age [mean, years], prior lines of therapy [median], and extramedullary disease [yes or no]. The MAIC was performed for the following outcomes OS, TTNT and TTD.

A22. In Section B.2.8.2.3 Covariates selection Page 69. Only three of the most important factors identified by clinical experts, could be included in the MAIC,

based on the availability of baseline characteristics in the NCRAS dataset: age [mean, years], prior lines of therapy [median], and extramedullary disease [yes or no]. However, in Table 30, page 70, it appears as though sex and race were included in MAIC analysis. Can the Company clarify if sex and race matched/adjusted in MAIC to compare Belamaf vs. PomDex?

Response: The three treatment effect modifiers and prognostic factors (also referred to as covariates) included in the MAIC are age [mean, years], prior lines of therapy [median], and extramedullary disease [yes or no]. Sex and race were not considered in the MAIC.

Section B: Clarification on cost-effectiveness data

Excel model spreadsheets

B1. Please, can the Company clarify which currency codes in the National Schedule of NHS costs have been used to identify the Admin Costs for the first infusion and Cycle 4+?

Response: Belamaf is administered via a short 30-minute intravenous (IV) infusion in the absence of any infusion-related reactions. To appropriately reflect the shorter administration times the cost of the first infusion for Belamaf was identified as £361.53, currency code SB12Z (deliver simple parenteral chemotherapy at first attendance, NHS Reference Costs 2020/21[81]). The subsequent cost of infusions for cycle 4+ was identified as £237.21 currency code SB97Z (same day chemotherapy admission or attendance, regular day admission, NHS Reference Costs 2020/21[81]).

For Bortezomib (PanoBorDex) the first infusion cost was identified as £526.52, currency code SB14Z (deliver complex chemotherapy, including prolonged infusional treatment, at first attendance, NHS Reference Costs 2020/21[81]). The subsequent cost of complex infusions for cycle 4+ was identified as £470.62 currency code SB15Z (deliver subsequent elements of a chemotherapy cycle, NHS Reference Costs 2020/21[81]). The Company notes an error in the “Data Store” worksheet where the incorrect currency code was reported. This has been updated but does not affect the incremental cost-effectiveness ratio (ICER). The updated cost-effectiveness model is provided alongside this clarification response.

PRIORITY QUESTION B2. Please can the company clarify which type and speciality are considered for "Physician Visit" in the cost inputs? And why the NHS tariff for 2021 based on the HRG or Unit cost for social and health care have not been referred to instead of reference 21 which is a NICE TA?

Response: The Company notes that the value used was taken from TA510 but should have been taken directly from the NHS Reference Costs for 2020/21. Thus, the value has been updated to Total Outpatient Attendance - Consultant Led, Service Code 303: Clinical Haematology £199.38.[81]

This has been amended in the cost-effectiveness analysis and updated results for the base case are available in Appendix A.

PRIORITY QUESTION B3. Please can the company clarify why the NICE TA 510 has been cited for components of the concomitant therapy cost rather National Schedule of NHS cost or other national approved tariffs?

Response: The values taken from TA510 were sourced from an NHS Blood and Transplant pricing proposals document which is no longer accessible via the link provided in TA510. The Company thus recognises the need to update these costs based on the 2020/21 NHS Reference Costs.[81] As such, the updated cost of concomitant therapies used in the model are presented in Table 8.

Table 8: Unit costs of concomitant therapies

Resource	Unit cost (£)	Source
GCSF	52.70	BNF, Filgrastim pre-filled disposable injection[82]
RBC transfusion	497.06	Schedule of NHS costs, SA44A, service code 303[81]
Platelet transfusion	497.06	

These costs have been amended in the cost-effectiveness analysis and updated results for the base case are available in Appendix A.

PRIORITY QUESTION B4. Please can the company clarify why NICE TA427 has been cited as the reference for the unit cost of end-of-life care? It seems what the mentioned TA has incorporated in the economic model is the total cost for all cycles of that economic analysis. End-of-life care unit cost could be found

as an equivalent to "Palliative medicine" with a lower amount at "National Schedule NHS FY2020-21".

Response: The Company suggests that the value which has been used in the submission should be kept as the base case. This one-off cost accounts for the costs of the last eight weeks prior to death, as in TA427 reported on page 223.[83] Scenario analyses using the average cost of £867 (2015 cost year) reported in TA427 inflated to 2020/21 using the Personal Social Services Research Unit (PSSRU) 2021 indices[84] at £968.82 are provided in Appendix A along with a scenario using the mean end-of-life cost given in TA510, £853.58 inflated to a 2021 cost of £973.08 per person using inflation indices from the PSSRU 2021.[83,84] This cost takes into account the proportion of patients receiving care in both home and hospital settings, something which cannot be estimated using the schedule of NHS costs alone, and so these costs are preferred over that suggested in the question for the scenario analyses.

B5. Please can the company clarify, which currency codes have been used for the procedures extracted from Ref. 8? (e.g., below):

Abdominal distension	1,274.36
Abdominal pain	561.98
Anemia	1,030.40
…	

Response: The currency codes used for procedures extracted from the NHS schedule of costs 2020/21[81] are as in Table 9. The Company notes that some of these costs were incorrect and have been updated as per Table 9.

Table 9: NHS Currency codes used to cost for adverse events in the cost-effectiveness model

Adverse event	Code	Unit cost
Abdominal distension	FD05A, FD05B	Weighted average gives £868.33 (updated)
Abdominal pain	FD05A, FD05B	Weighted average gives £868.33 (updated)
Anaemia	SA04G, SA04H, SA04J, SA04K, SA04L	As in the cost-effectiveness analysis (£1,030.40)

Adverse event	Code	Unit cost
Dehydration	KC05G-KC05N	Weighted average gives £1,802.71 (updated)
Diarrhoea	FD10J, FD10K, FD10L, FD10M	As in the cost-effectiveness analysis (£2,010.60)
Fatigue	SA01G, SA01H, SA01J, SA01K	As in the cost-effectiveness analysis (£2,116.59)
Hypercalcemia	KC05J, KC05K, KC05L, KC05M, KC05N	As in the cost-effectiveness analysis (£1,802.71)
Hypotension	SA08G, SA08H, SA08J	As in the cost-effectiveness analysis (£1,568.24)
Leukopenia	SA08G, SA08H, SA08J	As in the cost-effectiveness analysis (£1,568.24)
Neutropenia	SA08G, SA08H, SA08J	As in the cost-effectiveness analysis (£1,568.24)
Pneumonia	DZ11K-DZ11V	As in the cost-effectiveness analysis (£2,651.59)
Sepsis	WJ06A-WJ06J	As in the cost-effectiveness analysis (£3,286.98)
Syncope	EB08A, EB08B, EB08C, EB08D, EB08E	As in the cost-effectiveness analysis (£1,412.42)
Thrombocytopenia	SA12G, SA12H, SA12J, SA12K	As in the cost-effectiveness analysis (£1,069.63)

The errors have been amended in the cost-effectiveness analysis and updated results for the base case are available in Appendix A.

PRIORITY QUESTION B6. Please clarify at which part of TA510 or the updated edition the cost of "Asthenia" has been presented?

Response: The cost of asthenia is taken as £727.55 from Table 71 Page 217 of the TA510 Company Submission[83] and has been inflated from cost year 2014/2015 to cost year 2021/2021 using inflation indices from the PSSRU,[85] to give the cost used in the model of £812.99.

B7. Please clarify at which part of the NICE TA658 the relative intensity for PAM has been identified at 91%? It seems TA658 reports an assumption for a scenario analysis at 100%.

Response: The relative dose intensity of pomalidomide (POM) is 90.1% sourced from MM-010.[86] The Company are unclear as to where the EAGs value of 91% has come from. There is a typographic error in the cost inputs sheet of the cost-effectiveness model where this is incorrectly referenced, this has been updated and does not affect the ICER. Please note this is correctly referenced within Document B of the Company's submission.

B8. Please clarify what was the reason to leave the imputation for the missing value of QoL, regarding that only [redacted] of patients had the utility observation at both baseline and EOT?

Response: No imputation was performed for the missing data because the pattern of missingness is not random. Hence, analyses were done for the observed available data.

B9. Please clarify whether the "Dexamethasone relative dose intensity" is the same as what has been stated in the references?

Response: The relative dose intensity (RDI) of dexamethasone is 90.1% sourced from MM-010.[86] As mentioned in response to Question B7. Please clarify at which part of the NICE TA658 the relative intensity for PAM has been identified at 91%? It seems TA658 reports an assumption for a scenario analysis at 100%., there is a typographic error for the reference in the cost inputs sheet of the cost-effectiveness model which has now been updated. Whilst MM-010 only reports a single value for Pom as part of the PomDex regimen, this is assumed to be the same for Dex. This is consistent with how the RDI is reported in MM-003.[87] To remain consistent with the source for adverse events (AEs), MM-010 was used for RDI.

B10. Please clarify the probabilities of Adverse Events for POMDEX are the same with reference number 1 (NCT01311687)? Inconsistencies are listed in the table below:

Company Spread Sheet, (cost inputs sheet)	NCT01311687 (Serious Adverse Events Table)
Anaemia:32.99%	Anaemia: 10/300 (3.33%)
Fatigue: 5.92%	Fatigue: 3/300 (1%)

Leukopenia:7.99%	Leukopenia: seems not available! The closest term is leukoencephalopathy: 0.33%
Neutropenia: 49.7%	Febrile neutropenia: 6.33%
Pneumonia: 12.87%	Pneumonia: 19%
Thrombocytopenia: 18.95%	Thrombocytopenia: Not reported?

Response: This is a typographic error found on the cost inputs sheet of the cost-effectiveness model. The correct reference should be MM-010 (NCT01712789) and has now been updated and does not affect the ICER.[86] Please note this is correctly referenced in the datastore of the model and Document B of the Company's submission and therefore does not affect results.

PRIORITY QUESTION B11. Please clarify how the disutility value from a breast cancer study (Ref. 9) has been used as input for the multiple refractories?

Response: In the absence of published literature specific to multiple myeloma, a targeted literature review was performed to source the disutility value for hypercalcemia. The value reported in Milne et al. 2006 was deemed to represent the best alternative.[88]

However, the Company acknowledge the importance of sourcing disutility values within the disease area, therefore the Company have updated the cost-effectiveness model with a revised estimate taken from TA658 which reports a disutility of 0.08.[73] Updated results for the base case are available in Appendix A.

PRIORITY QUESTION B12. Please clarify where the disutility value for Keratopathy is stated in NICE TA369 (Ref. 43)?

Response: The disutility value for keratopathy was sourced from Table B32 Utilities elicited by time trade-off (TTO) on page 171 of the Company submission for TA369[89]. The utility for "severe dry eye" (0.16, standard deviation [SD] 0.14) was considered a reasonable proxy to inform the disutility associated with keratopathy following UK eye care professional's feedback.

PRIORITY QUESTION B13. Please clarify where the disutility values for Pneumonia, Neutropenia, and Fatigue were sourced. Anaemia is stated as TAR510 (Ref. 29).

Response: The disutility values for pneumonia, neutropenia and fatigue were sourced from TA510 in the same way as anaemia.[83]

B14. Please provide the QoL details for the "off-treatment" group. The EAG suggest there is no considerable difference in QoL between "on-treatment" and "off-treatment" (~0.03)?

Response: The cost-effectiveness model health states were split into on-treatment and off-treatment and data collected via patient reported outcomes in the DREAMM-2 trial for response/ no response were used as a proxy in the absence of data split by treatment status. Numbers of patients upon which these utility calculations are based can be found in the CS, Document B.3.4.2.3 Table 61.

PRIORITY QUESTION B15. Please clarify why the full form of model of the Proskorovsky et al. QoL mapping method (2014) has not been used?

Response: Four models were fitted in the Proskorovsky et al.[90] quality of life (QoL) mapping method:

- Model 1A: Mapping equation using both Cancer 30-item Quality of Life Questionnaire (QLQ-C30) and Multiple Myeloma Module Quality of Life Questionnaire (QLQ-MY20) (full model)
- Model 1B: Mapping equation using both QLQ-C30 and QLQ-MY20 (trimmed model including only statistically significant predictors with $p<0.1$)
- Model 2A: Mapping equation using both QLQ-C30 only (full model)
- Model 2B: Mapping equation using both QLQ-C30 only (trimmed model including only statistically significant predictors with $p<0.1$)

In the Company analysis model 1B was selected (i.e. the trimmed mapping model using both QLQ-C30 and QLQ-MY20):

Mapped EQ-5D-3L utility score = 0.25763 + 0.00165 × Global Health Status/QoL Score + 0.00467 × Physical Functioning Score – 0.00293 × Pain Score + 0.00089197 × Insomnia Score + 0.00157 × Future Perspective Score

In their publication, Proskorovsky et al. explained that model 1B "*fits the data as well as the full model*" with very similar adjusted R-square statistics (0.7015 for full model 1A and 0.7028 for trimmed model 1B). Furthermore, they explain that both 1B and 2B provide almost equal predictive ability.

Therefore, model 1B was selected because both measurements were available and the adjusted R-Square statistic for this model was the highest of all 4 models

(adjusted R-square was 0.7015, 0.7028, 0.6956 and 0.6941 in models 1A, 1B, 2A, 2B, respectively).

Severity modifier

PRIORITY QUESTION B16. It appears the Company has applied the severity weight to the threshold instead of the QALYs. Please clarify why this approach was taken when NICE's evaluations manual section 6.2.16 states "The committee may apply a greater weight to QALYs if technologies are indicated for conditions with a high degree of severity." Please provide updated analyses with the appropriate weight applied to the QALYs instead of the threshold.

Response: This has been actioned in the Company model ("Results", cell I11 and I15) with the corresponding ICERs presented in "Results", cell K11 and K15.

Updated results for the base case are available in Appendix A.

B17. Please clarify why willingness to pay has been considered based on the severity modifier for the base case (this is an STA submission).

Response: Thank you for clarifying that the modifier should be applied to the incremental QALYs. This has now been applied as described in the response to PRIORITY QUESTION B16. It appears the Company has applied the severity weight to the threshold instead of the QALYs. Please clarify why this approach was taken when NICE's evaluations manual section 6.2.16 states "The committee may apply a greater weight to QALYs if technologies are indicated for conditions with a high degree of severity." Please provide updated analyses with the appropriate weight applied to the QALYs instead of the threshold.

Section C: Textual clarification and additional points

General CS clarifications

C1. Can the company explain why duplicates and triplicates of appendix documents were provided in the CS?

Response: The Company will re-upload the appendices with updated titles describing the confidentiality markings displayed in each version of the appendices.

C2. A large variety of acronyms and abbreviations are scattered through 170 pages which it difficult to read. TTD is decoded as 'time to discontinuation', or as 'time to discontinuation or death'. However, in TABLE 8 TTD is decoded as 'time to death'. Similarly, in Section B.2.5.1.8 Time to treatment discontinuation (TTD), Table 22, page 53 and B.2.5.2.2 Time to treatment discontinuation or death (TTD), page 63, Table 26 the CS lists the following;

- **DREAMM-2-Belamaf: TTD=Time to treatment discontinuation (Table 22, page 53)**
- **NCRAS-PomDex: TTD=Time to treatment discontinuation or death (Table 26, page 63)**

  a) **Do the definitions of TTD differ between the two studies? Table 29, page 69 lists them as the same outcome.**

  b) **Please generate a definitive list of all abbreviations and acronyms used in document B**

Response:

a) In the NCRAS study TTD is defined as the earliest of: last administration plus 1 cycle length; start of a new line minus 1 day; death during follow-up.

In the DREAMM-2 trial, TTD is defined as time to discontinuation or death. We note that in the DREAMM-2 trial no discontinuation of the study treatment due to death was recorded (See Clinical Study Report [CSR] Table 1.0020 Summary of Treatment Status and Reasons for Discontinuation of Study Treatment).[91]

b) The list of all abbreviations and acronyms used in Document B is provided in Table 10.

Table 10. List of abbreviations and meanings

Abbreviation	Meaning
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike Information Criterion
ASCT	Autologous stem cell transplant
BAFF-R	B cell-activating factor receptor
BCMA	B cell maturation antigen
BCVA	Best corrected visual acuity
BIC	Bayesian Information Criterion
BNF	British National Formulary
Bor	Bortezomib
CBR	Clinical benefit rate
CDF	Cancer Drug Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CRAB	Hyper**c**alcemia, **r**enal insufficiency, **a**naemia, and **b**one lesions
CTCAE	Common Terminology Criteria for Adverse Events
Dara	Daratumumab
Dex	Dexamethasone
DoR	Duration of response
DSU	Decision Support Unit
DT-PACE	Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide
EAP	Expanded Access Program
ECOG	Eastern Cooperative Oncology Group
EHA	European Hematology Association
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire
EORTC-QLQ-MY20	European Organisation for Research and Treatment of Cancer Multiple Myeloma Module Quality of Life Questionnaire
EOT	End of treatment
EQ-5D	European Quality of Life Five Dimension
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FLC	Free light chain
GBP	Great British Pound
GCSF	Granulocyte stimulating factor
HDAC	Histone deacetylase
HDT	High dose therapy
HES	Hospital Episode Statistics
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IA	Interim analysis

Abbreviation	Meaning
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IPD	Individual patient data
IRC	Independent Review Committee
IRR	Infusion related reaction
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
KVA	Keratopathy and visual acuity
LCI	Lower limit of confidence interval
Len	Lenalidomide
LoT	Line of therapy
LY	Life year
LYG	Life years gained
mAb	Monoclonal antibody
MAIC	Matched adjusted indirect comparison
Mean (SD)	Mean (standard deviation)
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare Regulatory Agency
MIMS	The Monthly Index of Medical Specialities
MM	Multiple myeloma
MR	Minimal response
MRD	Minimum residual disease
N	Number
N/A	Not applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NPP	Named patient programme
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PanoBorDex	Panobinostat + bortezomib + dexamethasone
PAS	Patient Access Scheme
PASLU	Patient Access Schemes Liaison Unit
PD	Progressive disease
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazard
PI	Proteasome inhibitor
PLD	Patient-level data
PomDex	Pomalidomide + dexamethasone
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status

Abbreviation	Meaning
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
Q3W	Once every 3 weeks
RDI	Relative dose intensity
R-ISS	Revised International Staging System
RRMM	Relapsed/refractory multiple myeloma
RTDS	National Radiotherapy Dataset
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
sCR	Stringent complete response
SCT	Stem cell transplant
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
TA	Technology appraisal
TACI	Transmembrane activator calcium modulator and cyclophilin ligand interactor
TCR	Triple class refractory
TSD	Technical Support Document
TSNT	Time to start of next therapy
TTD	Time to discontinuation or death
TTNT	Time to next treatment
TTP	Time to progression
TTR	Time to response
Tx	Treatment
UCI	Upper limit of confidence interval
UK	United Kingdom
UKMF	UK Myeloma Forum
US	United States
VGPR	Very good partial response
WTP	Willingness-to-pay
1L	First line
2L	Second line
3L	Third line
4L	Fourth line
5L	Fifth line
5L+	Fifth line and beyond

C3. The CS variously refers to "ICR", "independent" and "investigator" review. Please clarify the definition each.

Response: For DREAMM-2, an Independent Review Committee (IRC) was utilised to assess efficacy endpoints of the study (note, independent reviewer-assessed efficacy is the same as IRC assessed efficacy). Additional information can be found

in the DREAMM-2 study protocol[77], Appendix 3 and in the IRC Charter. Response evaluation was performed by the Investigator and by an IRC according to the IMWG Uniform Response Criteria for Multiple Myeloma.[92]

The primary efficacy endpoint was overall response rate (ORR) based on IRC assessment of responses. The ORR was defined as the percentage of participants with a confirmed PR or better, according to the 2016 IMWG Response Criteria[93] by the IRC.

The secondary efficacy endpoints were ORR (based on investigator assessment, not conducted in the final analysis), clinical benefit rate (CBR), DoR, Time to Response, PFS, Time to Progression, and OS.

C4. Information about time to event analyses is scattered throughout the text. For ease of reference please supply a glossary for all these including full description and definitions of number of participants, start time, event(s), censoring(s) and maximum follow up.

Response: The glossary of time to event analyses definitions is provided in Table 11.

Table 11. Glossary of time to event analyses definitions

Description	Definition
Censoring(s)	Censoring denotes those patients who have not been counted as having an event and therefore are discounted from the event analysis. E.g. Table 27 of Document B (page 45) shows censored patients for whom the event is not available either because of the loss to follow-up or because the event has not occurred at the time of the analysis.
Event(s)	An occurrence in the study relating to either the title of the table or content in the table, e.g. Table 17 of Document B (page 45) relates to time to progression, with events noted as disease progression or death.
Maximum follow-up	This is the longest follow-up time relating to the study.
Median	The value separating the higher half from the lower half of a data sample, a population, or a probability distribution.
Months from line start	This is the number of months from the line of treatment starting, e.g. Table 25 of Document B (page 62).
Number of patients/participants	The number of people included in each group e.g. Table 17 of Document B (page 45) notes the number of patients who have either: progressed or died (event), been censored, or for whom follow-up ended, or is ongoing.
N at risk	The number of patients at risk of an event occurring at the time point listed.
Start time/date (adverse event)	The time/date at which the participant experienced an adverse event.

Description	Definition
Start time/date (treatment)	The time/date of which a participant began treatment.
Survival probability	The probability of the patient being alive at the time point listed.
Time-to-event endpoint	The probability of the endpoint listed occurring at the time point listed.
Time to next treatment	time from randomization until the date of start of follow-up anti-cancer treatment or death due to any cause.
Time to progression	The time from randomisation until the earliest date of progression-free disease or death due to progressive disease.
Time to response	The time between the date of randomisation and the first documented evidence of response (partial response or better), among patients who achieved a response (confirmed partial response or better).
Time to treatment discontinuation or death	Time from initiation until the date of discontinuation of study treatment or death due to any cause (in the DREAMM-2 trial). The time on the treatment until the patient discontinues or dies (in the NCRAS study). Specifically, the definition used in the NCRAS study is as follows: 'TTD was defined as the earliest of: last administration plus 1 cycle length; start of a new line minus 1 day; death during follow-up'.
1st quartile	25% of data points are found in this quartile.
3rd quartile	75% of data points are found in this quartile.
95% confidence interval	There is a 95% chance that the true mean of the population lies within this interval.

Survival analysis / cost-effectiveness general clarifications

C5. Please confirm that in Figures 32 and 33 the use of "PFS" and of "progression free survival" refer to TTNT analyses presented in the clinical section of Document B

Response: We can confirm that the TTNT analyses have been used to inform the proportion of patients in the progressed health states. In absence of PFS data for PomDex from NCRAS, Belamaf and PomDex TTNT were compared and used as a proxy for PFS in the economic model.

C6. Regarding Figure 35. Please confirm KM line shown corresponds to the KM line in Figure 19.

Response: The Company confirms this is correct.

C7. Regarding Figure 36. Please confirm that the KM line corresponds to that shown in Figure 28 of the clinical section

Response: The Company confirms this is correct.

C8. Please confirm that in the economic model sheets "Survival summary" and "D2 survival" all columns labelled "progression-free survival" provide TTNT data.

Response: The Company confirms this is correct.

C9. In the economic model sheet "Survival summary" please identify the details and source for the "All-cause risk of death column".

Response: The all-cause risk of death column calculates the risk of dying per cycle for the general population. This is compared to the per cycle risk of dying for patients with multiple myeloma receiving Belamaf using DREAMM-2 data, or PomDex and PanoBorDex using NCRAS data. Overall survival is capped by the all-cause risk of death to ensure there are no cycles in which patients with multiple myeloma have a lower risk of dying than the general population.

Calculations used to determine the all-cause risk of death can be found in the "Data Store", cells J269:R5763. General population mortality was sourced from the Office for National Statistics (ONS).[94] We apologise that this reference had not been included but can confirm that it has been added to the updated model sheet in cell D371.

C10. Regarding Figure 37. Please confirm that the yellow and black KM lines correspond to the KM plots shown in Figures 28 and 19 respectively.

Response: The Company confirms this is correct.

C11. Will the company provide (or indicate the location) the figures for OS, TTNT, and TTD face to face comparing DREAMM-2 IPD [Belamaf unadjusted KM curve] vs. DREAMM-2 IPD [Belamaf adjusted KM curve] vs. NCRAS aggregate data [PomDex KM curve].

Response: Please see Figure 29, Figure 30 and Figure 31 of Document B.2.8.2 which compares DREAMM-2 IPD [Belamaf unadjusted KM curve] vs. DREAMM-2 IPD [Belamaf adjusted KM curve] vs NCRAS aggregate data [PomDex KM curve] for OS, TTNT and TTD, respectively.

C12. Appendix D Fig 3 page 65 presents a consort diagram for DREAM 2 based on Jan 2020? follow up. Please present same for final follow up or direct EAG to appropriate Appendix.

Response: Please see Figure 1 below.

Figure 1. DREAMM-2 CONSORT flow diagram (final analysis)[95]

References

1. Lonial S, Lee HC, Badros A, *et al.* Longer Term Outcomes With Single-Agent Belantamab Mafodotin in Patients With Relapsed or Refractory Multiple Myeloma: 13-Month Follow-Up From the Pivotal DREAMM-2 Study. *Cancer* 2021. 127: 4198–4212.
2. Lonial S, Nooka A, Thulasi P, *et al.* P-202: Characterization of ocular adverse events in patients receiving Belantamab Mafadotin for ≥12 months: post-hoc analysis of DREAMM-2 study in relapsed/refractory Multiple Myeloma. *Clin Lymphoma Myeloma Leukemia* 2021. 21: S149–S150.
3. Popat R, Badros AZ, Kumar S, *et al.* Can Patient-Reported Ocular Symptoms Guide Dose Modifications in Patients with Relapsed/Refractory Multiple Myeloma Receiving Belantamab Mafodotin? *Blood* 2021. 138: 2746.
4. Terpos E, Badros A, Popat R, *et al.* Relationship between corneal exam findings, best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin (belamaf). *J Clin Oncol* 2021. 39:
5. Lonial S, Nooka AK, Thulasi P, *et al.* Recovery of ocular events with longer-term follow-up in the DREAMM-2 study of single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma. *Br J Haematol* 2021. 193: 53–54.
6. Eliason L, Correll J, Martin M, *et al.* Patient-Reported Experiences during and Following Treatment with Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study. *Blood* 2020. 136: 1.
7. Popat R, Lonial S, Voorhees PM, *et al.* DREAMM-2: Single-agent belantamab mafodotin (BELAMAF) effects on patient-reported outcome (PRO) measures in patients with relapsed/refractory multiple myeloma (RRMM). *HemaSphere* 2021. 5: 35.
8. Trautmann-Grill K, Lonial S, Nooka AK, *et al.* Characterization of ocular adverse events in patients receiving belantamab mafodotin (Belamaf) for ≥12 months: Post-hoc analysis of dreamm-2 study in relapsed/refractory multiple myeloma (RRMM). *Oncol Res Treat* 2021. 44: 181.
9. Nooka A, Lee HC, Badros AZ, *et al.* Infusion-Related Reactions (IRRs) in the DREAMM-2 Study of Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). *Blood* 2020. 136: 22–23.
10. Popat R, Kazantzi A, Farooq A, *et al.* Ocular Health of Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Baseline Data from the DREAMM-2 Trial of Belantamab Mafodotin (Belamaf). *Blood* 2020. 136: 43–44.
11. Richardson PG, Lee HC, Abdallah A-O, *et al.* Single-agent belantamab mafodotin for relapsed/refractory multiple myeloma: analysis of the lyophilised presentation cohort from the pivotal DREAMM-2 study. *Blood Cancer J* 2020. 10:

12. Lonial S, Lee HC, Badros A, *et al.* MM-219: Pivotal DREAMM-2 Study: Single-Agent Belantamab Mafodotin (Belamaf; GSK2857916) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to Proteasome Inhibitors and Immunomodulatory Agents, and Refractory and/or Intolerant to Anti-CD38 Monoclonal Antibodies (mAbs), Including Subgroups with Renal Impairment (RI) and High-Risk (HR) Cytogenetics. *Clin Lymphoma Myeloma Leukemia* 2020. 20: S301–S302.
13. Lee HC, Cohen AD, Chari A, *et al.* DREAMM-2: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) and renal impairment. *J Clin Oncol* 2020. 38:
14. Lonial S, Lee HC, Badros A, *et al.* DREAMM-2: Single-agent belantamab mafodotin in relapsed/refractory multiple myeloma refractory to proteasome inhibitors, immunomodulatory agents, and refractory and/or intolerant to anti-CD38 mABs. *HemaSphere* 2020. 4: 442.
15. Lonial S, Lee HC, Badros A, *et al.* DREAMM-2: Single-agent belantamab mafodotin in patients with relapsed/refractory multiple myeloma (RRMM)-outcomes by prior therapies. *HemaSphere* 2020. 4: 423–424.
16. Richardson PG, Lee HC, Abdallah A-O, *et al.* DREAMM-2 pivotal study: Analysis of the lyophilized presentation cohort of single-agent belantamab mafodotin for relapsed/refractory multiple myeloma. *HemaSphere* 2020. 4: 483.
17. Lonial S, Nooka AK, Thulasi P, *et al.* MM-078: Characterization of Ocular Adverse Events in Patients Receiving Belantamab Mafodotin (Belamaf) for ≥12 Months: Post Hoc Analysis of DREAMM-2 Study in Relapsed/Refractory Multiple Myeloma (RRMM). *Clin Lymphoma Myeloma Leukemia* 2021. 21: S419.
18. Lonial S, Nooka A, Thulasi P, *et al.* Characterization of ocular adverse events in patients receiving belantamab mafadotin for ?12 months: post-hoc analysis of dreamm-2 study in relapsed/refractory multiple myeloma. *Hemasphere* 2021. 5: 486-487.
19. Baines AC, Ershler R, Kanapuru B, *et al.* FDA Approval Summary: Belantamab Mafodotin for Patients with Relapsed or Refractory Multiple Myeloma. *Clin Cancer Res* 2022. doi:10.1158/1078-0432.CCR-22-0618
20. Kortüm M, Terpos E, Badros A, *et al.* Relationship between corneal exam findings, best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin (GSK2857916; belamaf; BLENREP). *Oncol Res Treat* 2021. 44: 204.
21. Terpos E, Badros A, Popat R, *et al.* MM-103: Relationship Between Corneal Exam Findings, Best-Corrected Visual Acuity (BCVA), and Ocular Symptoms in Patients with Relapsed or Refractory Multiple Myeloma (RRMM) Receiving Belantamab Mafodotin (GSK2857916; Belamaf). *Clin Lymphoma Myeloma Leukemia* 2021. 21: S421.
22. Eliason L, Correll J, Martin M, *et al.* Patient-reported experiences during and following treatment with belantamab mafodotin (BELAMAF) for relapsed/refractory multiple myeloma (RRMM) in the DREAMM-2 study. *HemaSphere* 2021. 5: 34.

23. Lonial S, Lee HC, Badros A, *et al.* Pivotal DREAMM-2 study: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). *J Clin Oncol* 2020. 38:
24. Cohen AD, Trudel S, Lonial S, *et al.* DREAMM-2: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) and high-risk (HR) cytogenetics. *J Clin Oncol* 2020. 38:
25. Lonial S, Lee HC, Badros A, *et al.* Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *The Lancet Oncology* 2020. 21: 207–221.
26. Terpos E, Badros A, Popat R, *et al.* Relationship between corneal exam findings, best-corrected visual acuity (bcva), and ocular symptoms in patients with relapsed or refractory multiple myeloma (rrmm) receiving belantamab mafodotin. *HemaSphere* 2021. 5: 472.
27. Lee HC, Cohen AD, Chari A, *et al.* DREAMM-2: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/ refractory multiple myeloma (RRMM) and renal impairment. *HemaSphere* 2020. 4: 461–462.
28. Cerchione C, Catalano L, Nappi D, *et al.* DOMESTIC OPPORTUNITY IN HEAVILY PRETREATED MULTIPLE MYELOMA NOT ELIGIBLE TO HOSPITAL-BASED TREATMENT: ROLE OF POMALIDOMIDE-DEXAMETHASONE. *Haematologica* 2022. 107: 86–87.
29. Cerchione C, Catalano L, Nappi D, *et al.* Pomalidomide-Dexamethasone in the Management of Heavily Pretreated Multiple Myeloma. *Blood* 2021. 138: 5022.
30. Nappi D, Catalano L, Pane F, *et al.* MM-415: Pomalidomide-Dexamethasone in the Management of Heavily Pretreated Multiple Myeloma. *Clin Lymphoma Myeloma Leukemia* 2021. 21: S442.
31. Cerchione C, Catalano L, Nappi D, *et al.* Pomalidomide-dexamethasone in the management of relapsed/refractory multiple myeloma. *HemaSphere* 2021. 5: 801–802.
32. Cerchione C, Martinelli G, Nappi D, *et al.* Pomalidomide-dexamethasone in the management of heavily pretreated multiple myeloma. *HemaSphere* 2021. 5: 48.
33. Cerchione C, Catalano L, Nappi D, *et al.* Pomalidomide-Dexamethasone in the Management of Heavily Pretreated Multiple Myeloma. *Blood* 2020. 136: 1.
34. Cerchione C, Martinelli G & Catalano L. Pomalidomide-dexamethasone in the management of heavily pretreated multiple myeloma. *Am J Hematol* 2020. 95: S5.
35. Cerchione C, Catalano L, Nappi D, *et al.* MM-389: Pomalidomide-Dexamethasone in the Management of Heavily Pre-Treated Multiple Myeloma. *Clin Lymphoma Myeloma Leukemia* 2020. 20: S311.
36. Celgene. A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Pomalidomide in Combination With Low-Dose Dexamethasone Versus High-Dose Dexamethasone in Subjects With Refractory Multiple Myeloma or Relapsed and Refractory Multiple Myeloma and Companion

Study (NIMBUS). *clinicaltrials.gov* <https://clinicaltrials.gov/ct2/show/NCT01311687>
37. van Beurden-Tan CHY, Sonneveld P & Groot CAU-D. Multinomial network meta-analysis using response rates: relapsed/refractory multiple myeloma treatment rankings differ depending on the choice of outcome. *BMC Cancer* 2022. 22:
38. Dimopoulos M, Terpos E, Boccadoro M, *et al.* Apollo: phase 3 randomized study of subcutaneous daratumumab plus pomalidomide and dexamethasone (D-PD) versus pomalidomide and dexamethasone (PD) alone in patients (PTS) with relapsed/refractory multiple myeloma (RRMM). *Blood* 2020. 136: 5-6.
39. NCT02990338. Multinational Clinical Study Comparing Isatuximab, Pomalidomide, and Dexamethasone to Pomalidomide and Dexamethasone in Refractory or Relapsed and Refractory Multiple Myeloma Patients. *https://clinicaltrials.gov/show/NCT02990338* 2016. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02048223/full>
40. Ichinohe T, Kuroda Y, Okamoto S, *et al.* A multicenter phase 2 study of pomalidomide plus dexamethasone in patients with relapsed and refractory multiple myeloma: the Japanese MM-011 trial. *Exp Hematol Oncol* 2016. 5: 11.
41. Maouche N, Kishore B, Bhatti Z, *et al.* Panobinostat in combination with bortezomib and dexamethasone in multiply relapsed and refractory myeloma; UK routine care cohort. *PLoS ONE* 2022. 17:
42. Maouche N, Kishore B, Bhatti Z, *et al.* Panobinostat in combination with bortezomib and dexamethasone for heavily pre-treated myeloma: A UK real-world multi-centre cohort. *Br J Haematol* 2020. 189: 121–122.
43. Bird S, Sriskandarajah P, Kaiser M, *et al.* A ‘real-world’ study of panobinostat, bortezomib and dexamethasone in a very heavily pre-treated population of myeloma patients. *Clin Lymphoma Myeloma Leukemia* 2019. 19: e244–e245.
44. Bird S, Pawlyn C, Nallamilli S, *et al.* MM-296: A Real-World Study of Panobinostat, Weekly Bortezomib, and Dexamethasone in a Very Heavily Pre-Treated Population of Multiple Myeloma Patients. *Clin Lymphoma Myeloma Leukemia* 2020. 20: S306.
45. Leleu X, Attal M, Arnulf B, *et al.* Phase 2 randomised open label study of 2 modalities of pomalidomide (CC4047) plus low-dose dexamethasone in patients with multiple myeloma, refractory to both lenalidomide and bortezomib. IFM 2009-02. 2011. 96: 419-419.
46. Leleu X, Attal M & Arnulf B. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: intergroupe Francophone du Myélome 2009-02. *Blood* 2013. 121: 1968–1975.
47. Wester R, Dinmohamed AG, van der Holt B, *et al.* Pomalidomide in Patients With Relapsed and/or Refractory Multiple Myeloma: A Prospective Study Within the Nationwide Netherlands Cancer Registry. *HemaSphere* 2022. 6: E683.

48. Park H, Byun JM, Yoon S-S, *et al.* Cyclophosphamide addition to pomalidomide/dexamethasone is not necessarily associated with universal benefits in RRMM. *PLoS ONE* 2022. 17:
49. Abeykoon JP, Vaxman L, Patel SV, *et al.* Ocular toxicity of commercially available belantamab mafodotin in patients with advanced multiple myeloma. *Blood* 2021. 138: 2711.
50. Del Giudice ML, Gozzetti A, Antonioli E, *et al.* Real-Life Experience with Pomalidomide plus Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma: A Retrospective and Prospective Study. *Medicina (Kaunas)* 2021. 57:
51. Shragai T, Lavi N, Gatt M, *et al.* Belantamab mafodotin treatment for patients with relapsed/refractory myeloma via gsk expanded access program: Real-world data. *HemaSphere* 2021. 5: 484–485.
52. Shragai T, Gatt M, Jarchowsky O, *et al.* Real-world outcomes of belantamab mafoditin treatment for patients with relapsed/ refractory myeloma via GSK expanded access program. *HemaSphere* 2020. 4: 458–459.
53. Becnel M, Ferreri CJ, Feng L, *et al.* Retrospective, single-center, real-world experience of belantamab mafodotin in relapsed/refractory multiple myeloma. *JCO* 2022. 40: 8060–8060.
54. Talbot et al. P-276 Real-world study of the efficacy and safety of belantamab mafodotin (GSK2857916) in relapsed or refractory multiple myeloma based on data from the nominative ATU in France: IFM 2020-04 study. International Myeloma Society 19th Annual Meeting and Exposition. 2022. Available at: https://events.jspargo.com/IMW22/CUSTOM/pdf/IMS2022Abstracts.pdf.
55. Trudel S, Cohen AD, Richardson PG, *et al.* Safety and tolerability of single-agent belantamab mafodotin in heavily pre-treated patients with relapsed/refractory multiple myeloma: Pooled data from DREAMM-1 and DREAMM-2. *HemaSphere* 2020. 4: 429–430.
56. Nikolaou A, Ambavane A, Shah A, *et al.* Belantamab mafodotin for the treatment of relapsed/refractory multiple myeloma in heavily pretreated patients: a US cost-effectiveness analysis. *Expert Review of Hematology* 2021. 14: 1137–1145.
57. Dimopoulos M, Campana F, Bury D, *et al.* Health-related quality of life in heavily pretreated and renally impaired patients with relapsed/ refractory multiple myeloma receiving isatuximab plus pomalidomide and dexamethasone: ICARIA-MM study. *Hemasphere* 2020. 4: 473-474.
58. Dimopoulos D, Terpos E, Boccadoro M, *et al.* Treatment of patients with relapsed/ refractory multiple myeloma with pomalidomide and dexamethasone with or without subcutaneous daratumumab: patient-reported outcomes from Apollo. *Hemasphere* 2021. 5: 490-.
59. Delforge M, Shah N, Rodriguez-Otero P, *et al.* Health state utility valuation in patients with triple-class-exposedrelapsed and refractory multiple myeloma treated with the bcma-directed car t cell therapy, idecabtagene vicleucel (IDE-Cel,BB2121): results from the Karmma trial. *Blood* 2020. 136: 14-15.

60. 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.
61. Popat R, Lonial S, Voorhees PM, *et al.* DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) Effects on Patient-Reported Outcome (PRO) Measures in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). *Blood* 2020. 136: 27–28.
62. Oriol A, Richardson PG, Mateos M-V, *et al.* HORIZON (OP-106): Melflufen Plus Dexamethasone (dex) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM) - Health-Related Quality of Life (HRQoL) Analysis. *Blood* 2020. 136: 27–29.
63. Shah N, Mojebi A, Ayers D, *et al.* Indirect treatment comparison of idecabtagene vicleucel versus conventional care in triple-class exposed multiple myeloma. *J Comp Eff Res* 2022. 11: 737–749.
64. Martin T, Lin Y, Agha M, *et al.* Health-Related Quality of Life in the Cartitude-1 Study of Ciltacabtagene Autoleucel for Relapsed/Refractory Multiple Myeloma. *Blood* 2020. 136: 41–42.
65. Delforge M, San Miguel J, Bertin KB, *et al.* Quality of life in patients with relapsed and refractory multiple myeloma treated with the bcmatargeted CAR T cell therapy idecabtagene vicleucel (IDE-CEL; BB2121): Results from the KarMMa trial. *HemaSphere* 2020. 4: 457–458.
66. Popat R, Lonial S, Lee HC, *et al.* DREAMM-2: Belantamab mafodotin effect on disease symptoms and health-related quality of life in patients with relapsed/refractory multiple myeloma (RRMM). *HemaSphere* 2020. 4: 802.
67. Engelhardt M, Ihorst G, Singh M, *et al.* Health-related quality of life (HRQOL) reported by patients with multiple myeloma (MM) in Germany. *Oncol Res Treat* 2020. 43: 157.
68. Richardson PG, Larocca A, Leleu X, *et al.* The Burden of Relapsed/Refractory Multiple Myeloma: An Indirect Comparison of Health-Related Quality of Life Burden across Different Types of Advanced Cancers at Baseline and after Treatment Based on HORIZON (OP-106) Study of Melflufen Plus Dexamethasone. *Blood* 2019. 134: 3487.
69. ASCO. 2022 ASCO Annual Meeting Proceedings. 2022.
70. Wagner L, Abonour R, Ailawadhi S, *et al.* P-136: Health-related quality of life (HRQL) among real-world Ide-Cel–eligible patients (pts) with relapsed/refractory Multiple Myeloma (RRMM): results from the Connect® MM registry. *Clin Lymphoma Myeloma Leukemia* 2021. 21: S109.
71. National Institute for Health and Care Excellence. NICE TA510: Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]. <https://www.nice.org.uk/guidance/ta783/evidence/appraisal-consultation-committee-papers-ta510-pdf-11016892909>

72. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510)| Guidance | NICE. <https://www.nice.org.uk/guidance/ta783>
73. National Institute for Health and Care Excellence. NICE TA658: Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. <https://www.nice.org.uk/guidance/ta658/documents/committee-papers-2>
74. National Institute for Health and Care Excellence. NICE TA427: Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. <https://www.nice.org.uk/guidance/ta427/documents/committee-papers>
75. National Institute for Health and Care Excellence. Final scope for the single technology appraisal of belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]. 2022. <https://www.nice.org.uk/guidance/gid-ta10568/documents/final-scope-2>
76. NHS England. Clinical Commissioning Policy: Bendamustine for relapsed multiple myeloma (all ages) NHS England Reference : 200604P. 2020.
77. GSK. Trial Protocol for DREAMM-2.
78. GSK. Reporting and Analysis Plan for A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses of the Antibody Drug Conjugate GSK2857916 in Participants with Multiple Myeloma Who Had 3 or More Prior Lines of Treatment, Are Refractory to a Proteasome Inhibitor and an Immunomodulatory Agent and Have Failed an Anti-CD38 Antibody (DREAMM 2).
79. Lonial S, Lee HC, Badros A, *et al.* Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer* 2021. 127: 4198–4212.
80. NICE. TA427. Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib. 2016.
81. England NHS. National Cost Collection for the NHS. <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>
82. National Institute for Health and Care Excellence. British National Formulary. <https://bnf.nice.org.uk/>
83. National Institute for Health and Care Excellence. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510)| Guidance | NICE. <https://www.nice.org.uk/guidance/ta783>
84. Unit Costs of Health and Social Care | PSSRU. <https://www.pssru.ac.uk/project-pages/unit-costs/>
85. Personal Social Services Research Unit (PSSRU). 2015 Unit Costs of Health and Social Care. 2015.

86. Dimopoulos MA, Palumbo A, Corradini P, *et al.* Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. *Blood* 2016. 128: 497–503.
87. Miguel JS, Weisel K & Moreau P. 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: 1055–1066.
88. Millne RJ, Heaton-Brown KH & Hansen P. Quality-of-life valuations of advanced breast cancer by New Zealand women. *Pharacoeconomics* 2006. 24: 281–92.
89. Overview | Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears | Guidance | NICE. <https://www.nice.org.uk/guidance/ta369>
90. Proskorovsky I, Lewis P, Williams CD, *et al.* Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes* 2014. 12: 35.
91. GSK DREAMM-2 CSR. Data on file. 2022.
92. Kumar S, Paiva B, Anderson KC, *et al.* International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet oncology* 2016. 17: 328–346.
93. Kumar S, Paiva B, Anderson KC, *et al.* International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet oncology* 2016. 17: 328–346.
94. National life tables: England - Office for National Statistics. <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables>
95. GSK. DREAMM-2 end of study manuscript, in preparation.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

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] [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 its associated 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>
<table>
<tr><th>Name of Company</th><th>Grants and project specific funding</th><th>Gifts, Honoraria and Sponsorship</th><th>Total (£)</th></tr>
<tr><td>Celgene</td><td>-</td><td>5,000</td><td>5,000</td></tr>
<tr><td>BMS</td><td>40,000</td><td>-</td><td>40,000</td></tr>
<tr><td>Janssen-Cilag</td><td>25,000</td><td>950</td><td>25,950</td></tr>
</table>
The table above shows the audited 2021 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work including clinical trials, and gifts, honoraria or sponsorship.
</td></tr>
<tr><td>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</td><td>No</td></tr>
</table>

5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission has been gathered from the myeloma patients and carers we engage with through our research and services programmes, including: - We conducted structured telephone interviews in October 2022 with relapsed/refractory myeloma patients specifically to support this appraisal. These interviews provide important experience and insight data from patients whose clinical condition is highly relevant and who have either received the treatment being appraised, or who are multiply relapsed and view this technology as a potential next step in their treatment pathway. - A multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. It has also been informed by analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays and posts to our online Discussion Forum.

Living with the condition

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 currently no cure, but treatment can halt its progress and improve quality of life. The complications of myeloma can be significant, debilitating and painful and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system which can lead to increased infections. *"I was diagnosed with myeloma in March 2014 and it has had a significant impact on my life."* *"Eventually just before the pandemic, the myeloma progressed to my spine and I gained 13 fractures just from bending over the bath to wash my hair."* Myeloma is also a relapsing and remitting cancer which evolves over time and becomes resistant to treatment. Most patients can be successfully retreated at relapse; however, remission is usually associated with diminishing duration and depth of response over time. Most patients can be successfully retreated at relapse; however, as patients multiply relapse their remission is usually associated with diminishing duration and depth of response over time. At first relapse the median time to next treatment is 13 months with only 58% of patients achieving a complete response/ very good partial response (CR/ VGPR) compared to 74% at diagnosis. At second relapse the time to next treatment reduces even further to 7 months with CR/ VGPR being achieved in less than half of patients.[1] *"It's very hard to switch off from having myeloma as it's always there. You are always aware that the current treatment will eventually fail - 4 weekly paraprotein/FLC checks are always stressful."* Multiply relapsed patients, the population covered in this appraisal, often experience an even more significant disease burden. They not only face a worse prognosis but also a greater symptomatic 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 patients' lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members, also impacts on patients' sense of control. *"Living with myeloma affects everything. I tried to keep working but I couldn't. There are periods of treatment that make working difficult as you have constant interruptions, which is challenging for both you and your employer."*

	"There are also social limitations - I try to do most socialising outside or in an airy environment to avoid viruses / covid. I would love to be able to frequent cosy pubs and restaurants." The individual and heterogeneous nature of myeloma means that some patients may tolerate a treatment well and others may not. In addition, myeloma evolves and becomes resistant to treatment. It is therefore essential to have a range of treatment options with different mechanisms of action at all stages of the myeloma pathway. *"Myeloma becomes so resistant so quickly, that's the biggest uncertainty. You never know what's going to come. It has a very unchartered course, as it's an entirely individual cancer."* 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 - Only 42% of carers were not given enough information at diagnosis about how myeloma may affect them[3] Living with myeloma is therefore often extremely challenging physically and emotionally for patients, carers, and family members. *"It's an emotional rollercoaster for your family as sometimes it seems like nothing, you're living a normal life and other times you're in hospital or on treatment that really affects you. As a parent, you don't have the energy to do the things you'd like to do with your children."* *"I cannot do many of the things that I used to, such as chores, DIY tasks or driving. I cannot lift heavy weights. I depend on my wife for doing lots of things such as driving or carrying things."*

[1] Bird and Boyd (2019) Multiple Myeloma: An Overview of Management Palliative Care and Social Practice 13:1-13 & Yong et.al (2016) Multiple Myeloma: Patient Outcomes in Real-World Practice Br J Heamatology 175:252-265
[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
[3] A Life in Limbo: A Myeloma UK research report on the experience of myeloma carers in the UK 2016: https://www.myeloma.org.uk/documents/a-life-in-limbo/

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Myeloma is an incredibly heterogenous condition with a large variability in age, comorbidities and fitness. Consequently, not all patients can receive the same treatment or intensity of dose. Therefore, treatment options must be based on the patient's fitness levels and ability to tolerate toxicities. For patients who relapse for the fourth time they have treatment options including: - Pomalidomide in combination with dexamethasone (TA427) - Panobinostat in combination with bortezomib and dexamethasone (TA380) - A combination of chemotherapy and a steroid with or without thalidomide (e.g. Melphalan and a corticosteroid) In the current treatment pathway it is worth noting that some patients will receive the CDF approved combination of Isatuximab, pomalidomide and dexamethasone (TA658) at fourth line of treatment. Consequently, those patients may be refractory to pomalidomide and dexamethasone when they reach fifth line, leaving them with the option to receive standard chemotherapy or enter a clinical trial. Patients are acutely aware of the fact that the range of treatment options available at fifth line and beyond is markedly narrower than those available at first or second line. Understandably, this can cause a great deal of worry for myeloma patients, as well as their carers and families, as there is a fear of reaching the 'end' of treatment options for their cancer. *"(…) for people in my situation who have gone through a long list of treatments, there is a serious concern that you're running out of options. I don't have many places left to go, apart from clinical trials, some of which can be pretty invasive and life-affecting."* The current standard clinical practice in myeloma is to treat patients with as many treatments and with as many different mechanisms of actions up front as possible. Therefore, triplet and even quadruplet combinations are now standard therapy in myeloma. Hence, this gap means that some patients must undergo sub-optimal treatment at a critical time in their disease pathway. Indeed, multiply relapsed/refractory patients follow with interest the development of innovative treatments and perceive aspects of the current treatment offer to be less than optimal. One patient we interviewed for this appraisal said: *"Some of the other remaining options are not so good."*

8. Is there an unmet need for patients with this condition?	As myeloma is a relapsing and remitting cancer, patients need to have effective treatments available at each relapse. Due to the nature of myeloma, it is crucial that clinicians are always one step ahead of the cancer and that there is another treatment option 'waiting in the wings' for patients to receive, particularly where the myeloma has mutated to the point that it will not respond to currently available treatments. Patients with relapsed or refractory myeloma after four or more therapies are all too familiar with this scenario. Their disease is resistant to most existing treatments and innovative mechanisms of action are required to bring it back under control. Otherwise, the progression of the cancer is unimpeded, with serious consequences for the patients' quality of life and survival. This constitutes a significant area of unmet need for the patient population covered by this appraisal. There is also a lack of data available on what works well for treating myeloma patients who have already passed through four or more therapies. The use of new drugs at this stage of the treatment pathway can help to generate new data and insights for the benefit of the myeloma research community as it continues to explore ways of addressing unmet need for patients. Currently, there is no treatment for myeloma approved for use on the NHS which uses a B cell maturation antigen (BCMA). This is a novel mechanism of action that targets BCMA protein on the surface of myeloma cells. The treatment under appraisal is the first non-cellular technology for treating myeloma that operates using this mechanism. Therefore, it has much potential to fulfil an unmet need for multiply relapsed/refractory myeloma patients. Overall, there is a need for a wide range of options at each stage of the treatment pathway given the heterogeneous and evolving nature of myeloma. However, breadth of choice remains limited for the more advanced stages of this pathway. *"There are many people like myself, further down the myeloma treatment pathway, who are relatively well and still have a lot to contribute to their own families and to society in general. I believe, offering more treatments choices at 4/5th line and beyond even, is really important, and in danger of being overlooked…"*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our engagement that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life. The DREAMM-2 clinical trial evaluated the use of belantamab mafodotin as a monotherapy in myeloma patients who had received at least three previous lines of treatment. The results from the trial show that, patients who achieved a very good partial response (VGPR) – which amounted to 19% of trial participants – had an estimated median PFS of 14 months.[4] In addition, although data availability makes it difficult to establish direct comparisons with the current standard of care, the trial's estimated median overall survival of 13.7 months is a good outcome in light of existing evidence on survival rates in triple-class refractory patients.[5] *"I have to say belantamab might sound like a gamble given the overall response rate, but if it works for 14 months this is a good remission when compared to what else is available to me at this stage in my treatment journey."* Patients we interviewed who were receiving belantamab mafodotin as treatment for their myeloma highlighted its effectiveness in controlling their disease. They expressed their relief at having found a new drug that allowed them to enter and maintain a period of remission, some lasting several months. *"I started taking belantamab mafodotin in mid-August 2021 and so far it has been totally effective in controlling my myeloma. I'm in remission thanks to this treatment.* *"I started taking belantamab mafodotin in November 2021 and it's been brilliant. I can honestly say that it's the best myeloma treatment that I've had in ten years."* *"I have been receiving Blenrep since July 2022. I've only had a few test results since then but, taking my level of Kappa Light chains as the key measure, the treatment does seem to be effective."* These patients also underlined how the results of their treatment to date had alleviated some of the mental and emotional stress that they experienced due to becoming refractory to several previous treatments. One patient commented: *"It's a huge relief to see that it is working and it has given me a new lease of life."* Patients consider the fact that the treatment regime for belantamab mafodotin involves the use of a single drug without combination with steroids a major advantage. This is based on their challenging experience of previous combination treatments with more immediate toxic effects. *"Anything with dexamethasone is difficult – the side effects of steroids are terrible in general."*

	"I also consider that monotherapy is a significant advantage - not loading the patient's body with excessive toxicity." Patients perceive the frequency of administration as a further advantage of this treatment as it has minimal impact on their day-to-day lives. Longer treatment intervals enable patients to have more control over their lives compared to feeling restricted or burdened by weekly hospital visits. The regime for belantamab mafodotin is therefore perceived as more 'patient-friendly' in comparison with the requirements of other treatments. *"Receiving belantamab just once every 3 weeks is a great advantage as it allows the patient to forget about treatment in-between times."* Another consideration for patients is the novelty of belantamab mafodotin as an anti-BCMA antibody, which expands the type of treatment options available to them. Indeed, the innovative nature of this treatment was recognised by the decision of the UK's Medicines and Healthcare products Regulatory Agency (MHRA) to grant Blenrep an 'innovation passport' as part of the ILAP process.[6] Multiply relapsed and refractory myeloma patients are especially dependent on the roll-out of innovative medicines and welcome the opportunity to access state-of-the-art treatments which have the potential to improve their chances of survival and quality of life. *"For me belantamab sounds like a more modern option than the other drugs that would be available afterwards anyway."* The ability to access a novel treatment, without steroids, delivering effective remissions cannot be underestimated for patients at this point in the treatment pathway. The benefits it delivers are hugely meaningful to patients and also give patients the hope that it is a bridge to further treatments which may become available soon – for example, CAR-T. This "bridge" to the next treatment is a significant factor for myeloma patients, particularly those who are multiply relapsed and who have direct experience of how future treatment options have opened up while they are in remission from existing or newly approved treatments.

[4]Lonial S, Lee HC, Badros A, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer*. 2021;127:4202. doi:10.1002/cncr.33809

[5]Usmani S, Ahmadi T, Ng Y, et al. Analysis of real-world data on overall survival in multiple myeloma patients with ≥ 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or double refractory to a PI and an IMiD. *The Oncologist*. 2016;21:1355–1361. doi:10.1634/theoncologist.2016-0104; Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33:2266-2275. doi:10.1038/s41375-019-0435-7

[6]The Pharma Letter, MHRA likes the look of two GSK cancer drugs, granting special status, 16 June 2022: https://www.thepharmaletter.com/article/mhra-likes-the-look-of-two-gsk-cancer-drugs-granting-special-status

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We know from our engagement that patients value treatments with fewer side effects with low severity ratings which stop when treatment ends. However, in practice patients will accept varying levels of toxicity in a treatment if it delivers good survival benefit and depending on the stage of their myeloma. The most common toxicities in the DREAMM-2 trial were grade ≥3 keratopathy (46%), best-corrected visual acuity (BCVA) decline (31%), thrombocytopenia (22%) and anaemia (21%); and, side effects causing the discontinuation of treatment (9%).[7] Among trial participants keratopathy, a condition involving changes to the cornea of the eye, and loss of visual acuity were frequently observed upon eye examination and these side effects were likewise highlighted by the patients we interviewed. One patient remarked: *"The effect on my eyesight is debilitating as it has been difficult to work on a computer screen and to read."* Although patients perceive the eye-related side effects of this treatment as a clear disadvantage, they do not believe that this takes away from its overall benefit. In general, many myeloma patients see side effects as something to be expected as part of their treatment; they are willing to accept the immediate disadvantages in a trade-off for long-term gains or manage to develop self-care strategies in cooperation with their healthcare team. In the case of belantamab mafodotin, both clinicians and patients feel that its side effects can be effectively managed through suitable ophthalmological care. *"Overall, although my experience of Blenrep has been challenging due to the eyesight issues, there are no other major problems, at least none which I can attribute for certain to the treatment."* *"The side effects that I've had with belantamab are minimal in comparison to those of other treatments. The eyesight problem is the only thing, but it's not a big issue and it does correct itself."* *"In the grand scheme of things, the eyesight issue is a small price to pay as there aren't many other treatment options left."* Moreover, trial evidence suggests that the eye-related side-effects are reversible and can be reduced with effective dose modification. The DREAMM-2 study found that the majority of patients with such side effects (77%) had recovered since their first eye examination.[8] The patients we interviewed for this appraisal likewise explained that dose delay or reduction had helped them to manage eye-related toxicity while sustaining an effective response to the treatment.

	"Due to the side effects on my eyes my third dose of Blenrep was delayed slightly and given at a reduced 75% dose, and now my fourth dose is also likely to be delayed. I'm continuing to discuss this with the ophthalmologist. I've heard that the treatment appears to continue working even with long pauses between the doses, which is encouraging." *"When I started it, they put me on a 3 weekly cycle, but they found that I was having visual acuity decline, so they had to reduce the dose and spread out the treatment to much longer intervals. When they went from 3 to 6 weeks, the paraprotein levels were holding very well, and then they went to 9 and 12 weeks and the levels were still holding well."* As with all myeloma treatments, due to the individual and complex nature of the cancer not all patients will respond well to belantamab mafodotin. However, it is important that belantamab is made available to allow doctors the flexibility to prescribe this treatment to multiply relapsed/refractory patients who they think will benefit clinically. *"I told the doctors that I preferred them to choose which treatment was going to make the most difference to my myeloma. It doesn't matter about the side effects as they are treatable and can be worked around, but before belantamab my myeloma was going up and up and was going to kill me."*

[7] Lonial S, Lee HC, Badros A, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer*. 2021;127:4206 doi:10.1002/cncr.33809
[8] Ibid.:4209

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?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients feel that there should be robust channels of cooperation between haematology and ophthalmology teams for the management of eye-related toxicity associated with belantamab mafodotin. Ideally, this cooperation should be based on a shared understanding concerning dose modification as there seems to be some discomfort with the current 'trial and error' approach. One patient we interviewed explained: *"Although the eye-related side effects seem to be reversible, no one seems to know how long it might take for things to stabilise following treatment. There doesn't seem to be clear guidance within the special access scheme on how long to pause the treatment due to these side effects. This is a little unsettling."*

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a clear unmet need for this technology as it will give patients a greater choice of options at their fifth line of treatment, including access to a novel therapy (anti-BCMA antibody). There is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. • Insights from our patient interviews clearly show that patients who received belantamab mafodotin had a positive experience and would recommend it for approval on the NHS. • Clinical trial data and insights from our patient interviews confirm that belantamab mafodotin can deliver benefits which are most important to patients: good PFS and quality of life. • Patients take the view that the frequently reported side effects on the eyes are manageable and do not negate the treatment's overall benefit. • Patients consider the monotherapy regime, without combination with steroids and administered on a multi-week cycle, as a distinct advantage of this treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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.

External Assessment Group Report

Title: *ID2701- Multiple myeloma (relapsed or refractory after 3 therapies) - Belantamab mafodotin*

Produced by	*Warwick Evidence*
Authors	*Dr Martin Connock, Honorary Senior Research Fellow, Warwick Medical School* *Dr Hesam Ghiasvand, Research Fellow, Warwick Medical School* *Iman Ghosh, Research Associate, Warwick Medical School* *Anna Brown – Information Specialist, Warwick Medical School* *Dr Mandy Maredza, Senior Research Fellow, Warwick Medical School* *Dr Alex Tsertvadze, Independent Consultant, Warwick Medical School* *Professor Amy Grove, Professor of HTA and Implementation Science, Warwick Medical School*
Correspondence to	*Amy Grove* *Warwick Evidence* *Division of Health Sciences* *Warwick Medical School* *University of Warwick* *Coventry, CV4 7AL* *A.L.Grove@warwick.ac.uk*
Date completed	*Date completed 07/12/2022*

Source of funding
This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135711.

Declared competing interests of the authors
None.

Acknowledgements
The EAG would like to acknowledge our clinical advisors and clinical quality assessor:
Emeritus Professor Steven Schey, Consultant Haematologist, Kings College Hospital
Professor Supratik Basu, Consultant Haematologist, Royal Wolverhampton NHS Trust
Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services Research. University of Warwick.

Rider on responsibility for report
The views 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:
Connock M, Ghiasvand H, Ghosh I, Brown A, Maredza M, Tsertvadze A, Grove A: ID2701- Multiple myeloma (relapsed or refractory after 3 therapies) - Belantamab mafodotin. A Single Technology Appraisal. Warwick Evidence, 2022.

Contributions of authors
Dr Martin Connock critiqued the company survival analysis and conducted EAG additional analysis. Dr Hesam Ghiasvand critiqued the cost-effectiveness evidence. Dr Mandy Maredza provided senior oversight of the cost-effectiveness analysis. Dr Alex Tsertvadze led the critique of the clinical effectiveness evidence with Iman Ghosh. Anna Brown critiqued and updated the company SLR searches. Professor Amy Grove led the project.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

List of acronyms

5L	Fifth Line
AD	Aggregate Data
AE	Adverse Events
AIC	Academic in Confidence
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCT	Allogeneic Stem Cell Transplantation
AUC	Area Under the Curve
Belamaf	Belantamab mafodotin
BNF	British National Formulary
CBR	Clinical Benefit Rate
CDF	Cancer Drug Fund
CIC	Commercial in Confidence
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Intervals
CR	Complete Response
CRD	Centre for Reviews and Dissemination
CS	Company Submission
DOR	Duration Of Response
DREAMM-2	Open-label study of Belantamab Mafodotin
DREAMM-3	Head-to-head study comparing Belamaf to PomDex
DSU TSD	Decision Support Unit Technical Support Document
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eGFR	Estimated Glomerular Filtration Rate
EHA	European Haematology Association
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	Standardised instrument for use as a measure of health outcome.
ESMO	European Society for Medical Oncology
ESS	Effective Sample Size
FDA	Food and Drug Administration
GSK	Glaxo SmithKline
HES	Hospital Episode Statistics
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratios
ICR	Institute of Clinical Research
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
INAHTA	International Network of Agencies for Health Technology Assessment

IPD	Individual Patient Data
IQR	Interquartile range
ITC	Indirect Treatment Comparisons
ITT	Intention To Treat
KM	Kaplan-Meier
Len	Lenalidomide
LVEF	Left Ventricular Ejection Fraction
LYG	Life Years Gain
MA	Medicine Approval
mAb	Monoclonal Antibodies
MAIC	Matched Adjusted Indirect Comparison
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Regulatory Agency
MM	Multiple Myeloma
MR	Minimal Response
MY20	Quality of Life Questionnaire
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	Net Monetary Benefit
NPP	Named Patient Programme
NR	Not Reported
ONS	Office for National Statistics
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
OWSA	One-Way Sensitivity Analysis
PAS	Patient Access Scheme
PanoBorDex	Panobinostat with Bortezomib and Dexamethasone
PD	Progressed Disease
PFS	Progression Free Survival
PI	Proteasome Inhibitor
PomDex	Pomalidomide plus Dexamethasone
PR	Partial Response
PS	Performance Status
PSA	Probability Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QLQ-MY20	European Organisation for Research and Treatment of Cancer Questionnaire
R-ISS	Revised International Staging System Stage
RCT	Randomised Control Trials
RDI	Relative Dose Intensity
RRMM	Relapsed or Refractory Multiple Myeloma
RTDS	National Radiotherapy Dataset

RWE	Real World Evidence
SACT	Systemic Anti-Cancer Therapy
sCR	Stringent Complete Response
SCT	Stem Cell Transplantation
SLR	Systematic Literature Review
SoC	Standard of Care
TCR	Triple Class Refractory
TTD	Time to Treatment Discontinuation
TTP	Time to Progression
TSNT	Time to Start of Next Treatment
TTNT	Termed Timed to Next Treatment/Time to Next Therapy
ULN	Upper Limit Normal
VGPR	Very Good Partial Response
WTP	Willingness To Pay

Table of Contents

Table of Tables

Table of Issues

Table of Figures

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 (starting at Section 2).

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table 1 presents a summary of the key issues identified in this appraisal of the clinical and cost-effectiveness of Belamaf (Belantamab mafodotin) within its full marketing authorisation for patients with relapsed or refractory multiple myeloma (RRMM) who have had at least four prior therapies, and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody, and whose disease has progressed on the last therapy.

Table 1 Summary of key issues and other issues

ID2701	**Summary of issue**	**Report sections**
Key Issues		
Issue 1	Appropriateness of pomalidomide plus dexamethasone (PomDex) as a valid comparator to Belamaf in the NHS context.	Table 3 3.5.1.3
Issue 2	Inappropriate source data presented as evidence for efficacy of Belamaf and PomDex	3.2.1 3.2.2
Other Issues		
Issue 3	Minor changes to the economic model	5.4.3 Table 2
Issue 4	Company proxy measure for progression free survival (PFS) termed timed to next treatment (TTNT)	3.5.1.1. 3.5.1.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows;

1. Inappropriateness of the comparators Note: no alternative appropriate comparator was identified.
2. Calculated utility weights
3. Severity modifier choice.

The impact on the company ICER is presented in Table 2. Full descriptions are provided in Section 5.4.

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 is modelled to affect QALYs by:

- The incremental Life Years Gain (LYG) is [redacted].
- The total QALYs with Belamaf is [redacted]
- The total QALYs with PomDex is [redacted]
- The incremental QALYs with a severity modifier at 1.7 is [redacted]
- The incremental QALYs without the severity modifier is [redacted].

Overall, the technology is modelled to affect costs by:

- The total cost of the Belamaf strategy is £[redacted]
- The total cost of the PomDex strategy is £[redacted]
- The incremental cost of Belamaf versus PomDex is £[redacted]

1.3 *The decision problem: summary of the EAG's key issues*

The EAG's key issue related to the decision problem are listed in the Issue 1 Table below.

Issue 1: Appropriateness of Pomalidomide plus dexamethasone (PomDex) as a comparator to Belamaf in the NHS context.

Report section	Table 5 3.5.1.3
Description of issue and why the EAG has identified it as important	Inappropriate/unavailable comparator options for 5L+ TCR MM patients. The EAG consider that there is no evidence available to demonstrate that PomDex is an active treatment for the patient group. The EAG remain unconvinced that PomDex is an appropriate comparison for this population (patients with MM, who had received 4 or more prior lines of treatment, are refractory to a PI, an IMiD and who had failed an anti-CD38 mAb). The EAG clinical advisors suggest that PomDex is very rarely used in this patient population as it would have already been used earlier in the pathway (from 4L+), and therefore, patients are considered refractory.
Description of issue and why the EAG has identified it as important	At the time of submission, • Evidence for PomDex in the CS was derived from aggregate data via the NCRAS real world evidence study. There are important differences between the two populations (intervention and comparator) regarding prognostic factors. Data on multiple prognostic factors is missing from the NCRAS data base which renders PomDex, based on NCRAS data, an invalid comparison for Belamaf. • DREAMM-2 was the only source of evidence available to compare Belamaf to PomDex. DREAMM-2 is a phase II, multicentre open-label randomised two-arm trial to investigate the efficacy and safety of two doses of Belamaf (2.5 mg/kg IV Q3W and 3.4 mg/kg IV Q3W) in patients with MM, who had received 3 or more prior lines of treatment, are refractory to a PI, an IMiD and who had failed an anti-CD38 mAb. The CS uses data from a single arm. The company base case efficacy inputs are unadjusted (naive) comparison data using one arm of DREAMM-2 (2.5 mg/kg) (97 ITT of whom [redacted] were UK patients) and [redacted] patients from NCRAS who received the recommended dose of PomDex. The EAG consider the efficacy results implausible.

What alternative approach has the EAG suggested?	None. No alternative comparator was identified. In the absence of a more appropriate comparator, the EAG have explored the Belamaf to PomDex additional evidence, ITC and head-to-head evidence (see Section 3.5.2.3). The EAG compared publicly available DREAMM-3 results in Table 20 together with values from DREAMM-2 and the NCRAS PomDex study. No significant effect was observed for the primary outcome of DREAMM-3 (HR [redacted] [redacted]), possibly bringing into question EMA licensing and the FDA fast-track licencing of Belamaf for RRMM.
What is the expected effect on the cost-effectiveness estimates?	Uncertain. The analysis used to inform the cost-effectiveness estimates are associated with very substantial uncertainties that are impossible to calibrate in a meaningful way. The EAG conclude that the cost-effectiveness results presented by the company are likely to be invalid.
What additional evidence or analyses might help to resolve this key issue?	Regarding the selection of comparator, the EAG accept that there is no alternative comparator available for consideration in this appraisal, and that PomDex was a listed comparator in the NICE Final Scope. The EAG consider inclusion of the efficacy results of the only head-to-head study comparing Belamaf to PomDex (DREAMM-3) in the economic analysis would provide more plausible cost-effectiveness results. Note, the DREAMM-3 study results became available after the CS was submitted.

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

The EAG's key issue related to the decision problem are listed in the Issue 2 Table below.

Issue 2: Inappropriate source data presented as evidence for efficacy of Belamaf and PomDex

Report section	3.2.1, 3.2.2
Description of issue and why the EAG has identified it as important	Naïve comparison efficacy outcomes used in company base case The EAG conclude that the CS fails to present evidence that demonstrates that Belamaf is a clinically effective intervention (lack of head-to head evidence). In particular, the outcomes of the two studies included as clinical evidence (DREAMM-2 and NCRAS) lack a control, and their populations may differ regarding prognostic factors. This is associated with very substantial uncertainties that are impossible to calibrate in a meaningful way, thereby likely invalidating the cost-effectiveness results presented by the company. The EAG agree with the company that the estimates produced via the anchored and unanchored MAIC (adjusted data) are implausible and contribute to further uncertainty in the economic analysis due to low patient numbers (see Section 3.4). It is evident that the MAIC adjustment improved the efficacy of Belamaf by developing IPD data where Belamaf 'patients' are more like NCRAS patients. However, since there is little overlap between the two sources compared, accompanied by missing values, unavailable data, and an inability to adjust for several important covariates, the EAG conclude that large amounts of bias impact on the efficacy results. Given these limitations, compounded with unavailable or missing data, the MAIC adjustment was incomplete (with small effective sample size [ESS] of [redacted]), rendering the efficacy outcomes biased. This is subsequently expressed as implausibly large HRs (with uninformative wide 95% CIs).
Description of issue and why the EAG has identified it as important	The unadjusted efficacy results input into the company base-case is subject to bias and lacks validity for an economic analysis. All results should be interpreted with caution.
What alternative approach has the EAG suggested?	None. The company did not provide unadjusted (before matching or naïve comparison-based) HRs for the efficacy outcome measures. This information would allow the EAG to assess the amount and direction of change in the values of important efficacy outcome measures used in the MAIC (as shown in Table 15 and Table 16).

What is the expected effect on the cost-effectiveness estimates?	Uncertain. The cost-effectiveness estimates should be viewed with extreme caution due to the incongruence and non-comparability between DREAMM-2 IPD and the NCRAS dataset due to differences in study design and study aims/purpose/patient populations/distribution of patient baseline characteristics (single arm vs. retrospective non-interventional real-world evidence- both inherently subject to bias). Without appropriate control groups, the EAG were unable to determine the true impact/direction of Belamaf.
What additional evidence or analyses might help to resolve this key issue?	Provision of unadjusted (before matching or naïve comparison-based) HRs for the efficacy outcome measures. This information will allow the EAG to assess the amount of matching/adjustment and the likely amount of bias removed by use of a MAIC. Note: Inclusion of the efficacy results of the only head-to-head study comparing Belamaf to PomDex (DREAMM-3) is preferred.

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

The EAG have not included key issues with the cost-effectiveness evidence. Due to the limitations of the clinical effectiveness evidence (Issue 1 and Issue 2) the EAG consider the cost-effectiveness results presented in the CS implausible. In brief,

- There is no head-to-head trial/or indirect evidence to capture the pure effects and costs of Belamaf against PomDex. Details of critiques can be found in Sections 3.2.1 and 3.2.2 of this report.

- The EAG argues the unadjusted approach results in large uncertainty around the ICER outputs which cannot be resolved with data available. See Sections 3.5 and 3.3.7 of this report.

1.6 *Other key issues: summary of the EAG's view*

The EAG highlight two 'other key issues' that may materially affect decision making. This includes the EAG preferred assumptions for economic assessment (Issue 3) which as described in detail in Section 5.4.3 and Table 2. These have minor impacts on the company ICER and do not meaningfully change the direction of the results. As the EAG were unable to generate more plausible results, this issue is not presented as a 'key' issue for technical engagement.

Issue 3: Minor changes to the economic model

Report section	5.4.3 Table 2
Description of issue and why the EAG has identified it as important	Changes to the company economic model which incorporate the EAG preferred assumptions. The evidence in this CS is incomplete to allow an adequate comparative and cost-effectiveness assessment of the technology of interest. The EAG consider the cost-effectiveness results are implausible.
What alternative approach has the EAG suggested?	None. Due to the limitations of the evidence, no meaningful alternative approach was identified (see Section 5.4). The EAGs preferred assumptions only address potential issues (1-4) identified in the company's modelling approach: 1. The EAG argue that the company's calculated utility weights is very optimistic for patients in such a heavily pre-treated population. Instead, the EAG uses the utility values of 0.647 equal to QoL for patients with one refractory MM treatment. 2. Application of a severity modifier at 1.2 for the incremental QALYs.
What is the expected effect on the cost-effectiveness estimates?	Changes to the preferred assumptions (1-2) alter the company's original base case ICER. NB: the EAG consider the cost-effectiveness estimates implausible. 1 ICER (change from company base case) £[redacted] with considering the company's severity modifier, and £[redacted] without considering the company's severity modifier. 2 ICER (change from company base case) £[redacted] (Impact on the ICER the £[redacted])
What additional evidence or analyses might help to resolve this key issue?	None. The EAG suggests that there is no such evidence presented in the CS to resolve Key Issues 1-2. Inclusion of the efficacy results of the only head-to-head study comparing Belamaf to PomDex (DREAMM-3) in the economic analysis would provide more plausible cost-effectiveness results. Note, the DREAMM-3 study became available after the CS was submitted.

Issue 4: Company proxy measure for progression free survival (PFS) termed timed to next treatment (TTNT)

Report section	3.5.1.1. 3.5.1.2
Description of issue and why the EAG has identified it as important	Inappropriate selection of proxy PFS measure: Time to start of next treatment (TSNT) is used to estimate proxy-PFS (TTNT) for intervention and comparator. A pre-specified ITT analysis of ICR-assessed PFS was undertaken in DREAMM-2[1, 2] (see CS Figure 11). This was not used in the company's economic model. Rather than model ITT PFS, the economic model employs a proxy-PFS TTNT. TTNT is defined in DREAMM-2 as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause."
Description of issue and why the EAG has identified it as important	TSNT is used to estimate proxy-PFS TTNT, for PomDex this is based on data for UK patients (likely to reflect NHS treatment). For the Belamaf arm, TSNT is based on data from 58 MM centres across eight jurisdictions, including seven centres with UK patients. The company assumes that healthcare systems across the centres are comparable in terms of treatment pathways and availability of technologies. The EAG was unable to determine the variation across countries. Therefore, the EAG considers the development of TSNT is unlikely to have been comparable across the two arms.
What alternative approach has the EAG suggested?	None. In **Error! Reference source not found.** the EAG have compared DREAMM-2[1, 2] IRC ITT KM analysis of PFS (as in CS Figure 11) with the proxy-PFS (TTNT) (as in CS Figure 19). The area under the curve (AUC) for proxy-PFS is greater than that for PFS; the use of proxy-PFS rather than PFS will tend to accumulate more QALYs
What is the expected effect on the cost-effectiveness estimates?	The proxy-PFS (TTNT) is unlikely to have been fairly estimated for Belamaf and PomDex. Since post-progression time is rated at lower quality of life than pre-progression time the larger the pre proxy-PFS is, relative to the post-proxy PFS, the greater the QALY accumulation.
What additional evidence or analyses might help to resolve this key issue?	Consider analysis using DREAMM-2[1, 2] IRC ITT KM analysis of PFS.

1.7 *Summary of EAG's preferred assumptions and resulting ICER*

The EAG have identified two preferred assumptions. Table 2 presents the impact of the EAG preferred assumptions on the ICER by considering a severity modifier of 1.7 according to the company's assigned severity modifier. EAG preferred

assumptions do not change the ICER in favour of PomDex and should be viewed as addressing issues in the company analysis. All ICERs presented in the EAG report should be interpreted with caution as more substantially, the EAG question the appropriateness and validity of a number of key model efficacy inputs (See Section 3.3.7). The EAG consider the ICER presented in the CS, implausible.

1. The company has calculated the utility weights at the general population's quality of life, the EAG argues this would be very optimistic for patients in such a heavily pre-treated population. In addition, the company has fed the model with data for QoL from the DREAMM-2 trial which had [redacted]. The EAG suggests a cap of QoL at the QoL of patients who have experienced one prior treatment line. Terpos et al. (2022)[3] applied 0.647 QoL at the baseline for the PFS state. This is applied in agreement with the company's other assumption about the independence of QoL from the treatment regimens. The base case ICER is £[redacted] with considering the company's 1.7 as the severity modifier, and £[redacted] without considering the company's severity modifier. Both show a dominating situation for Belamaf.

   By applying the EAG's suggested utility weights the results will be £[redacted] with considering the company's 1.7 as the severity modifier, and £[redacted] without considering the company's severity modifier. Both show a dominating situation for Belamaf.

2. For the company's QALY shortfall analysis, the absolute shortfall implies that a QALY weighting of 1x should be applied, whilst the EAG considers a proportional QALY shortfall of [redacted]% implies that a QALY weighting of 1.2x should be applied. As proportional QALY shortfall implies a greater severity level, the appropriate severity weighting is 1.2x.

   By applying the EAG's 1.2x as the severity modifier, the results will be [redacted]. This shows a dominating situation for Belamaf.

Table 2 Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICERs
Company's base case: The company applies a utility weight of [redacted] for patients on the treatment at the PFS state with a severity modifier of 1.7	£[redacted]	[redacted]	£[redacted]
The EAG's assumed a utility of 0.647 for patients on the treatment at the PFS state with a severity modifier of 1.7	£[redacted]	[redacted]	£[redacted]
Changes after the EAG's preferred assumptions (without the severity modifier)	£[redacted]	[redacted]	£[redacted]
Company's base case: **The company applies a severity modifier of 1.7**	£[redacted]	[redacted]	£[redacted]
The EAG assumed a severity modifier of 1.2	£[redacted]	[redacted]	£[redacted]
Changes after the EAG's preferred assumptions	£[redacted]	[redacted]	£[redacted]

No modelling errors were identified or corrected by the EAG (see Section 4.2.2). For further details of the exploratory analyses conducted by the EAG, see Section 3.5.

External Assessment Group Report

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

This single technology appraisal (STA) was conducted to appraise the clinical and cost-effectiveness of Belamaf (Belantamab mafodotin) within its full marketing (MA) authorisation for patients with relapsed or refractory multiple myeloma (RRMM) who have had at least four prior therapies, and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody, and whose disease has progressed on the last therapy. The Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion for Belamaf on 23 July 2020, whereas the European Medicines Agency (EMA) and Medicines and Healthcare Regulatory Agency (MHRA) granted a conditional MA for Belamaf on 25th August 2020 and 1st January 2021 respectively.[5, 6]

In the UK, the treatment options are limited for the patients categorised as RRMM, particularly, patients who have had four previous lines of therapies and/or triple-class refractory (TCR) (i.e., refractory to a PI, an IMiD and an anti-CD38 mAb). NICE have proposed treatment options for 5L+ RRMM patients,[7, 8] however, these options are limited and changeable (see Figure 1). Standard of care (SoC) recommendation for 5L+ patients who are also TCR are lacking (CS, Section B1.3.3.1, Page 19). In contrast, Belamaf is already recommended for RRMM patients outside of the UK for treating TCR patients, as per EHA-ESMO 2021 clinical guideline[9] and for patients in 5L+MM patients, according to the National Comprehensive Cancer Network (NCCN) 2022 guidelines.[10] The company conclude that Belamaf is needed as a treatment option in the NHS for 5L+ TCR patient population.

2.1.1 Disease overview

Multiple myeloma (MM) is a progressive and incurable bone marrow neoplasm, caused due to abnormal proliferation of plasma cell derived from B lymphocytes.[11] These large quantities of plasma cells result in overproduction of immunoglobulin of a single heavy and light chain, also known as monoclonal (M)-protein, at an expense of body's immune dysfunction. These cytogenetic abnormalities are identified among

90% of MM patients and are likely to progress to further genomic evaluation with the natural course of the disease.[12] Although several cells are present in the circulation, the majority of them are in the bone marrow and produces cytokines. Production of cytokine-initiated osteoclastic activities causes bone absorption, bone pain and fractures. Occasionally, plasma cells infiltrate into multiple organs and produces a number of symptoms such as renal failure, anaemia, and recurrent infection.[12, 13]

Typically, the clinical course of the disease includes periods of treatment and remission separated by unavoidable relapses, with duration of response to treatment decreasing with subsequent lines of treatment (CS section B 1.3.1.1, Page 13). However, the disease becomes more complex with its advancement and resistance to different classes of therapies occurs.[14] In advanced stages of MM, the health-related quality of life significantly decreases with high symptom burden and multi-organ involvement. The EAG clinical advisors agreed with this description of the clinical course and emphasised the reduction of treatment options as disease progresses.

2.2 *Background*

Globally, MM accounts for approximately 2% of all new cancer cases (estimated in 2016-2018). In the UK, 5,951 new cases of MM are detected each year, whereas death due to MM estimated to be 3,098, which is equivalent to more than eight deaths per day.[15] Like most other malignancies, the incidence of MM increases with age. In the UK an average 43% of new cases are in people who are 75 years and above.[15] Associated comorbidities at the older age further increases disease complexity and reduces treatment efficacy.

With the introduction of newer treatments in the treatment landscape of MM, progression free survival (PFS) and overall survival (OS) have significantly increased.[16] In the UK, the NICE treatment pathway recommends pomalidomide plus dexamethasone (PomDex) and panobinostat with bortezomib and dexamethasone (PanoBorDex) as treatment options for 5L+ RRMM patients. The EAG clinical advisor suggests treatments for 5L+ represents an unmet need and options for 5L+ TCR patients are “*vanishing low*” (personal communication).

In this context, the company's anticipated positioning of Belamaf in the treatment pathway of MM is as depicted in Figure 1. The EAG notes that TA573, TA505 and TA658 are only available to patients as part of the Cancer Drugs Fund. Additional evidence collection for these three technologies is currently underway. After this, NICE will decide whether or not to recommend their use on the NHS and updated guidance will be made available. Therefore, TA573, TA505 and TA658 are not considered in this appraisal.

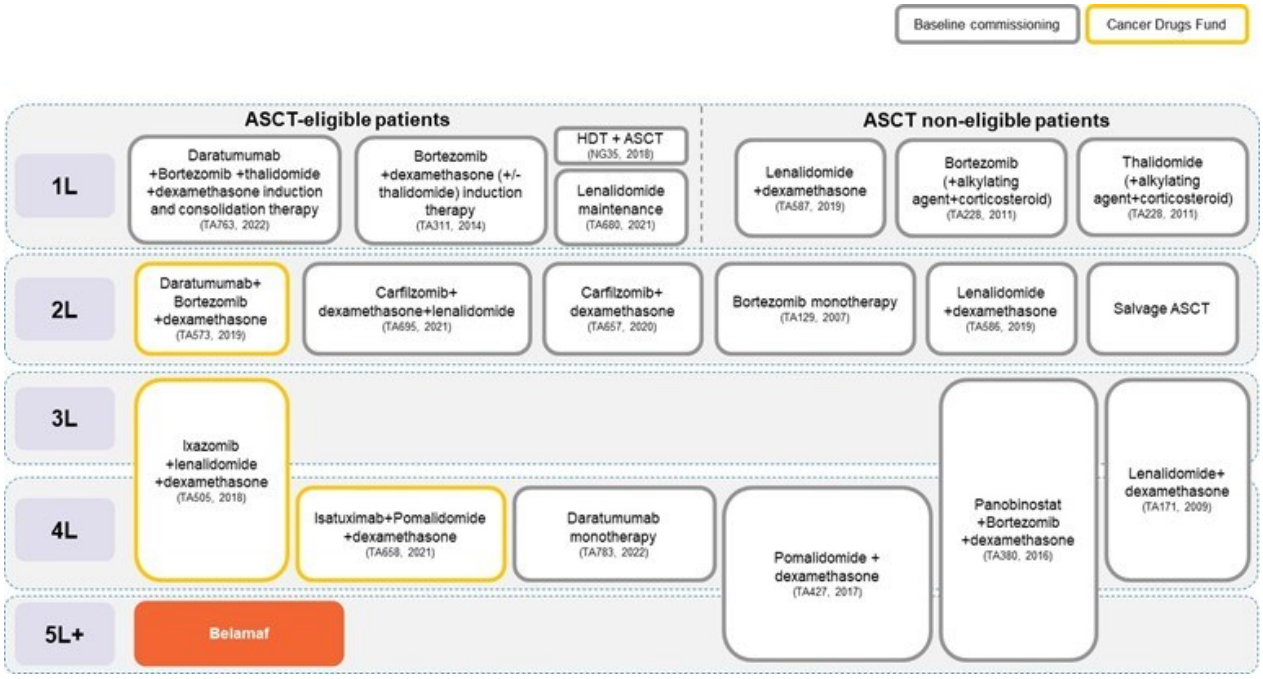


Figure 1 NICE treatment pathway in multiple myeloma and anticipated positioning of Belamaf (copied from CS, Section 1.3.3.3 page 22)

2.3 *Critique of company's definition of decision problem*

The CS decision problem predominantly matches the decision problem for the technology of interest, population, comparator, and outcomes as defined in the NICE's Final Scope.

There were differences in comparator and outcome definitions which were largely determined by the design of the pivotal trial. The EAG recognise that there is no alternative evidence to that presented in the CS and therefore, accepts the exclusion of Chemotherapy and time to next treatment. See Table 3 for further explanation.

Table 3: Summary of 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	Adults with relapsed or refractory multiple myeloma who have had at least 4 prior therapies, and whose disease is refractory to at least 1 proteasome inhibitor (PI), 1 immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody, and whose disease has progressed on the last therapy.	As per scope	N/A	N/A *The primary evidence came from the 2.5 mg/kg arm of DREAMM-2 trial which has evaluated the efficacy and safety of two doses of the antibody drug conjugate Belamaf in patients with MM, who had received 3 or more prior lines of treatment, are refractory to a PI, an IMiD and who had failed an anti-CD38 mAb*
Intervention	Belantamab mafodotin (Belamaf, Blenrep®)	As per scope	N/A	N/A
Comparator(s)	Established clinical management without belantamab mafodotin including: Pomalidomide plus dexamethasone (PomDex) Panobinostat with bortezomib and dexamethasone (PanoBorDex) Chemotherapy with or without a steroid and with or without thalidomide	Pomalidomide in combination with dexamethasone (PomDex) Panobinostat in combination with bortezomib and dexamethasone (PanoBorDex) (presented in Appendix M only)	PomDex is the most relevant comparator, representing current practice in the NHS. There is some use of PanoBorDex as observed in the NCRAS study however, clinical expert feedback suggests that the behaviour driving this usage is one of desperation. The Company does not consider combinations of chemotherapy and a steroid (with or without thalidomide) to be relevant comparators since these are used as palliative care. For the reasons outlined above and in Section B.1.3.3.1 (page 20), the main and most clinically	Whilst PomDex and PanoBorDex are listed in the NICE Final Scope as comparators, the EAG and our clinical advisors have severe concerns about the appropriateness of these comparators in the NHS context. The EAG clinical advisors state that PomDex is very rarely used in this patient population as it will have already been used earlier in the pathway (from 4L), and therefore patients are considered refractory. The same can be said for PanoBorDex (available from 3L). (Further detail provided in Section 3.5.1.3) However, the EAG accept that there are no alternative comparators available for consideration in this

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			relevant comparator considered for this appraisal is PomDex. For completeness and to acknowledge the usage observed in the NCRAS study, an analysis versus PanoBorDex is presented in Appendix M.	appraisal (see Figure 1**Error! Reference source not found.**). The company do not consider 'Chemotherapy with or without a steroid and with or without thalidomide' a representative comparator. The EAG clinical advisor agrees that this option is offered to patients as part of palliative care arrangements.
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Time to next treatment Adverse effects of treatment Health-related quality of life	As per scope with the exception of time to next treatment (TTNT)	TTNT was not collected in the DREAMM-2 trial; TTD is used to estimate the treatment duration (and therefore treatment costs of Belamaf and PomDex) in the economic analysis. TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause .	Outcomes partially match those outlined in the NICE final scope except for TTNT. The company's justification for the deviation are acceptable to the EAG. TTNT represents the totality of the evidence available from the pivotal trial.
Economic analysis	As per Reference Case	As per scope	N/A	N/A
Subgroups	N/A	N/A	N/A	N/A
Special considerations including issues related to equity or equality	None	None	N/A	N/A

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review*

The company conducted a clinical systematic literature review (SLR) to summarise the efficacy and safety evidence of Belamaf versus a relevant comparator in patients with relapsed/refractory multiple myeloma (RRMM) who received at least three prior lines of therapy. However overall, the SLR is of poor quality.

The interventions/comparators were limited to include Belamaf, pomalidomide plus dexamethasone (PomDex) and panobinostat plus bortezomib plus dexamethasone (PanoBorDex) (as per the NICE scope and decision problem see Table 3.) The database search was performed in May 2019 and updated in August 2022. A detailed description of the method and the findings of the SLR were reported in the Appendix D of the CS. Briefly, the SLR included systematic reviews with/without meta-analyses, indirect treatment comparisons (ITC), randomised controlled trials (RCTs), single-arm trials, and observational studies.

3.1.1 Searches

The company's search used an appropriate selection of bibliographic databases and other sources (CS Appendix D.1.1, Tables 3 and 4). Unfortunately, the search strategies used for the DARE and NIHR HTA databases and grey literature sources are not reported, so cannot be quality assessed by the EAG. As the NIHR HTA database is no longer updated, the EAG also recommends searching the INAHTA HTA database to ensure comprehensiveness.

The EAG consider that the SLR update search run in August 2022 (CS Appendix D.1.1 Table 7) is not a true update of the original 2019 search, as a different interface was used for the Embase and MEDLINE search. There are also some changes to the search terms. There are several features of the search strategies (CS Appendix D.1.1, Tables 5-9) that suggest the searches were not fully comprehensive. For example, in many cases, free text terms are only searched for in the title and abstract fields (omitting keyword, subject heading and drug trade name fields), and important thesaurus (MeSH/EMTREE) terms for cancer drug resistance or recurrence are not used. Study type filters are used in MEDLINE and Embase (see CS Appendix D Tables 5-7), despite there being no exclusion criteria based on study type (CS Appendix D.1, Tables 1 & 2). This omission

risks excluding relevant studies, especially as the filters do not include EMTREE, MeSH and free text terms for some types of study, such as case-control and non-randomised trials.

3.1.2 Inclusion criteria

Initially, the target population for the SLR were patients who had received at least three prior lines (3L+) of therapy [original SLR] (CS Appendix D.1, Table 1). However, on the SLR update (2022), this was changed to include patients who had received at least four prior lines of therapy, which is in line with the NICE scope for this appraisal. The methods of the reviews are described in detail in the CS, appendix D and are critiqued in Sections 3.1.3.1 and 3.1.3.2. The EAG are concerned that the results of the original SLR were not re-screened despite the change in population eligibility criteria from at least 80% having at least 3 prior lines of therapy to at least 70% with at least 4 prior lines (CS Appendix D.1, Table 2).

Despite concerns about the search method and inclusion criteria, the EAG considers it unlikely that any relevant studies have been missed. This is because the eligibility criteria for this appraisal are narrow in terms of population (line of therapy) and interventions of interest.

3.1.3 Study selection

The company adopted a systematic approach to select the relevant publications. The two-stage screening (termed as Level 1: title and abstract review, Level 2: full text review) was conducted by two independent researchers and disagreements were resolved by the involvement of a third researcher. Similarly, data abstraction was performed and checked by the reviewers and discrepancies were resolved by a third independent reviewer. The company stated that data extraction tables were aligned with University of York CRD and NICE reporting requirements (Section:1.3; Appendix D; Page 23). However, the EAG note that supporting information from *'other citations'* was not clearly defined in the CS. The company did not provide the data extraction table nor they have specified what data were extracted to summarise the evidence for the SLR.

3.1.3.1 Original SLR

The original SLR included 71 unique publications evaluating key standard of care treatments for 3L+ patients. The company provided a summary of evidence in Section 1.4, Table 10 (CS, Appendix D, Page 26). However, the EAG considers that the evidence map does not clearly define

all the 71 publications. The company stated that the evidence map (Table 10) identified only nine studies which were aligned with the company's SLR update i.e., relevant to the five lines of therapy (5L+) population and compared Belamaf with PomDex and/or PanoBorDex.

These nine studies include five unique RCTs across 11 publications, three single arm trials across five publications and one pooled analysis. The company provided further details of only four studies (two phase II RCTs and two single arm trials). This included evidence for the population and treatment of interest (see section 1.4, Table 11 and Table 12 CS, Appendix D page 28-29). The EAG was unable to ascertain why this information was only provided for four studies.

3.1.3.2 SLR update

The SLR update included a total of 88 publications (77 publications; 11 pieces of grey literature). The company stated that the selection criteria for the updated review were changed to 5L+ RRMM population, as this was closely aligned with the Belamaf licensed population in the NICE Final scope, and the decision problem (5L+ TCR MM) (see Table 3). However, the company did not provide detailed study characteristics for all the 88 publications. The EAG was unable to ascertain why information was only provided for 17 publications (see in Table 13 CS Appendix D, section 1.4, Page 30).

Eight of the 17 publications were real world evidence (RWE) studies, followed by three phase II, and three phase III trials, with the number of participants randomised or enrolled ranging from 32-455. The EAG note that only four of these 17 studies included a UK population, at clarification the company confirmed 3 patients were from the UK. The CS only presents clinical evidence from one study, DREAMM-2 [1, 2] (see CS Document B, B.2.2 page 24). The EAG could not ascertain why the company conclude that DREAMM-2 [1, 2] was the "*only identified trial*" (CS Document B, B.2.2 page 24) to evaluate the clinical efficacy and safety of Belamaf for the treatment of 5L+ patients.

The company listed the excluded studies and the reason for exclusion in CS Table 14 (CS Appendix D, section 1.4, Page 38-64) of which 124 publications were excluded for outcome, 89 publications for population, 62 publications for intervention and 26 publications for study/publication type. A single study was judged irrelevant because of its language of reporting.

3.1.1 Assessment of methodological quality

The company performed quality assessment of the two included studies using the 'Black and Down checklist'.[17] The studies of economic evaluations were assessed using the Drummond Checklist of Economic Evaluations. EAG critique of these assessments is provided separately in Sections 3.2.1.1, 3.2.2.1 and 4.1.

In summary, the clinical SLR is of poor quality. It contains errors in the search, study selection and reasons for exclusion of studies. The updated SLR presented in CS Appendix D does not clearly support the relevant clinical effectiveness evidence listed in Document B Section B.2.2.

3.2 *Critique of trials of the technology of interest, the company's analysis and interpretation*

The clinical evidence presented in the CS for Belantamab mafodotin (Belamaf) and relevant comparator treatments was obtained from two data sources:

- DREAMM-2 [1, 2] trial Individual Patient Data (IPD). DREAMM-2 [1, 2] was an open label, two arms (2.5 mg/kg and 3.4 mg/kg), phase II, randomised trial, and
- The National Cancer Registration and Analysis Service (NCRAS) RWE dataset.

A detailed summary of DREAMM-2 [1, 2] was reported in the CS Document B section 2.2.1 (Table 3; page 24). Since the SLR did not identify any studies reporting PomDex in 5L+ TCR MM (5 line and beyond and triple class refractory multiple myeloma) patients, the company used an England-based dataset (NCRAS) to generate the comparative efficacy data for PomDex (CS; Section 2.2.2, page 25). The EAG critiques the two sources of clinical evidence in Sections 3.2.1**Error! Reference source not found.** and 3.2.2.

3.2.1 DREAMM-2

DREAMM-2 [1, 2] is a dose-ranging study with two dose regimens using 2.5 mg/kg and 3.4 mg/kg of BELAMAF. The clinical safety and efficacy of Belamaf was evaluated exclusively from a specific arm (2.5mg/kg dose) of the DREAMM-2[1, 2] trial. The EAG note that there was no control arm, and the 2.5 mg/kg regimen outcomes were used as evidence in the CS. The primary analysis for all efficacy endpoints was based on the ITT population (reported in CS Document B Section B.2.5.1).

A total of 97 patients who had received at least three prior lines of therapy and R/R to a PI, an IMiD and an anti-CD38 mAb were included in the intent-to-treat (ITT) population for the safety and efficacy analysis.

Patients were recruited in 58 MM centres of eight countries (Australia, Canada, France, Germany, Italy, Spain, the United Kingdom, and the United States). The study included seven centres in the UK. During clarification the company confirmed [redacted] patients were from the UK. Seventy four percent of the population were white with a median age of 65 years.

The prior lines of therapy ranged from 3-21, with a median of seven. Baseline characteristics of the intervention arm (2.5 mg/kg Dose) were reported in CS Section 2.3.1.2 (Table 7; Page 30). As there was no control arm, the patient characteristics of the ITT population were compared with the 5L+ TCR patients (i.e. ITT minus the [redacted] patients who received three prior lines). The EAG agree that patient characteristics were largely comparable between these two groups, except that the number of prior lines of therapy received (in the ITT population, [redacted] patients ([redacted]%) received three prior lines of therapy which is outside the scope of the appraisal and hence were not considered in the analysis).

Only one dose reduction, 2.5 mg/kg to 1.92 mg/kg was permitted after the first cycle of treatment if there were reported toxicities. Patient withdrawals are detailed in CS Section 2.3.1.2 (Table 7; Page 30). At the time of submission in the 2.5 mg/kg cohort [redacted]% of patients had discontinued treatment.

The efficacy endpoints evaluated in DREAMM-2[1, 2] trial included response rates (overall, partial, very good partial, complete, stringent complete), overall survival (OS), progression-free survival (PFS), time to treatment discontinuation (TTD), time to next treatment (TTNT), clinical benefit rate (CBR), time to response (TTR), time to progression (TTP), duration of response (DOR), minimal residual disease (MRD), and health-related quality of life (HRQOL).

3.2.1.1 Risk of bias DREAMM-2

The company submitted a complete quality appraisal of DREAMM-2[1, 2] trial in Appendix D page 66. The EAG had concerns about the applicability and validity of the checklist selected to evaluate the trial (Downs and Blacks).[17] Therefore, the EAG independently assessed the DREAMM-2[1, 2] trial following the list of assessment criteria reported by Cochrane Risk of Bias tool.[18] Table 4 presents the EAG risk of bias assessment and the supporting detail.

Overall, for both doses of the DREAMM-2 trial (note the CS only considers one arm 2.5 mg/kg) the EAG judged that there was low risk of bias in appropriate randomisation, concealment in treatment allocation, analysis of missing data and outcome data reporting. However, risk of bias was unclear for blinding of outcome assessment and reporting of other potential source of bias. In contrast, 'blinding of the participants and personnel' was rated as at high risk of bias.

Table 4 EAG Risk of bias assessment of DREAMM-2[1, 2] trial using Cochrane RoB tool for randomised trials

Criteria	Assessment	Judgement (CS page number and section)
Random sequence generation.	Low risk of bias	Patients were randomly assigned in a 1:1 ratio to Belamaf 2.5 mg/kg IV Q3W or Belamaf 3.4 mg/kg IV Q3W, through central assignment of a randomisation number, generated by the Company's Clinical Statistics Department. (CS, Section 2.3.1.1, Page 25). However, the EAG point out that this information is irrelevant for this appraisal, because the 3.4 mg/kg dosage is not further considered by the company.
Allocation concealment.	Low risk of bias	A centrally generated randomisation schedule with permuted blocks (block size of 4) was used to conceal treatment allocation (Lonial 2020).
Blinding of participants and personnel	High risk of bias	As this trial was open-label, the trial coordinators had access to the patient-level data throughout the study. (CS, Section 2.3.1.1, Page 26).
Blinding of outcome assessment	Unclear risk of bias	As this trial was open-label, the trial coordinators had access to the patient-level data throughout the study, it is not clear if outcome assessors were blinded to the treatment assigned. (CS, Section 2.3.1.1, Page 26).

Incomplete outcome data	Low risk of bias	Missing data have been imputed using appropriate methods i.e., the primary analysis for all efficacy endpoints was based on the ITT population. (CS; Table 8, Section 2.3.1.3, Page 33).
Selective reporting.	Low risk of bias	Per-protocol outcome reported in CS (section 2.3.1.1 page 25)
Other sources of bias	Unclear risk of bias	No other type of bias specified

3.2.1.2 Outcomes DREAMM-2

The primary outcome of the DREAMM-2[1, 2] (ITT population) was overall response rate (ORR) by IMWG standard criteria. This classification divided the population into “responders” and “non-responders”. The EAG note that response in a study with no comparator does not imply causation due to the intervention. Therefore, a response in this study may only identify individuals with relatively superior prognosis. As such the study design of DREAMM-2[1, 2] would only provide information about what dose and what population may be appropriate for future investigation.

Secondary outcomes included PFS and OS. However, the EAG conclude that because no control arm was included in DREAMM-2,[1, 2] it is not possible to assess how much of the observed PFS and OS can be attributed to an effect of Belamaf and how much would have happened anyway (without Belamaf intervention).

3.2.1.2.1 Summary

Although DREAMM-2 [1, 2] may be useful for certain purposes (e.g., determining appropriate dosing), as a Phase II study, it is highly unlikely that it is an appropriate source of clinical evidence to inform a cost-effectiveness analysis which is useful for decision makers. Causation cannot be determined between the intervention (Belamaf) and the primary and secondary outcomes, and there is no comparison of the treatment arm with an appropriate control arm receiving an alternative therapy.

Therefore, the necessary requirements for the estimation of the cost-effectiveness cannot be well determined in this appraisal and results presented in Section 5.1, company cost-effectiveness results, should be interpreted with great caution. See Section 3.5 for the EAG’s alternative clinical effectiveness analysis which is included in the cost-effectiveness scenario analysis which should also be interpreted with caution (Section 5.4).

3.2.2 National Cancer Registration and Analysis Service dataset (PomDex)

The company-initiated RWE NCRAS study was a descriptive, retrospective, non-interventional study. It comprised of [redacted] English patients who were "closely aligned" with the DREAMM-2[1, 2] population and diagnosed with MM between January 2013 and December 2019. Details of the study design and conduct are provided in CS Document B Section B.2.3.2. Briefly, NCRAS uses routine, England patient-level health data (combining linked data from the Hospital Episode Statistics (HES), the Systemic Anti-Cancer Therapy dataset (SACT), National Radiotherapy Dataset (RTDS) and Office for National Statistics (ONS) mortality data). The CS includes the NCRAS study as the primary comparative efficacy evidence which informs the base-case cost-effectiveness analysis (see Section 4.2).

In brief, the study adopted a hierarchical approach to identify the relevant adult patients for whom sufficient data were available (such as date of diagnosis, stage at diagnosis and age at diagnosis). However, only [redacted] patients who received the recommended dose of PomDex were considered as a comparison. In the NCRAS dataset, [redacted]% of the patient population were white with a mean age of [redacted] years (SD 10). A complete description of the NCRAS population characteristics was reported in the CS, Table 11 (Section 2.3.2.2, Page 37).

Although PanoBorDex was considered a relevant comparator to Belamaf in the NICE Final Scope, (see Table 3 Section 2.3) the company only included the PomDex arm as the source of comparative efficacy evidence.

3.2.2.1 Quality assessment NCRAS

A quality assessment of the NCRAS study was conducted by the company using the Black and Down checklist.[17] A comparison of the EAG's and company's assessment is reported in the Table 5.

The EAG agrees with majority of the company's assessments. However, as the NCRAS study is a real-world dataset, it has several uncertainties across methodological domains. Uncertainties include; no specific hypothesis, loss to follow up data, absence of efficacy response data, no

safety data, and lack of representativeness of a wider UK patient population. The EAG disagreed with the company's assessment of quality for the validity and reliability of the outcome measure. This is because progression was not measured in the NCRAS data set and time to next therapy (TTNT) was considered instead. In addition, no detail as to how missing data was addressed in the survival analyses was reported in the CS.

Table 5 Quality assessment results for NCRAS dataset using the Black and Down checklist (differences in BOLD)

Criteria	**Company Judgement (Appendix D, Table 16, page 68)**	**EAG judgement**
Is the hypothesis/ aim/ objective of the study clearly described?	*Unable to determine*	Unable to determine: No hypothesis or objective was described
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	*Unable to determine*	Unable to determine.
Are the characteristics of the patients included in the study clearly described?	*Yes*	Yes
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	*Not applicable – groups of subjects were not compared in this study*	Not applicable: no comparator
Are the main findings of the study clearly described?	*Unable to determine – only descriptive data has been provided*	Unable to determine: the outcome relevant to the DREAMM 2 were sought out
Does the study provide estimates of the random variability in the data for the main outcomes?	*Yes – confidence intervals have been provided for survival estimates*	Yes: 95% CI reported
Have all important adverse events that may be a consequence of the intervention been reported?	*No – data on adverse events are not available*	No
Have the characteristics of patients lost to follow-up been described?	*No*	No
Have actual probability values been reported?	*No*	No
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	*Not applicable – this was not a consented research study as data were from national registration and routine healthcare databases. Exclusion due to CDF means possible selection bias.*	Not applicable
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	*Not applicable – this was not a consented research study as data were from national registration and routine healthcare databases. Exclusion due to CDF means possible selection bias.*	Not applicable

Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	*Yes – all Trusts providing care through the NHS in England are mandated to submit data for the datasets used, so the data should be nationally representative*	**Unable to determine**
Was an attempt made to blind study subjects to the intervention they have received?	*No – not a blinded study/ comparison*	No: blinding not reported
Was an attempt made to blind those measuring the main outcomes of the intervention?	*No – not a blinded study/ comparison*	No: blinding not reported
If any of the results of the study were based on 'data dredging', was this made clear?	*Not applicable – no results were based on data dredging*	**Unable to determine**
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	*Yes – Kaplan-Meier survival analyses account for length of follow-up*	Yes: follow up for survival analysis were conducted
Were the statistical tests used to assess the main outcomes appropriate?	*Not applicable – no statistical hypothesis tests were performed and only descriptive results are provided*	Not applicable
Was compliance with the intervention/s reliable?	*Not applicable – this was not an interventional study*	**Unable to determine**
Were the main outcome measures used accurate (valid and reliable)?	*Partial – mortality endpoints are valid and reliable. TTNT and TTD were based on algorithms applied to routine data so are as valid and reliable as possible in the absence of explicitly collected data.*	**No** 'As progression is not recorded within the NCRAS database, TTNT was considered instead. This is in line with previous studies conducted using real-world datasets in multiple myeloma such as the SACT dataset in England' No analysis for missing data reported.
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	*Not applicable – there were no intervention groups but all data is drawn from national data sources.*	Not applicable: non interventional study
Were study subjects randomised to intervention groups?	*Not applicable – there were no intervention groups*	Not applicable: non interventional study
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	*Not applicable – there were no intervention groups*	Not applicable non interventional study
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	*Not applicable – only descriptive analysis was performed*	Not applicable

Were losses of patients to follow-up taken into account?	*Yes – Kaplan-Meier analysis accounts for loss to follow-up*	Yes: Kaplan-Meier analysis accounts for patients lost to follow-up or still alive at the end of the study period by means of censoring. (CS Document B, Table 10, page 36)
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	*Not applicable – no treatment effect was assessed as it was a descriptive study only*	Not applicable: no treatment effect was assessed as it was a descriptive single-arm study.

3.2.2.2 Outcomes NCRAS

The NCRAS study included data about PomDex treatments. In the CS, PomDex served as a proxy-comparator to Belamaf for both the ITC (see Section 3.3.1) and in the economic analysis (Section 5). Full details of the NCRAS study, outcomes and analysis are presented in CS Document B pages 35-40).

In brief, NCRAS only supplied data for OS, time to treatment discontinuation (TTD) and TTNT. No results for quality of life, for PFS or for ORR were collected or reported in the CS. To remedy lack of data for PFS the company generate a “proxy-PFS” outcome for the NCRAS study, and the DREAMM-2[1, 2] study.

3.2.2.3 Adverse events

Adverse events (AE) in DREAMM-2[1, 2] are reported in CS Document B Table 33. The most reported AE was keratopathy ([redacted]%), thrombocytopenia ([redacted]%), anaemia (21%) and decreased lymphocyte count decreased ([redacted]%). Keratopathy was the primary AE leading to discontinuation (CS Document B Table 34). The EAG agrees with the company that [redacted] between the study 13 month follow up (13 Jan 2020) and the final analysis (4 May 2022).

3.2.2.3.1 Summary

The EAG note again, that there was no control arm in the NCRAS study. Therefore, it is impossible to gauge how much of the “proxy-PFS” and of OS can be attributed to an effect of PomDex and how much would have happened anyway. The EAG, therefore, consider the NCRAS

study inappropriate for the purpose of comparison with the DREAMM-2 study and entirely inappropriate for cost-effectiveness analysis.

The necessary requirements for the estimation of the cost-effectiveness cannot be determined in this appraisal and results presented in Section 5.1, company cost-effectiveness results, should be interpreted with great caution. See Section 3.5 for the EAG's alternative clinical effectiveness analysis which is included in the cost-effectiveness scenario analysis which should also be interpreted with caution because of the lack of appropriate available data on which to draw (Section 5.4).

3.2.3 Efficacy results DREAMM-2[1, 2] and NCRAS

Section B.2.5 of the CS Document B provides the clinical effectiveness results from DREAMM-2 [1, 2] and the NCRAS study for OS, TTNT and TTD. The company also present efficacy outcomes results for PanoBorDex but reiterate that they do not consider it a main comparator in this appraisal (see Table 2).

DREAMM-2[1, 2] measured and reported efficacy results for ORR, and duration of response (DOR) as hazard ratios (HR) please see CS Document B Tables 14-15. Health related quality of life changes from baseline are presented in CS Document B Figures 21-22. The EAG include in

Table 6, the efficacy results which are drawn from (via ITC [see Section 3.3]) the company's clinical effectiveness evidence which informed the cost-effectiveness analysis. The EAG consider that the results presented in

Table 6 should be interpreted with caution.

The lack of a control arm in both DREAMM-2[1, 2] and the NCRAS means that the clinical effects of Belamaf and of PomDex are both extremely uncertain.

Table 6 Summary of efficacy outcomes: median time (in months) to event (Belamaf vs. PomDex vs. PanoBorDex)

Efficacy outcome	DREAMM-2[1, 2] Trial arm (IPD) Belamaf[β]		NCRAS dataset (AD)	
	(ITT; n=97)[£]		PomDex (n=[redacted])	PanoBorDex (n=[redacted])
PFS (median # of months 95% CI)	[redacted]		Not available	Not available
OS (median # of months 95% CI)	[redacted]		[redacted]	[redacted]
TTNT (median # of months 95% CI)	[redacted]		[redacted]	[redacted]
TTD (median # of months 95% CI)	[redacted]		[redacted]	[redacted]

CI=confidence interval; AD=aggregate data; IPD=individual patient data; NCRAS=National Cancer Registration and Analysis Service; TTNT=time to next therapy; TTD=time to treatment discontinuation; PomDex=pomalidomide plus dexamethasone; ITT=intention-to-treat; Belamaf=Belantamab mafodotin
£ In ITT sample, [redacted] patients ([redacted] received only three prior lines of therapy which is outside of the population considered in this appraisal
[β] based on 4 May 2022 post-hoc analysis

3.2.3.1 Summary

In summary the designs of both studies, DREAMM-2[1, 2] and NCRAS, included in the submission are, in the opinion of the EAG, inappropriate for the purpose of cost-effectiveness analysis. The two separate single arm studies cannot be reasonably compared with each other. They draw from entirely different geographical populations and are selected in entirely different ways (e.g., one for research, one from standard clinical practice). The conduct of each of the studies is different as is the underlying rationale for data collection. In neither case, was outcomes data being collected for the purposes of undertaking clinical or cost-effectiveness analysis. There is a high likelihood extensive adjusted (and un-adjustable) confounding existing when comparing the two studies. The cost-effectiveness results presented in Section 5.1 are therefore, unreliable and of extreme uncertainty.

3.3 *Critique of trials identified and included in the indirect comparison*

As described in Section 3.1 the company conducted an SLR of studies reporting clinical efficacy and safety of Belamaf and other relevant comparator treatments licensed in the UK among

patients with R/RMM who received at least 4 prior lines of therapy and were triple class-refractory (5L+ TCR MM). This aligned with the NICE Final Scope and decision problem (See Table 3). Information on searches (original and update), study inclusion/selection, and data extraction performed for the Company's SLR are provided in the company submission (Appendix D) and in Sections 3.1.1, 3.1.2, and 3.1.3 of this EAG report.

No studies were identified (randomised, non-randomised, or observational) which would provide a head-to-head comparison of the safety and/or efficacy of Belamaf to PomDex (or PanoBorDex) in 5L+ TCR patients. The EAG agree with this conclusion.

The SLR identified only one study that evaluated the clinical efficacy and safety of Belamaf for the treatment of 5L+ TCR MM patients (DREAMM-2[1, 2] see Section **Error! Reference source not found.** for EAG critique). The SLR did not identify any studies of the specified relevant comparator (e.g., PomDex) administered in the 5L+ TCR MM patient population that would be eligible for inclusion in an ITC (vs. Belamaf). To generate evidence for the comparator (PomDex or PanoBorDex) efficacy in the 5L+ TCR MM population, the company conducted the RWE NCRAS study to describe the characteristics, treatments, and outcomes for 5L+ TCR MM patients in the UK (Document B, Appendix O) (see Section 3.2.2 for EAG critique).

In the absence of randomised studies comparing Belamaf (in DREAMM-2[1, 2]) to PomDex (NCRAS dataset) and the lack of connected network (i.e., no common comparator) across the DREAMM-2[1, 2] and NCRAS dataset due to both being single-arm evidence, the company conducted an unanchored matched adjusted indirect comparison (MAIC) to assess the comparative efficacy of Belamaf 2.5 mg/kg versus PomDex (or PanoBorDex).

3.3.1 Sources of data included in the MAIC

3.3.1.1 The DREAMM-2 trial

DREAMM-2[1, 2] evaluated the efficacy and safety of two doses of Belamaf: 3.4 mg/kg (unlicensed in the UK dose) and 2.5 mg/kg (licensed in the UK dose). The CS reported only on the study arm that received the licensed 2.5 mg/kg dose of Belamaf (Document B). The MAIC analysis included

this one arm of DREAMM-2[1, 2] (n=97 ITT sample).[1, 2] See EAG critique in Section 3.2.1 and published literature.[1, 2]

3.3.1.2 The NCRAS dataset

The NCRAS dataset was the only source of comparative efficacy evidence for the relevant comparator (PomDex) in the relevant patient population (5L+ TCR MM) provided in the CS (Document B, Appendix O). As described in 3.2.2, NCRAS is a descriptive, retrospective, non-interventional study using routine, England patient-level health data (combining linked data from the HES, the SACT, RTDS and ONS mortality data). Data were collected for patients diagnosed with MM between 1st January 2013 and 31st December 2019.

Patients became eligible for inclusion into the cohort if they had received 5L + (4 or more lines of treatment and TCR). A series of inclusion and exclusion criteria were applied to narrow down the total number of patients starting from the initial sample of all RRMM adult patients residing in England, diagnosed in 2013-2019 (n=[redacted]) to only patients with 5L+ TCR MM (n=[redacted]) for whom sufficient data was available (date of diagnosis, stage at diagnosis and age at diagnosis). Furthermore, [redacted] patients receiving drugs within the CDF were also excluded, leaving a sample of [redacted] patients with 5L+ TCR MM of whom [redacted] received PomDex at a dose in line with its licensed indication (pomalidomide median index dose of 4 mg (interquartile range: 3 mg – 4 mg). The final sample of [redacted] PomDex patients was used in the MAIC analysis. The company did not report the dose of Dexamethasone administered to this NCRAS cohort of patients.

Furthermore, the NCRAS dataset of [redacted] patients with 5L+ TCR MM served as a source of the second comparator PanoBorDex (dose not reported) for which a cohort of [redacted] patients was identified and selected.

Both cohorts of patients (PomDex n=[redacted] and PanoBorDex n=[redacted]) served as a source of the target population (relevant comparators as specified in the NICE Final scope, Table 3) included in the company's clinical (MAIC analyses) as well as economic analyses(see Section 5.1).
Further details of the methodology used in the NCRAS dataset RWE study is provided in the company's protocol.[19]

3.3.2 MAIC methodology

MAIC is a population adjustment method that uses available IPD from one or more studies for one treatment to match important baseline patient characteristics to those from aggregate data (AD) of a published study of another treatment. Initially, matching is performed on inclusion and exclusion criteria used in the compared IPD and AD (comparator treatment, target population). Then propensity score matching is used to re-weight IPD so that its mean baseline clinical characteristics match those of the published aggregate data of the target population. After matching, the mean outcome of IPD is recalculated (in the matched IPD sample) and compared with the observed mean outcome of the AD in the published study report.

The requirement for a MAIC is the availability of IPD (e.g., that for DREAMM-2) for at least one of the treatments included in the comparison and AD for other compared treatments. Although an anchored MAIC (when a common comparator is available) is usually preferred, an unanchored MAIC is the only method available to adjust for cross-trial differences in the absence of connected networks or if there are only single-arm studies, as is the case with the CS. However, the conduct of an unanchored MAIC requires stronger assumptions than that for an anchored MAIC, i.e., the cross-study differences need to be adjusted not only with respect to all treatment effect modifiers but also for all prognostic variables. One inherent limitation of this methodology in that there will always be unknown confounding variables, unmeasured effect modifiers or prognostic factors that are not balanced between the two data sources (IPD and AD).[20]

To minimise the impact of bias in the treatment effect estimates, the following conditions are desirable to be satisfied when conducting a MAIC:

- similar study inclusion/exclusion criteria, with IPD criteria equally or more inclusive than those in the AD for a comparator treatment study,
- available information on important baseline patient characteristics for AD of the comparator treatment study,
- lack of substantial protocol-based differences between IPD and AD (design, blinding, follow-up length, study setting, outcome definitions), and
- comparable overlap in baseline patient characteristics across IPD and AD.[21]

In the CS, the company conducted an unanchored MAIC using the IPD for Belamaf (Belamaf 2.5 mg/kg arm from DREAMM-2[1, 2] trial) and AD for PomDex (via the NCRAS dataset), according to the recommendations and guidance of the NICE DSU TSD.[20] Further details about the MAIC analysis are provided in the Company submission (Document B and Appendix O).

3.3.3 MAIC feasibility assessment

In order to assess the feasibility and its impact on the conduct of the unanchored MAIC, the company compared study features, outcomes, and effect modifiers/prognostic factors between the DREAMM-2[1, 2] trial and NCRAS study. The EAG summarises and critiques the feasibility below.

3.3.3.1 Study features

The company considered and compared various study features such as study design, study setting, inclusion/exclusion criteria, and blinding between the DREAMM-2[1, 2] trial and NCRAS study Table 7. The EAG conclude that the majority (6 out of 9) of study features are not comparable between the two datasets.

Table 7 Selected features and their definitions in DREAMM-2[1, 2] and NCRAS. (Differences in BOLD)

Study feature	DREAMM-2[1, 2] trial IPD (Belamaf) arm	NCRAS dataset AD (PomDex or PanoBorDex)	Comparability (EAG assessment: Yes or No)
Design	Phase II, multicentre open-label, active-control randomised trial	Retrospective, non-interventional RWE study	No (clinical trial vs. observational study)
Study setting	Secondary care	Secondary care	Yes
Locations	58 locations including US, Australia, Canada, France, Germany, Italy, Spain, UK	England	**No**
Study inclusion criteria	Diagnosis: Histologically or cytologically confirmed diagnosis of MM as defined in IMWG 2014 criteria. Initial criteria: Adult RRMM 4L+ TCR patients Final criteria: Adult RRMM 5L+ TCR patients ECOG PS: 0-2. Adequate organ function: ANC ≥ 1.0x10^9/L	Diagnosis: Histologically or cytologically confirmed diagnosis of MM in 2013-2019. Adult RRMM 5L+ TCR patients. Resident of England at the date of diagnosis of RRMM. ECOG PS: 0-4.	**No**

	Hemoglobin ≥ 8.0 g/dL Platelets ≥ 50 X 10^9/L Bilirubin ≤ 1.5X ULN ALT ≤ 2.5X ULN eGFR ≥ 30 ml/min per 1.73 m^2 LVEF ≥ 45%		
Study exclusion criteria	Systemic anti-MM or high dose steroid therapy within ≤14 days or five half-lives or plasmapheresis within 7 days prior to the first dose of study drug. Systemic treatment with high dose steroids (equivalent to >=60 mg prednisone daily for >=4 days) within the past 14 days if administered to treat MM or non-MM disease. Prior allogeneic stem cell transplant. Symptomatic amyloidosis, active plasma cell leukaemia, prior allogeneic SCT, corneal epithelial disease, mucosal or internal bleeding, major surgery within the last four weeks, active renal condition, serious or unstable pre-existing medical, psychiatric disorder or other conditions, malignancy, pregnant or lactating female. Laboratory abnormalities that could interfere with patient's safety.	Diagnoses via death certificate only. No recorded date of diagnosis (negating the selection of incident cases diagnosed during pre-specified study window time 2013-2019). No recorded stage at diagnosis such that advanced and recurrent disease cannot be reliably differentiated. Administration of some anti-CD38 regimens. Patients who have received drugs that are within the CDF.	**No**
Refractoriness (as inclusion criterion)	Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease (PD) while on therapy.[22]	Individuals were classed as refractory to a treatment class (PI, IMiD, anti-CD38 mAb) where a new line was initiated within 60 days of completion of the PI, IMiD or anti-CD38 mAb-containing line with the exception of Bortezomib since it is given as a fixed treatment duration.	**No**

Blinding	No	No	Yes
Cross-overs	No	NR	**No**
Relevant treatment	Belamaf 2.5mg/kg	PomDex, PanoBorDex	N/A

RWE=real world evidence; PI=proteasome inhibitor; IMiD=immunomodulatory drug; mAb=monoclonal antibody; Belamaf=Belantamab mafodotin; IPD=individual patient data; PomDex=pomalidomide plus dexamethasone; PanoBorDex=panobinostat plus bortezomib plus dexamethasone; AD=aggregate data; EAG=evidence review group; NCRAS=National Cancer Registration and Analysis Service; 5L=5th line; TCR=triple class refractory; PI= proteasome inhibitor; IMiD=immunomodulatory drug; mAB=monoclonal antibody; IMWG= International Myeloma Working Group; OS=overall survival; ECOG PS= Eastern Cooperative Oncology Group Performance Status; SCT=stem cell transplantation; NR-not reported; CDF=cancer drug fund; ANC=absolute neutrophil count; ULN=Upper limit of normal; ALT=alanine aminotransferase; eGFR=estimated glomerular filtration rate; LVEF=left ventricular ejection fraction;

3.3.3.2 Efficacy outcomes

The company compared efficacy outcomes, including disease progression, censoring and their definitions between the DREAMM-2[1, 2] trial IPD and the NCRAS AD study, as shown in Table 8. The following three common efficacy outcomes were identified or derived across the two studies and included in the MAIC analysis: overall survival (OS), time to next treatment (TTNT), and time to treatment discontinuation (TTD). Although progression-free survival (PFS) was measured and reported in DREAMM-2,[1, 2] it was not available for the NCRAS study, so TTNT was provided as a proxy for PFS (see 3.2.1.2 and 3.5.1.1 for further details on the proxy PFS outcome). TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. Only two of five efficacy outcomes which were assessed in the two studies were comparable.

Table 8 Efficacy and other outcomes and their definitions across DREAMM-2[1, 2] and NCRAS studies compared. Differences in BOLD

Efficacy outcome measure	DREAMM-2[1, 2] trial IPD (Belamaf) arm	NCRAS dataset AD (PomDex or PanoBorDex)	Comparability (EAG assessment: Yes or No)
OS	Defined as the time from randomisation until death due to any cause. Patients who withdrew consent from the study or were lost to follow-up were censored at the time of withdrawal or loss to follow-up.	Defined as the time from initiation of the index line of treatment (LoT) and until failure (all-cause death) and estimated using Kaplan Meier methodology. Patients lost to follow-up or still alive at the end of the study period were censored.	Yes

Efficacy outcome measure	DREAMM-2[1, 2] trial IPD (Belamaf) arm	NCRAS dataset AD (PomDex or PanoBorDex)	Comparability (EAG assessment: Yes or No)
TTNT (as proxy for PFS)	Although PFS was measured in DREAMM-2,[1, 2] it was not reported for the NCRAS study, so TTNT was used instead). TTNT was not measured in the DREAMM-2[1, 2] trial (not pre-specified).	As PFS was not measured for the NCRAS database, TTNT was used as a proxy for PFS. TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. Patients lost to follow-up or still in same line of treatment at the end of the study period were censored.	**No**
TTD	Treatment discontinuation was defined as the first of death, unacceptable toxicity, disease progression, lost to follow-up/withdrawal, study termination, and protocol based study criteria.[22] This is analysed from the safety population.	Treatment discontinuation was defined as the first of death or the date of any drug administration that is followed by a gap of >60 days and was estimated using Kaplan-Meier methodology.	**No**
Disease progression	IMWG consensus criteria[22, 23]	Not defined/measured	**No**
Censoring (for OS)	Patients who withdraw consent from the study Lost to follow-up Alive at end of follow-up	Patients lost to follow-up or still alive at the end of the study period were censored.	Yes

OS=overall survival; TTD=time to discontinuation; TTNT=time to next treatment; TSNT=time to start of next treatment; PFS=progression-free survival; EAG=evidence review group; NCRAS=National Cancer Registration and Analysis Service; LoT=line of treatment IMWG= International Myeloma Working Group

3.3.3.3 Treatment effect modifiers and prognostic factors

The conduct of a valid unanchored MAIC assumes 'conditional constancy of absolute effects', i.e., all treatment effect modifiers and prognostic factors across the two treatment arms compared are evenly distributed or accounted for. If this assumption is violated, some form of bias is likely to distort the effect estimates of interest. In reality, it is impossible to completely satisfy this assumption given missing data, and unmeasured and/or unknown effect modifiers and prognostic factors.[20]

The company selected, a priori a set of effect modifiers/prognostic variables in relation to OS/PFS according to feedback received from MM clinical experts supplemented by targeted literature searches of similar analyses (see Table 9). The CS states that "*three England-based consultant haematologists were engaged to validate the indirect and mixed treatment comparisons*", the company suggest that experts were selected due to their expertise in MM as well as having experience with Belamaf [redacted]. The EAG could not verify the independence of these clinical advisors. Although biographies of the clinical experts were presented in Appendix Q of the CS, details of their conflicts of interest, specifically related to this technology, were not provided.

The list of effect modifiers/prognostic variables were used to verify the availability of these variables reported as baseline characteristics for both DREAMM-2[1, 2] IPD and NCRAS AD. The EAGs assessment of feasibility is presented in Table 9.

Table 9. The list of pre-selected treatment effect modifiers and prognostic variables. Differences in BOLD

Effect modifier/prognostic variable	DREAMM-2[1, 2] (Belamaf)	NCRAS (PomDex)	MAIC feasibility (EAG assessment: Yes or No)
	available: Yes or No		
Age	Yes	Yes	Yes
Sex	Yes	Yes	Yes
Weight (kg)	Yes	Not available	**No**
Race/ethnicity	Yes	Yes	Yes
ECOG performance status	Yes	Yes (with missing values)	**No**
Renal impairment	Yes	Not available	**No**
R-ISS stage	Yes	Yes (with missing values)	**No**
Prior ASCT	Yes	Not available	**No**
High risk cytogenetics	Yes	Not available	**No**
Lytic bone lesions	Yes	Yes	Yes
Extramedullary disease	Yes	Yes	Yes
Number of prior lines of therapy	Yes	Yes	Yes
Median time from diagnosis	Yes	Not available	**No**
Type of MM (secretory vs. non-secretory)	Yes	Not available	**No**
Myeloma immunoglobulin type	Yes	Not available	**No**

ASCT= autologous stem cell transplant R-ISS=revised international staging system stage; ECOG PS= Eastern Cooperative Oncology Group Performance Status; Belamaf=Belantamab mafodotin; PomDex=pomalidomide plus dexamethasone; EAG=evidence review group; NCRAS=National Cancer Registration and Analysis Service

3.3.3.4 EAG critique of feasibility assessment

The EAG notes that there are numerous marked differences between the DREAMM-2[1, 2] and NCRAS datasets with respect to design, locations, and study inclusion/exclusion as presented in Table 7, Table 8, and
Table 9. For example, the DREAMM-2[1, 2] IPD was trial-based data as opposed to the NCRAS dataset which was non-interventional observational RWE case study. Whereas DREAMM-2[1, 2] IPD was drawn from patients in multiple locations, the NCRAS dataset included only UK-based patients. The inclusion criteria for ECOG PS were narrower in DREAMM-2[1, 2] versus those for the NCRAS dataset (range: 0-2 vs. range: 0-4) and this precluded matching of the DREAMM-2[1, 2] IPD to the NCRAS dataset. Consequently, the EAG suggest that since ECOG PS is a prognostic variable, this imbalance violated the transitivity assumption of the MAIC's validity (i.e., requirement to account for all effect modifiers and prognostic factors) which in turn could lead to bias in the results.
The exclusion criteria in regard to prior treatments for the NCRAS dataset was specified as 'patients that received drugs given within the CDF'. This presumably limited the NCRAS dataset in terms of representativeness and generalisability for the UK context.

Another important difference was in the definition of refractoriness to PI, IMiD and anti-CD38, which is based solely on prior exposure in the NCRAS dataset, but due to failure of the treatment in the DREAMM-2[1, 2] trial.

As for deviations regarding the efficacy outcomes, TTNT was used as a proxy for PFS, because PFS was not reported for the NCRAS dataset. Moreover, TTNT was not directly measured for the DREAMM-2[1, 2] IPD. The EAG was unable to assess the comparability of the definition of disease progression since the NCRAS dataset did not report this information. As for TTD, treatment discontinuation for DREAMM-2[1, 2] was defined more stringently by additionally incorporating unacceptable toxicity, disease progression (which was unavailable for NCRAS), protocol-based stopping criteria, study withdrawal, and study termination.

The assessment of availability of information on the pre-selected treatment effect modifiers and prognostic factors in terms of feasibility is provided in
Table 9. The data on weight, 'renal impairment', 'high risk cytogenetics', 'type of MM', 'myeloma immunoglobulin type', and 'prior ASCT' were not available for the NCRAS dataset. Additionally, data for 'ECOG PS' and 'R-ISS stage' was missing in the NCRAS dataset. Median time from diagnosis was not available for the NCRAS dataset.

The missing values for some patients or unavailable data (for the above-mentioned factors) precluded matching in the MAIC analysis, further detail is provided in Table 10. The Company also stated that the inclusion of factors with missing data (i.e., ECOG PS, R-ISS stage) would drastically reduce the effective sample size (ESS) and study power, thereby leading to unreliable results. Thus, based on the availability of baseline characteristics reported in the NCRAS dataset, only three factors were included in the MAIC for matching the DREAMM-2[1, 2] IPD to the NCRAS database (age, median number of prior lines of treatment, and extramedullary disease).

In summary, the EAG believes that feasibility for a valid MAIC analysis has been seriously undermined given the incomparability and incongruity of the two datasets compared. The EAG consider efficacy results generated from the MAIC (see Section 3.3.7), to be extremely uncertain and agree with the company that it should not be used to inform the economic assessment.

Table 10 Treatment effect modifiers and prognostic variables and their inclusion in MAIC analysis.

Effect modifier/prognostic variable	Included in unanchored MAIC analysis (Yes/No)	Reason for not including in MAIC
Age	Yes	N/A
Sex	No	The Company stated that the proportion of males was broadly comparable across the datasets compared and therefore 'Sex' was not included in MAIC (Document B, page 68).
Weight (kg)	No	Not available in NCRAS dataset
Race/ethnicity	No	The Company stated that most patients were white (DREAMM-2 [1, 2] : [redacted] vs. NCRAS: [redacted] with the inclusion of Black patients (DREAMM-2 [1, 2] : [redacted]% vs. NCRAS: [redacted]%) and Asian patients (DREAMM-2 [1, 2] : [redacted]% vs. NCRAS: [redacted]%) (Document B, page 68).
ECOG performance status	No	Missing values for [redacted] patients in NCRAS dataset. The Company believed that the inclusion of this covariate

		would markedly reduce ESS and reliability of the estimate and study power.
Renal impairment	No	Not available in NCRAS dataset
R-ISS stage	No	Missing values for [redacted] patients in NCRAS dataset. The Company believed that the inclusion of this covariate would markedly reduce ESS and reliability of the estimate and study power.
Effect modifier/prognostic variable	**Included in unanchored MAIC analysis (Yes/No)**	**Reason for not including in MAIC**
Prior ASCT	No	Not available in NCRAS dataset
High risk cytogenetics	No	Not available in NCRAS dataset
Lytic bone lesions	No	Incorrect data
Extramedullary disease	Yes	N/A
Number of prior lines of therapy	Yes	N/A
Median time from diagnosis	No	Not available in NCRAS dataset
Type of MM (secretory vs. non-secretory)	No	Not available in NCRAS dataset
Myeloma immunoglobulin type	No	Not available in NCRAS dataset

ASCT=allogeneic stem cell transplantation; R-ISS=revised international staging system stage; ECOG PS= Eastern Cooperative Oncology Group Performance Status; MAIC=matched adjusted indirect comparison; ESS=effective sample size; NCRAS=National Cancer Registration and Analysis Service

3.3.4 Unanchored MAIC analysis and statistical approach

An unanchored MAIC analysis was conducted according to the recommendations and guidance of the NICE DSU TSD.[20] The company used a logistic regression-based propensity-score method of moments approach to re-weight DREAMM-2[1, 2] IPD (Belamaf) with respect to age, median number of prior lines of treatment, and extramedullary disease to match the NCRAS dataset for both PomDex and PanoBorDex separately.

The efficacy outcomes where then recalculated for DREAMM-2[1, 2] IPD were re-calculated using weighted formulas, and were compared to the observed outcomes in the NCRAS dataset. Treatment effects were estimated using a robust sandwich estimator and expressed as weighted HRs (for OS, TTNT, and TTD) with 95% confidence intervals (95% CIs) based on Cox-proportional hazards model and the corresponding weighted Kaplan-Meier (KM) estimates.

3.3.5 Patients' baseline characteristics across the DREAMM-2 trial and the NCRAS dataset

The patients' baseline characteristics compared across the DREAMM-2[1, 2] trial and the NCRAS dataset (PomDex and PanoBorDex) are provided in Table 11. As expected, there were notable differences between DREAMM-2[1, 2] IPD and the NCRAS dataset in the following variables: ECOG PS, R-ISS stage, extramedullary disease, lytic bone lesions, and number of prior therapies. The EAG note that some of these differences could be due to missing values. For example, in the NCRAS dataset some data on 'ECOG PS' ([redacted] and 'R-ISS stage' ([redacted]) were missing. Another contributing factor to these differences was the complete absence of data in the NCRAS dataset on weight, 'renal impairment', 'high risk cytogenetics', 'type of MM', 'myeloma immunoglobulin type', and 'prior ASCT'.

In general, the pattern of distribution given the available data across the two sets of data (DREAMM-2[1, 2] IPD and the NCRAS AD) suggested a worse prognosis for patients in the DREAMM-2[1, 2] trial versus those in the NCRAS dataset. With a [redacted] of patients in the DREAMM-2 trial with extramedullary disease ([redacted]), lytic bone lesions ([redacted] and a higher median number of prior lines of treatment ([redacted]). However, ECOG status was lower (better) in the DREAMM-2 trial.

One notable difference was in regards to ethnicity/race with a higher proportion of Black/African Americans in the DREAMM-2[1, 2] compared with the NCRAS AD ([redacted]). The NCRAS dataset sample included a [redacted] of elderly patients (75 years of age or older) compared to DREAMM-2[1, 2] IPD ([redacted]).

Table 11. Baseline characteristics of three cohorts compared for MAIC analysis: Belamaf (DREAMM-2[1, 2]) vs. PomDex (NCRAS dataset) vs. PanoBorDex (NCRAS dataset).

Baseline patient characteristic	Intervention arm		
	DREAMM-2 [1, 2] Trial–IPD Belamaf (n=97) ITT[£]	NCRAS AD PomDex (n=[redacted])	NCRAS AD PanoBorDex (n=[redacted])
Line of treatment/ refractoriness	5L + TCR MM patients	5L + TCR MM patients	5L + TCR MM patients
Male n (%)	[redacted]	[redacted]	[redacted]
Age mean (SD)	[redacted]	[redacted]	[redacted]
Age median (range)	[redacted]	NR	NR
Age group (years) n (%)			

<18	[redacted]	[redacted]	NR
18-<65	[redacted]	[redacted]	NR
65-<75	[redacted]	[redacted]	NR
75≤	[redacted]	[redacted]	NR
Race n (%)			
Black/African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Weight (kg) mean (SD)	[redacted]	NR	NR
Weight (kg) median (range)	[redacted]	NR	NR
ISS disease stage n (%)			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
ECOG PS n (%)			
0-2	[redacted]	[redacted]	[redacted]
3-4	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Type of MM n (%)			
Non-secretory	[redacted]	NR	NR
Secretory	[redacted]	NR	NR
Extramedullary disease n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Lytic bone lesions n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Prior therapy exposure n (%)			
PI	97 (100.0)	[redacted]	[redacted]
IMiD	97 (100.0)	[redacted]	[redacted]
Len	97 (100.0)	[redacted]	[redacted]
mAB (anti-CD38)	97 (100.0)	[redacted]	[redacted]
Lines of therapy completed at entry median (range)	7.0 (3.0, 21.0)	[redacted]	[redacted]
Lines of therapy completed at entry n (%)			
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]

9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
>10	[redacted]	[redacted]	[redacted]
Myeloma light chain n (%)			
Kappa	[redacted]	NR	NR
Lambda	[redacted]	NR	NR
Missing	[redacted]	NR	NR
Myeloma immunoglobulin n (%)			
IgA	[redacted]	NR	NR
IgG	[redacted]	NR	NR
IgM	[redacted]	NR	NR
IgD	[redacted]	NR	NR
IgE	[redacted]	NR	NR
Missing	[redacted]	NR	NR
High risk cytogenetics n (%)			
Yes	[redacted]	NR	NR
Other (non-high risk, not done, or missing)	[redacted]	NR	NR

AD=aggregate data; IPD=individual patient data; 5L=5th line; TCR=triple class refractory; ECOG=Eastern Cooperative Oncology Group; PS=performance status; NCRAS=National Cancer Registration and Analysis Service; ISS=international staging system; MM=multiple myeloma; NR=not reported; PI= proteasome inhibitor; IMiD=immunomodulatory drug; mAB=monoclonal antibody; Len= Lenalidomide; PomDex=pomalidomide plus dexamethasone; ITT=intention-to-treat; Belamaf=Belantamab mafodotin; PanoBorDex=panobinostat plus bortezomib plus dexamethasone
[redacted] patients ([redacted] received only three prior lines of therapy which is outside of the population considered in this appraisal

3.3.6 Patients' baseline characteristics across DREAMM-2 (before and after matching) and the NCRAS dataset

3.3.6.1 DREAMM-2 IPD compared to NCRAS AD (PomDex)

Baseline patient characteristics before and after weighting/adjusting DREAMM-2[1, 2] IPD versus NCRAS AD (PomDex) are provided in Table 12. The EAG notes that substantial between-group differences still persist between the adjusted DREAMM-2[1, 2] IPD (Belamaf) when compared with the NCRAS AD (PomDex). The noticeable differences are observed for ethnicity (White: [redacted] respectively) and lytic bone lesions ([redacted]). Lytic bone lesions' were reported as present only in [redacted] of RRMM 5L + TCR patients (in the NCRAS arm) which is implausibly low. The missing data for ISS stage and ECOG PS precludes a meaningful comparison of differences between the two treatment groups of Belamaf versus PomDex. The same applies also to all baseline characteristics (i.e., effect modifiers and prognostic factors) data not available for NCRAS dataset (weight, 'renal impairment', 'high risk cytogenetics', 'type of MM', 'myeloma immunoglobulin type', and 'prior ASCT).

The EAG notes a drastic drop in the sample size of DREAMM-2[1, 2] IPD after adjustment from [redacted] (effective sample size), which suggests a high level of uncertainty in the effect estimates. The NCRAS dataset's small sample size of [redacted] patients further limits the interpretability of the comparative efficacy of Belamaf versus PomDex.

Table 12. Baseline patient characteristics before and after weighting/adjusting DREAMM-2 IPD for Belamaf arm versus PomDex (aggregate data from NCRAS study).

Baseline characteristic	DREAMM-2 [1, 2] Trial – IPD Belamaf (n=97) ITT Unadjusted	DREAMM-2 [1, 2] Trial – IPD Belamaf (ESS=[redacted]) Adjusted	NCRAS dataset – AD PomDex (n=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
Race: White (%)	[redacted]	[redacted]	[redacted]
Race: Black (%)	[redacted]	[redacted]	[redacted]
Race: Asian (%)	[redacted]	[redacted]	[redacted]
Race: Other (%)	[redacted]	[redacted]	[redacted]
Race: Unknown (%)	[redacted]	[redacted]	[redacted]
Sex (% male)	52.6	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]
Lytic bone lesions (% with)	[redacted]	[redacted]	[redacted]
High risk cytogenetics (% with)	[redacted]	[redacted]	[redacted]
Prior stem cell transplant (% with)	[redacted]	[redacted]	[redacted]
ECOG status = 0-2 (%)	[redacted]	[redacted]	[redacted]
ECOG status = 3-4 (%)	[redacted]	[redacted]	[redacted]
ECOG status = unknown (%)	[redacted]	[redacted]	[redacted]
Extramedullary disease (%)	22.7	[redacted]	[redacted]
ISS Stage = 1 (%)	22.7	[redacted]	[redacted]
ISS Stage = 2 (%)	34.0	[redacted]	[redacted]
ISS Stage = 3 (%)	43.3	[redacted]	[redacted]
ISS Stage = unknown (%)	[redacted]	[redacted]	[redacted]

Prior lines of therapy (median number)	7.0	[redacted]	[redacted]

ESS=effective sample size; AD=aggregate data; IPD=individual patient data; 5L=5th line; ECOG=Eastern Cooperative Oncology Group; PS=performance status; NCRAS=National Cancer Registration and Analysis Service; ISS=international staging system; PomDex=pomalidomide plus dexamethasone; Belamaf=Belantamab mafodotin; PanoBorDex=Panobinostat plus bortezomib plus dexamethasone; ITT=intention to treat

3.3.6.2 DREAMM-2 IPD compared to NCRAS AD (PanoBorDex)

Baseline patient characteristics before and after weighting/adjusting DREAMM-2[1, 2] IPD vs. NCRAS AD (PanoBorDex) are provided in
Table 13. Again, the EAG notes substantial between-group differences which still persist between the adjusted DREAMM-2[1, 2] IPD (Belamaf) and the NCRAS AD (PanoBorDex). The noticeable differences are observed for ISS Stage ([redacted]), and lytic bone lesions ([redacted]). 'Lytic bone lesions' present only in [redacted] of RRMM 5L + TCR patients (in NCRAS arm) is implausibly low. The missing data for ISS stage and ECOG PS precludes a meaningful comparison of differences between the two treatment groups of Belamaf versus PanoBorDex. The same applies also to all baseline characteristics data (i.e., effect modifiers and prognostic factors) not available for NCRAS dataset (weight, 'renal impairment', 'high risk cytogenetics', 'type of MM', 'myeloma immunoglobulin type', and 'prior ASCT).

The EAG notes a drastic reduction in the sample size of DREAMM-2[1, 2] IPD after adjustment from [redacted] (effective sample size), which suggests high uncertainty in the effect estimates. The NCRAS dataset's small sample size of [redacted] patients further limits the interpretability of the comparative efficacy of Belamaf versus PanoBorDex.

Table 13. Baseline patient characteristics before and after matching/adjusting DREAMM-2 IPD for Belamaf arm versus PanoBorDex (aggregate data from NCRAS study).

Baseline characteristic	DREAMM-2[1, 2] Trial – IPD Belamaf (n=97) ITT Unadjusted	DREAMM-2[1, 2] Trial – IPD Belamaf (ESS=[redacted]) Adjusted	NCRAS dataset– AD PanoBorDex (n=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
Race: White (%)	[redacted]	[redacted]	[redacted]
Race: Black (%)	[redacted]	[redacted]	[redacted]

Race: Asian (%)	[redacted]	[redacted]	[redacted]
Race: Other (%)	[redacted]	[redacted]	[redacted]
Race: Unknown (%)	[redacted]	[redacted]	[redacted]
Sex (% male)	52.6	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]
Lytic bone lesions (% with)	[redacted]	[redacted]	[redacted]
High risk cytogenetics (% with)	[redacted]	[redacted]	[redacted]
Prior stem cell transplant (% with)	[redacted]	[redacted]	[redacted]
ECOG status = 0-2 (%)	[redacted]	[redacted]	[redacted]
ECOG status = 3-4 (%)	[redacted]	[redacted]	[redacted]
ECOG status = unknown (%)	[redacted]	[redacted]	[redacted]
Extramedullary disease (%)	22.7	[redacted]	[redacted]
ISS Stage = 1 (%)	22.7	[redacted]	[redacted]
ISS Stage = 2 (%)	34.0	[redacted]	[redacted]
ISS Stage = 3 (%)	43.3	[redacted]	[redacted]
ISS Stage = unknown (%)	[redacted]	[redacted]	[redacted]
Prior lines of therapy (median number)	7.0	[redacted]	[redacted]

ESS=effective sample size; AD=aggregate data; IPD=individual patient data; 5L=5th line; ECOG=Eastern Cooperative Oncology Group; PS=performance status; NCRAS=National Cancer Registration and Analysis Service; ISS=international staging system; PomDex=pomalidomide plus dexamethasone; Belamaf=Belantamab mafodotin; PanoBorDex=Panobinostat plus bortezomib plus dexamethasone; ITT=intention to treat

3.3.7 Summary efficacy outcomes

Based on crude comparison (shown in

Table 14) Belamaf compared with PomDex was associated with no improvement in median OS ([redacted] ([redacted]) months vs. [redacted] months) with overlapping 95% confidence intervals. There was no difference for Belamaf compared with PomDex in median time to TTNT ([redacted] ([redacted]) months vs. [redacted] ([redacted]) months) again with overlapping 95% confidence intervals or in TTD ([redacted] ([redacted]) months vs. [redacted] ([redacted]) months) although there is a hint that TTD may be higher for the NCRAS arm than for the DREAMM-2 arm.

Table 14. Summary efficacy outcomes: median time (in months) to event (Belamaf vs. PomDex vs. PanoBorDex)

Efficacy outcome	DREAMM-2[1, 2] Trial arm (IPD) Belamaf[β]	NCRAS dataset (AD)	
	(ITT; n=97)[£]	PomDex (n=[redacted])	PanoBorDex (n=[redacted])
OS (median # of months 95% CI)	[redacted]	[redacted]	[redacted]
TTNT (median # of months 95% CI)	[redacted]	[redacted]	[redacted]
TTD (median # of months 95% CI)	[redacted]	[redacted]	[redacted]

CI=confidence interval; AD=aggregate data; IPD=individual patient data; NCRAS=National Cancer Registration and Analysis Service; TTNT=time to next therapy; TTD=time to treatment discontinuation; PomDex=pomalidomide plus dexamethasone; ITT=intention-to-treat; Belamaf=Belantamab mafodotin
£ In ITT sample, [redacted] patients ([redacted] received only three prior lines of therapy which is outside of the population considered in this appraisal [β] based on 4 May 2022 post-hoc analysis

The MAIC adjusted results indicated that the only difference was that Belamaf demonstrated a statistically significant [redacted] in TTD compared to PomDex (HR=[redacted] 95% CI[redacted]). Although differences were found in OS (HR=[redacted] 95% CI: [redacted]) and TTNT (HR=[redacted] 95% CI: [redacted]), the EAG note that the differences in these HR estimates are not statistically significant with a high degree of uncertainty in terms of wide confidence intervals, as shown in Table 7.

Table 15. MAIC summary results – Unanchored MAIC efficacy outcomes (Belamaf vs. PomDex)

Efficacy outcome	Unadjusted HR (95% CI)		Adjusted HR (95% CI), p-value
	DREAMM-2 [1, 2] Trial arm IPD (ITT; n=97)[£]	NCRAS AD PomDex (n=[redacted])	Matched DREAMM-2 [1, 2] Trial arm IPD ESS=[redacted]
OS	Not available		[redacted]
TTNT	Not available		[redacted]
TTD	Not available		[redacted]

HR=hazard ratio; CI=confidence interval; AD=aggregate data; IPD=individual patient data; 5L=5th line; TCR=triple class refractory; NCRAS=National Cancer Registration and Analysis Service; ESS=effective sample size; TTNT=time to next therapy; TTD=time to treatment discontinuation; PomDex=pomalidomide plus dexamethasone; ITT=intention-to-treat; MAIC=matching-adjusted indirect comparison; Belamaf=Belantamab mafodotin
£ In ITT sample, [redacted] patients ([redacted] received only three prior lines of therapy which is outside of the population considered in this appraisal

The MAIC adjusted results indicated that Belamaf was associated with statistically significant [redacted] in OS, TTNT, and TTD compared to PanoBorDex (Table 16). The EAG suggest that

these estimates be interpreted with caution given the small samples and implausibly large magnitude of HRs [redacted] of Belamaf.

Table 16. MAIC summary results - Unanchored MAIC efficacy outcomes (Belamaf vs. PanoBorDex)

Efficacy outcome	Unadjusted HR (95% CI)		Adjusted HR (95% CI), p-value
	DREAMM-2 [1, 2] Trial arm IPD (ITT; n=97)£	NCRAS AD PanoBorDex ([redacted])	Matched DREAMM-2 [1, 2] Trial arm IPD ESS=[redacted]
OS	Not available		[redacted]
TTNT	Not available		[redacted]
TTD	Not available		[redacted]

HR=hazard ratio; CI=confidence interval; AD=aggregate data; IPD=individual patient data; 5L=5th line; TCR=triple class refractory; NCRAS=National Cancer Registration and Analysis Service; ESS=effective sample size; TTNT=time to next therapy; TTD=time to treatment discontinuation; PanoBorDex=Panobinostat plus bortezomib plus dexamethasone; ITT=intention-to-treat; MAIC=matching-adjusted indirect comparison; Belamaf=Belantamab mafodotin
£ In ITT sample, [redacted] patients ([redacted]) received only three prior lines of therapy which is outside of the population considered in this appraisal

Visual examination of KM plots presented in the CS (Document B, Figures 29-31 and Appendix D, Figures 1-3) suggests that adjustment of the Belamaf arm to the NCRAS dataset appreciably [redacted] all three outcomes (OS, TTNT, and TTD) compared with pre-matched data (unadjusted Belamaf) for PomDex/PanoBorDex. Note that the MAIC provides the effect of Belamaf versus PomDex (or PanoBorDex) expected in the NCRAS population.

It is evident that the MAIC adjustment [redacted] the efficacy of Belamaf by making IPD patients more like the NCRAS. However, since there is little overlap between the two sources compared, accompanied by missing values, substantial unavailable data, and an inability to adjust for several important covariates, the EAG conclude that large amounts of bias impact the efficacy results. The company did not provide unadjusted (before matching or naïve comparison-based) HRs for the efficacy outcome measures. This information would allow the EAG to assess the amount and direction of bias removed by matching/adjustment used in MAIC (as shown in Table 15 and Table 16).

3.4 *Critique of the indirect comparison*

3.4.1 Relevance of the company's choice of comparator (NCRAS aggregate dataset)

The EAG was unable to identify an appropriate relevant comparator to Belamaf in the RRMM 5L + TCR population. As described in Table 3, the EAG clinical advisors questioned the plausibility of PomDex and PanoBorDex in NHS practice as most RRMM 5L+ will have received these treatments previously. However, they recognise that other comparators are not available for inclusion in this appraisal (unless as part of the CDF e.g., IsaPomDex TA658).

The EAG consider that the relevance and representativeness of the choice of comparators (NCRAS dataset: RRMM 5L + TCR patients treated with PomDex, PanoBorDex) included in the CS MAIC should be viewed with caution for the following reasons:

- Incongruence between DREAMM-2[1, 2] IPD and the NCRAS dataset due to differences in study design and study aims/purpose
    - DREAMM-2[1, 2] IPD is multicentre randomised controlled trial-based, whereas the NCRAS dataset is retrospective non-interventional real world study evidence - based.
- Non-comparability (or little overlap) between the DREAMM-2[1, 2] IPD and the NCRAS dataset with respect to the distributions of patient baseline characteristics (treatment effect modifiers and/or prognostic factors) suggests a potentially poorer prognosis in DREAMM-2[1, 2] IPD patients.
    - However, it is very important to note that this non-comparability may be due to different inclusion/exclusion criteria used in the two data sources and in the extent and character of missing data.
- Non-comparability (or little overlap) persisted even after the DREAMM-2[1, 2] IPD was adjusted and matched to the NCRAS dataset. This was supported by the very small ESS value of [redacted].
- Unavailable and missing data in several important effect modifiers/prognostic factors in NCRAS dataset preventing matching/adjustment procedures on these factors.
- Due to CDF restrictions, the NCRAS dataset excluded [redacted] PomDex RRMM 5L + TCR patients who were treated with CDF-funded drugs at any time during their entire treatment history.

- The small sample size of the NCRAS dataset (PomDex n=[redacted] and PanoBorDex n=[redacted]) is unlikely to provide a representative comparator relevant to the UK practice settings of this line of treatment.
- The EAG found no evidence of whether PomDex induces any response (according to International Myeloma Working Group) at all in RRMM 5L + TCR patients. Unlike the DREAMM-2[1, 2] trial, the NCRAS dataset did not provide response rates.
    - The only efficacy data reported by the company (KM curves for OS, TTNT, and TTD) does not enable the EAG to assess if PomDex (or PanoBorDex) has any efficacy response (for example on OS) relative to no intervention or placebo in this patient population.

3.4.2 Feasibility and conduct of MAIC

The EAG notes several limitations with respect to the feasibility and conduct of the MAIC (outlined in Table 17).

These limitations stem from numerous marked differences across the DREAMM-2[1, 2] and the NCRAS datasets with respect to design (trial-based vs. retrospective RWE study), location (multicentre global vs. England), study inclusion/exclusion criteria (e.g., narrower ECOG PS in the DREAMM-2[1, 2], prior treatments), definition of refractoriness, efficacy outcomes (e.g., TTNT was used as a proxy of PFS; for DREAMM-2[1, 2]), disease progression (not available in NCRAS), unavailable data on important factors in NCRAS (weight, 'renal impairment', 'high risk cytogenetics', 'type of MM', 'myeloma immunoglobulin type', and 'prior ASCT'), and partially missing data in NCRAS ('ECOG PS' and 'R-ISS stage').

The missing values for some patients or completely unavailable data for the above-mentioned factors precluded matching in the MAIC analysis on the majority of the pre-specified treatment effect modifiers/prognostic factors (see Section 3.3.2 for detail). As a result, the unanchored MAIC was adjusted for only three factors (age, extramedullary disease, and number of prior lines of treatment).

The EAG consider that the feasibility of MAIC was subverted at the outset because the requirement to account for all effect modifiers and prognostic factors in an unanchored MAIC could

not be met. The company rightfully stated that the inclusion of factors with missing data (i.e., ECOG PS, R-ISS stage) would further reduce ESS and study power, thereby leading to even more unreliable results. It is unclear in the CS, how the missing values and incomplete outcome data including losses to follow-up were handled in the NCRAS dataset. In addition, one inherent limitation of MAIC is the inability to adjust for 'unknown' treatment effect modifier factors which are likely to contribute to overall bias in the CS efficacy (and later, cost-effectiveness) results.

Table 17. Sources of bias and uncertainty in unanchored MAIC analyses (Belamaf vs. PomDex and Belamaf vs. PanoBorDex).

Study domain	EAG issue
Anchoring/common comparator	• Since there was no common comparator, an unanchored MAIC was conducted which requires stronger assumptions (need for similarity of the compared study groups not only in all treatment effect modifiers but also all prognostic factors).
Source of data/design	• DREAMM-2[1, 2] was a multi-centre randomised trial, whereas NCRAS was a retrospective non-interventional RWE study.
Location	• DREAM-2 trial (58 centres in North America, Australia, France, Germany, Italy, and UK) vs. NCRAS (UK, England).
Dosage in the comparator (NCRAS dataset)	• The NCRAS study does not systematically provide the doses and related details (dose reduction, delay) received by each patient in the PomDex/PanoBorDex cohort. For example, Pomalidomide median dose in PomDex arm was 4 mg (IQR: 3 mg – 4 mg). However, the Dexamethasone dose was not reported. No dose was reported for the PanoBorDex cohort. • This limitation could undermine the relevance and generalizability of the comparators to the UK populations of interest.
Refractoriness	• The definition of refractoriness varies across the DREAMM-2 [1, 2] and NCRAS datasets (Table 7)
Outcome of interest	• TTNT was used as a proxy for PFS because NCRAS did not collect PFS information. TTNT was not reported in DREAMM-2 [1, 2] • The EAG team was unable to assess the comparability of the definition of disease progression since the NCRAS dataset did not report this information. • TTD, was defined more stringently in the DREAMM-2 [1, 2] trial, occurring additionally in case of unacceptable toxicity, disease progression (which was unavailable for NCRAS), protocol-based stopping criteria, study withdrawal, and study termination.

Unavailable or missing data (for treatment effect modifiers, prognostic factors)	• Due to unavailable or missing values (in the NCRAS dataset), it was not possible to adjust the cross-study differences for a number of important baseline patient characteristics likely to impact on outcome, such as weight, ISS disease stage, ECOG status, high risk cytogenetics, type of MM (secretory vs. non-secretory), myeloma immunoglobulin type, renal impairment, and prior stem cell transplant. • No adjustment was made for lytic bone lesions because in the PomDex and PanoBorDex groups only 5-6% of patients were classified as having lesions which was considered an incorrect number.
Cross-trial differences in baseline patient characteristics (pre-adjustment)	• The DREAMM-2 [1, 2] and NCRAS dataset cohorts displayed markedly different distributions of important baseline patient characteristics (with no missing values), suggesting a poorer prognosis for patients from the DREAMM-2 [1, 2] trial with a [redacted] compared to both NCRAS dataset cohorts (PomDex and PanoBorDex).
Cross-study differences in baseline patient characteristics (post-adjustment)	• Cross-study differences still persisted in the adjusted dataset for lytic bone lesions (Belamaf [redacted] vs. PomDex [redacted] vs. PanoBorDex [redacted]). Other cross-study differences were due to missing values in the NCRAS dataset.
Effective sample size	• The MAIC adjustment using covariate matching reduced the IPD sample of Belamaf from 97 to [redacted] (effective sample size), indicated very little overlap between the two cohorts compared. • The NCRAS dataset served as the comparator arms (PomDex and PanoBorDex) in the MAIC analyses providing rather small samples (n=[redacted] and [redacted], respectively), thereby limiting the generalisability of the cohorts to the UK population and rendering a high degree of uncertainty and inconclusiveness in the effect estimates for Belamaf vs. PomDex.
MAIC analysis and results	• Visual examination of KM plots (CS Document B, Figures 29-31 and Appendix D, Figures 1-3) for OS, TTNT, and TTD reveals a violation of the constancy assumption of hazard ratio over time. • Visual examination of the KM plots relevant to MAIC results reveals that the adjusted Belamaf and PomDex KM curves for OS and TTNT (Document B, Figures 29-30) are located sufficiently close to each other to support comparison.

RWE=real world evidence; PFS=progression-free survival; TTD=time to discontinuation; TSNT=time to the start of next therapy; TTNT=time to next therapy; PomDex=pomalidomide plus dexamethasone; IPD=individual patient data; NCRAS=National Cancer Registration and Analysis Service; ISS=international staging system; MM=multiple myeloma; Belamaf=Belantamab mafodotin; PanoBorDex=panobinostat plus bortezomib plus dexamethasone; IQR=interquartile range

The EAG believes that in principle, an unanchored MAIC analysis was a correct choice of analysis in the absence of head-to-head comparison studies or connected networks. However, the relevance of the comparator source (i.e., the NCRAS database) is questionable due to its small sample size and limited generalisability as well as major differences and a small degree of overlap in study inclusion/exclusion criteria, baseline factors, outcome definitions across in the DREAMM-2[1, 2] trial IPD and the NCRAS dataset. Given these limitations, compounded with unavailable or missing data, the MAIC adjustment was incomplete (with a small ESS of [redacted]), rendering the efficacy outcomes biased. These are subsequently expressed as implausibly large HRs (with uninformative wide 95% CIs).

In summary, the EAG considers that the feasibility for a valid MAIC analysis has been seriously undermined given the incomparability and incongruity of the two datasets compared. Since neither DREAMM-2 [1, 2] nor NCRAS studies had a control arm, the EAG conclude the comparison lacks validity for an economic analysis. The company presented a similar conclusion and therefore, the CS base case in the economic analysis reverts to an unadjusted naive comparison of the outcomes in the two studies (both lacking control arms whose populations are known to differ based on important prognostic factors).

3.5 *Additional work on clinical effectiveness undertaken by the EAG*

In an attempt to address the severe problems identified in the company's approach to analysis, the EAG have undertaken additional work on clinical effectiveness. The EAG were unable to generate results that could meaningfully inform EAG scenario analysis. The EAG preferred assumptions compared to the CS model base case are listed in Section 5.4.3.

3.5.1 Data used in the submission

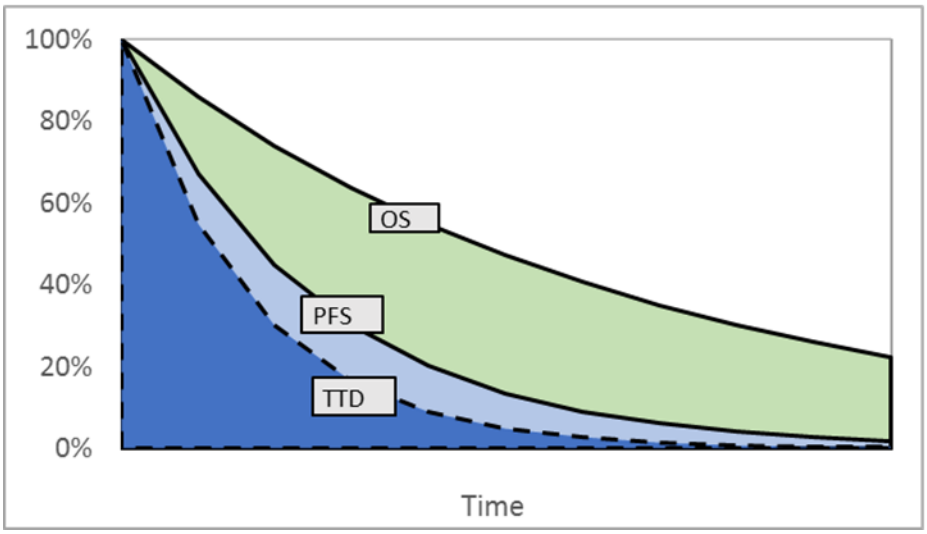
DREAMM-2[1, 2] and the NCRAS database study provided data for the CS (see Section 3.2 for critique). Overall, the EAG remains unconvinced by the inclusion of these two data sources for determining the clinical effectiveness of Belamaf. The lack of a control arm in DREAMM-2[1, 2] and the NCRAS suggests that efficacy data used in economic analysis presented in Section 5 of this report is extremely uncertain.

3.5.1.1 The submission's partitioned survival model

The EAG has included the following section which presents a commentary on the time to event outcomes that have been used, or could have been used, in the submission's development of a partitioned survival economic model. In all cases the CS selects Weibull parametric models to extrapolate outcome results beyond the "observed" KM.

A common form of partitioned survival model uses models of PFS and of OS and an area under the curve procedure to develop measures of time spent in the pre-progression state (AUC the PFS model) and in the post-progression state (AUC of the OS model minus AUC of the PFS model; i.e. the time represented by the area between the two curves.[24] Pre-progression is associated with better quality of life than post-progression so that the greater the relative proportion of time in pre-progression the greater the relative proportion of time spent in pre-progression, the greater the relative QALY accumulation. Frequently, treatment with a new drug is stopped when a patient progresses, so that in these cases pre-progression time equates to time on treatment and post-progression time to post treatment time. In the CS, partitioned survival was summarised in CS Figure 33 (reproduced as EAG Figure 2).

CS Figure 33



Distribution of patients in progression-free, progressed and death health states.

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

Note: In this Figure PFS is a "proxy-PFS" (TTNT).

Figure 2 Distribution of patients in progression-free and on treatment, progression-free and off-treatment, progressed and death health states

Although a pre-specified ITT analysis of ICR-assessed PFS in DREAMM-2[1, 2] was undertaken (see CS Figure 11) this was not used in the company's economic model. Rather than model ITT PFS, the economic model employs a proxy for PFS (proxy-PFS) termed "time to next treatment" (TTNT). TTNT was used instead. This procedure partitions "pre proxy-PFS time" into pre proxy-PFS time "alive not progressed on treatment" (dark blue in

Figure 2) and pre proxy PFS time “alive not progressed off treatment” (light blue in Figure 2); the remaining time between proxy-PFS and OS being quasi-equivalent to post-progression time.

Since post-progression time is rated at lower quality of life than pre-progression time the larger pre proxy-PFS is, relative to post-proxy the greater the QALY accumulation. In **Error! Reference source not found.** the EAG have compared DREAMM-2[1, 2] IRC ITT KM analysis of PFS (as in CS Figure 11) with the proxy-PFS (TTNT) (as in CS Figure 19). The AUC for proxy-PFS is greater than that for PFS; the use of proxy-PFS rather than PFS will tend to accumulate more QALYs as indicated in

Figure 3, note that the Weibull models mirror this.

Reproduced from CS figures 11 and 19

Figure 3 Comparison of KM plots of PFS and proxy-PFS (DREAMM-2)

3.5.1.2 Equitable determination of proxy-PFS

TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. For PomDex this is based on data for UK patients (i.e. those in the NCRAS database). For the Belamaf arm, TSNT is based on data from 58 MM centers across eight jurisdictions, including some UK patients. The speed in acquiring and administering next treatments will depend on multiple factors likely to be different across centres and jurisdictions such as: capacity to fund these therapies (HTA/financial factors) and the ability to deliver them (organisational factors). With regard to the former, it seems a large assumption that health systems in all these different countries will equally be able to fund subsequent therapies, and from an organisational perspective there may be important variations across territories (due for example to shortage of medical skills, nurses and the constraints of COVID 19). Furthermore, practice within a trial such as DREAMM-2 (with only [redacted] UK patients) is likely to differ from that operating in the real world in the UK (i.e., in the NCRAS study). Substantial variations in speed in acquiring and administering subsequent therapies seem likely across countries.

In short, whereas TSNT (and thus TTNT) in the PomDex arm is likely to reflect the experience for UK patients, the EAG consider it unlikely that this is the case for the Belamaf arm of DREAMM-2. In the EAG's opinion the development of TSNT is unlikely to have been equitable across the two arms.

3.5.1.3 Choice of "proxy-comparator"

After literature search and SLR, the submission was unable to find any study that presented useful results for a suitable comparator to Belamaf in 5L+ treatment for a TCR population. Since PomDex is recommended by NICE as 4L+ treatment and was identified in the NICE final scope, the CS posits that, in absence of an alternative, PomDex represents "*the only source*" of *"comparative efficacy evidence" (CS Document B page 67)* for a proxy-comparator to Belamaf.

Consequently, the CS conducted the "NCRAS-study" (National Cancer Registration and Analysis Service -study) aiming to identify 5L+ patients who were TCR. The database contained [redacted] TCR patients receiving 5L+ therapies (CS Document B Figure 7). Out of [redacted] patients [redacted] were identified as receiving "index" PomDex, and this population was used as proxy-comparator to Belamaf.

Unlike DREAMM-2[1, 2], the NCRAS study did not report overall response rates (OR, by IMWG standard criteria). Therefore, there is no evidence in the CS to suggest a beneficial, null or harmful influence of this intervention on OS. The EAG suggests that the PomDex OS KM plot and its Weibull model could merely reflect what would have happened in the absence of PomDex treatment. But note that it is nevertheless associated with drug acquisition costs in the submission economic analysis (see Section 4.2.8). In the CS economic base case, drug acquisition represents [redacted] of the total cost for the proxy-comparator. The EAG suggest that PomDex may be a futile intervention in this population but associated with significant costs for the NHS; the economic model Tornado diagram (CS Document B Figure 50) demonstrates that PomDex dose density and therefore cost, has a large influence on model output. As stated in Section 2.1, the EMA license indication states PomDex *"is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy".* Therefore, this means PomDex use even when futile, will not abrogate its EMA license.

3.5.1.4 Time to event outcomes in DREAMM-2 (ITT population [N=97])

The CS base case economic model (see later Section 5.1) made a naïve comparison of outcomes from DREAMM-2[1, 2] with those from an identified proxy-comparator (PomDex) NCRAS study (described in Section 3.2.3).

DREAMM-2[1, 2] reported favourable ORR (according to IMWG standard criteria) for some patients following intervention with Belamaf. These are summarised in CS Document B Table 14; of the 97 patients in the ITT population, [redacted] experienced a response classified as either sCR, or CR, or VGPR or PR; a further [redacted] experienced a Minimal response (MR), [redacted] "stable disease" and [redacted] "progressive disease" and [redacted] were non-evaluable. The median duration for the [redacted] responses was [redacted] months.

The EAG note that response rate is time varying; such data comparing outcome (OS) by response category does not imply causation. Literature suggests that "*It is generally impossible to refute the possibility that response is just a marker that selects the good prognosis patients: those who would have survived longer even if the therapy had no effect".*[25]. Therefore, these responses presented in the CS, do not reliably infer that Belamaf will exert a beneficial OS effect. The CS makes no inference regarding this severe limitation. How much of OS seen in the trial ITT population that can be specifically attributable to an effect of Belamaf, and how much would have happened anyway without Belamaf is unknown. This is because the fundamental weakness of DREAMM-2[1, 2] for decision making is the lack of a control arm. The 97 patients at the start will survive for an unknown time without any Belamaf treatment. However, for economic analysis it is assumed that all the OS in DREAMM-2[1, 2] is an effect of Belamaf and similarly, in NCRAS all OS is an effect of PomDex. The EAG could find no evidence in the submission to support these assumptions.

EAG Figure 4 summarises the DREAMM-2[1, 2] KM plots (95% CIs) that were modelled for the base case economic analysis (TTD, proxy-PFS (TTNT), and OS). The EAG note that all plots have rather wide 95% CIs, reflecting the relatively small number of participants. The Belamaf OS KM plot used in the naïve analysis for cost-effectiveness is relatively mature ([redacted] events in 97 patients, ~ [redacted] mature) but is somewhat disjointed with several alterations in trajectory. For this reason,

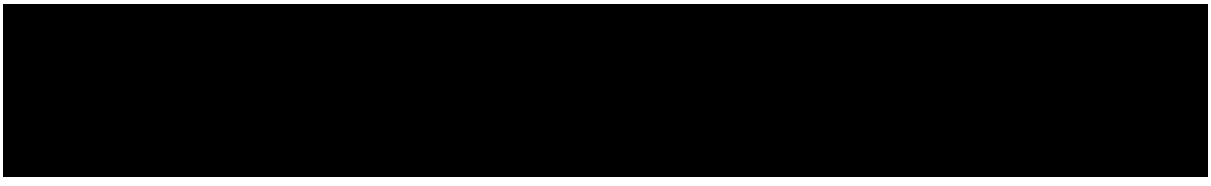
parametric models of OS are unlikely to generate good visual fit. CS Document B Table 20 reports the median survival as [redacted] months (95% CI: [redacted]).

OS = overall survival; proxy PFS = time to next treatment (TTNT); TTD = time to discontinuation

Figure 4 Kaplan-Meier plots for outcomes used in the submission's base case economic analysis

The EAG note that for OS, the Weibull shape parameter is fairly close to unity and so Weibull and exponential models are very similar. Of the six standard parametric models explored, the CS adopted the Weibull model on the basis of expert clinical advice (see Section 3.3.3.3 for review of experts), on the plausibility of extrapolation, information criteria scores (AIC BIC), and goodness of visual fit.

The EAG briefly explored other models (Rayleigh, bathtub, and cubic spline) but these did not provide superior models. The EAG agree that the Weibull model is a reasonable choice for OS, but point out the poor visual fit. The CS makes similar argument for selecting Weibull models for proxy-PFS and for TTNT and again, although the visual fit is poor in all cases. The EAG find these reasonable through lack of more plausible alternatives. The CS Weibull models are summarised in Figure 5.



OS = overall survival; proxy PFS = time to next treatment (TTNT); TTD = time to discontinuation

Figure 5 DREAMM-2 [1, 2] 2 Weibull models extrapolated to about 13 years

The undiscounted unadjusted OS Weibull model delivers approximately [redacted] life years (LY) ([redacted] LY after adjustment and discounting (CS Document B, Table 92). How much of this is attributable to Belamaf is unknown because of the DREAMM-2 study's lack of a control arm. The 97 live patients that entered the study will have survived for some time even without Belamaf treatment and this survival needs to be subtracted from that seen with Belamaf in order to gauge how much survival benefit is specifically due to Belamaf; also some of the modelled OS with Belamaf may be attributable to other unknown mechanisms.

As standard of care/palliative care or "no Belamaf" arm was unavailable from DREAMM-2 the CS undertook an SLR in an attempt to identify a possible proxy-control that might be used to compare with DREAMM-2 [1, 2]. A critique of the SLR and of the search strategy employed can be found in EAG report Section 3.1. The CS points out that in TA427 NICE recommends PomDex for 4L+ therapy i.e.: "*after 3 previous treatments*" but that there is no established standard of care for 5L+ patients who are also TCR. In the absence of such, the company undertook an analysis of patients in the NCRAS data set who received PomDex as at least 5L+ therapy and this has been included as a proxy control arm for the DREAMM-2 [1, 2] outcomes (EAG critique is provided in Section 3.2.2).

The NCRAS study, like DREAMM-2[1, 2], is a two-arm trial with no comparator arm study so that the proportion of observed OS that can be specifically attributed to the influence of PomDex is

uncertain. If populations in DREAMM-2[1, 2] and in the NCRAS are well aligned then a naïve comparison between outcomes might be justified, if controls allowed allocation of effect due to intervention, and if PomDex were indeed a valid comparator for the NHS.

However, these conditions are not met (as described in Section 3.3.3). The CS found that differences persisted between the two groups after matching was undertaken. Hence the base case economic analysis is based on naive comparison of outcomes in two studies lacking control whose populations differ regarding prognostic factors. Since neither DREAMM-2[1, 2] nor NCRAS studies had a control arm the EAG conclude that the comparison lacks validity for inclusion in an economic analysis.

3.5.2 Time to event outcomes in NCRAS study (proxy-comparator population [N=65])

KM plots (95% CIs) for TTD, proxy-PFS (TTNT), and OS are shown in Figure 6 (Figure a; Figure b) depicts the submission's Weibull models. Median OS was [redacted] (95% CI: [redacted]) months.

Figure A Kaplan-Meier plots for outcomes reported for the submission's proxy-control and used in the base case economic analysis

OS = overall survival; proxy PFS = time to next treatment (TTNT); TTD = time to discontinuation

Figure B NCRAS POMDEX study Weibull models extrapolated to about 13 years

OS = overall survival; proxy PFS = time to next treatment (TTNT); TTD = time to discontinuation

Figure 6 KM plots (95% CIs) for TTD, proxy-PFS (TTNT), and OS

As with DREAMM-2 [1, 2], the KM 95% CIs are wide and the goodness of visual fit of Weibull models is moderate. For each of the outcomes the CS thoroughly explored a proportional hazards property between PomDex and Belamaf and concluded that a PH assumption was not strongly supported and therefore, all outcomes were modelled separately for each arm.

The EAG agree that this approach is reasonable. Of the six standard models explored in the submission the EAG consider the Weibull choice reasonable, allowing the same parametric form to be used for both intervention and proxy-comparator. However, as already mentioned, the OS KM plot and its Weibull model could merely reflect what would have happened in the absence of PomDex treatment; as a 5L intervention for TCR patients PomDex may be a futile intervention but with associated very appreciable drug costs for the NHS.

3.5.2.1 Comparison of reported outcomes; Belamaf vs. PomDex

In Table 18, the EAG compares the KM median for outcomes in DREAMM-2 [1, 2] and the NCRAS studies. TTD KM have been compared by arm in Figure 7.

Table 18 Median values reported for time to event outcomes in DREAMM-2 and NCRAS studies

Outcome	Belamaf median (95% CI) months	PomDex median (months)
TTD	[redacted] *"safety population" (N = 95)*	[redacted]
Proxy PFS (TTNT)	[redacted]	[redacted]
OS	[redacted]	[redacted]
PFS (ITT; N 97)	[redacted]	[redacted]

[redacted]

TTD=time to treatment discontinuation POMDEX= Pomalidomide and dexamethasone
Belamaf= belantamab

Figure 7 Comparison of KM plots for TTD (ITT DREAMM-2 vs. NCRAS PomDex)

As can be seen, discontinuation of both treatments is rapid; consistent with reported medians; uncertainty is appreciable and 95% CIs largely overlap. Discontinuation may be faster for Belamaf than PomDex over the first 8 months. Influential reasons for fast discontinuation for Belamaf are unclear to the EAG; a relatively small portion of patients continued on Belamaf beyond 8 months. TTNT (proxy PFS) was possibly also more rapid for Belamaf than PomDex reflecting medians of [redacted] and [redacted] months respectively. Belamaf patients may experience more rapid uptake of subsequent treatments (TTNT).

Figure 8 (part a) shows the proxy PFS KM plots for Belamaf and PomDex and compares these with observed PFS in the DREAMM-2[1, 2] ITT population. The 95% CIs of the proxy-PFS plots mostly overlap and both have larger median values than Belamaf ITT PFS. The submission's Weibull curves for proxy-PFS were similar (part b). On company clinical opinion a cut off at ~2 years was applied only to the PomDex model.

A Comparison of BELAMAF PFS with proxy-PFS for BELAMAF and for POMDEX

B Submission Weibull models of proxy-PFS

Figure 8 EAG Comparison of Belamaf PFS with proxy-PFS for Belamaf and for PomDex

Despite the rather similar proxy-PFS between arms, the OS KM plot for Belamaf implies very superior OS than is seen for PomDex (Figure 9 left vs right). Again because of lack of a “placebo / no Belamaf” control, the EAG conclude that it is impossible to gauge with confidence how much OS can be specifically allocated to Belamaf intervention or to the PomDex intervention.

Figure 9 Comparison of OS KM and Weibull models for Belamaf and PomDex

3.5.2.2 Further exploration of the MAIC analysis

The CS reports an unanchored MAIC of PomDex versus Belamaf using IPD data from DREAMM-2 [1, 2] and aggregate data from the NCRAS study (see Section 3.3.2 for critique). The CS did not consider the results sufficiently robust to be used as the base case in the cost-effectiveness analysis. The MAIC results were summarised in CS Document B Table 31, which is reproduced below as Table 19; the EAG assume the HR values refer to a comparison of adjusted (re-weighted) Belamaf versus PomDex, it seems ESS entries may be missing from the table.

Table 19 MAIC results: summary Belamaf versus PomDex

Endpoint	HR	95% CI	p-value
OS	[redacted]	[redacted]	[redacted]
TTNT	[redacted]	[redacted]	[redacted]
TTD	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, effective sample size; CI, confidence interval; HR, hazard ratio; OS, overall survival; TTD, time to treatment discontinuation; TTNT, time to next treatment.
HR<1 favours Belamaf. P-value<0.05 indicates statistical significance. 95% CIs that do not cross 1 indicate statistical significance.

KM analyses of outcomes are presented within the submitted economic model and is illustrated in CS Figures 29, 30 and 31 (summarised below in EAG Figure 10).

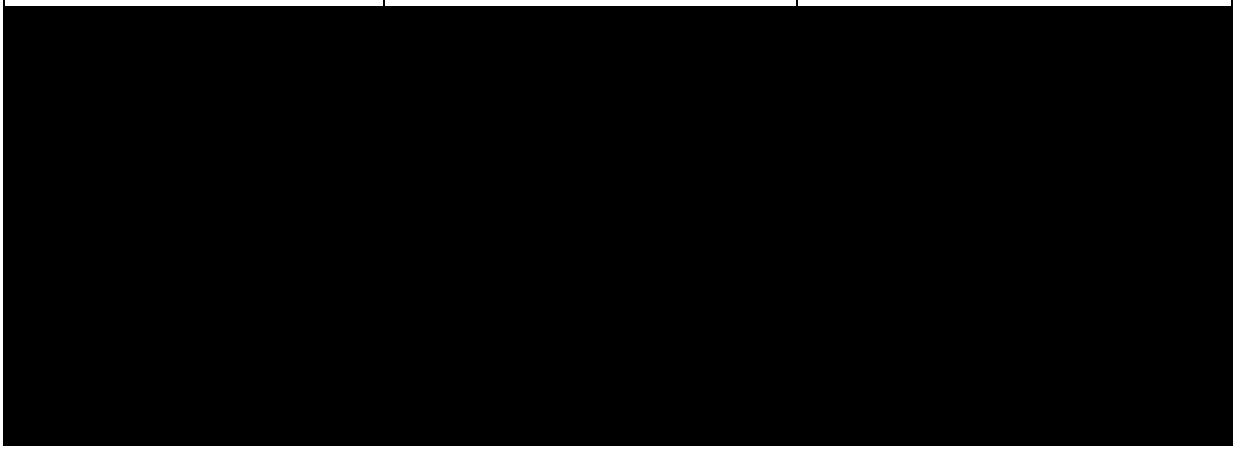
Figure 29 MAIC results vs. POMDEX: OS Kaplan-Meiers	**Figure 30** MAIC results vs. POMDEX: TTNT Kaplan-Meiers	**Figure 31** MAIC results vs. POMDEX: TTD Kaplan-Meiers
		

Figure 10 KM analyses of outcomes

The EAG found it difficult to reconcile some results presented in CS Figures (29 – 31) with HRs provided in CS Table 19 and/or with KM data in the economic model sheet (NCRAS MAIC KM). The EAG concerns include:

- **A] CS Figure 29:** The adjusted Belamaf plot and the unadjusted PomDex plots are quite close together and do not seem sufficiently different to support a HR of [redacted] as reported in Table 19. Within the economic model, the EAG was unable to find KM data corresponding to the adjusted BELAMAF plot and so the EAG could not test this.

- **B] CS Figure 30:** The adjusted Belamaf and PomDex plots look too close to support an HR of [redacted] (Belamaf vs. PomDex). The EAG was unable test this because in the economic model the EAG was unable to find KM data corresponding to the adjusted Belamaf plot.

- **C] CS Figure 31:** The line labelled PomDex is actually the line appropriate for TTD of PanoBorDex in the economic model sheet. The correct PomDex KM plot (TTD) taken from the economic model is shown below (Figure 11). Whether the quoted HR ([redacted]) applies for a comparison of adjusted Belamaf vs. PanoBorDex, or a comparison of adjusted Belamaf vs. PomDex is unclear. The former seems more likely.

TTD=time to treatment discontinuation POMDEX= Pomalidomide and dexamethasone
Belamaf= belantamab PanoBorDex= Panobinostat with bortezomib anddexamethasone

Figure 11 KM plots for TTD (data from submission economic model)

3.5.2.3 Relevant studies since submission which highlight gaps in the evidence

The CS states that in the absence of *"head-to-head studies comparing Belamaf to PomDex"* and of "*4L+ post-progression survival data"* the CS considers the NCRAS study "*the only source*" of *"comparative efficacy evidence".* Since the CS was produced, additional data from a head to head comparison of Belamaf versus PomDex has become available (DREAMM-3) and 4L+ studies have been published: of Isatuximab with PomDex[26], and of Panobinostat with bortezomib and dexamethasone[27]. In addition, the EAG searched for studies of PomDex comparing the effect of PomDex vs. placebo or vs. no POMDEX.

The EAG recognise that this did not form part of the original submission, but have included this information for completeness below:[24 25 28 29 30 31 32 33]

3.5.3 The DREAMM-3 study

Subsequent to the CS, results from the DREAMM-3 study became available in the public domain. In this RCT 325 participants who had received at least 2 prior lines and were dual class refractory

(to a proteasome inhibitor and to immune-modulator Lenalidomide) were randomised 2:1 to Belamaf or PomDex. The primary outcome was PFS with a primary completion date of September 2022; secondary outcomes included OS and ORR. The EAG have combined the publicly available DREAMM-3 results in

Table 20 together with values from DREAMM-2 and the NCRAS POMDEX studies. A press released is included in the APPENDIX.

Table 20 Median (95% CI) months reported for outcomes DREAMM-2, DREAMM-3, and NCRAS

Outcome	DREAMM-2 [1, 2] Belamaf	DREAMM 3 Belamaf	DREAMM 3 PomDex	NCRAS PomDex
OS	[redacted]	21.2	21.1	[redacted]
PFS	[redacted]	11.2	7.0	[redacted]
PROXY PFS	[redacted]	NA	NA	[redacted]
Differences between OS medians DREAMM-3 vs. DREAMM- 2 / NCRAS				
BELAMAF D3 vs BELAMAF D2		21.2 – [redacted] = [redacted]		
POMDEX D3 vs. NCRAS POMDEX		21.1 – [redacted] = [redacted]		
Differences between OS medians BELAMAF vs POMDEX				
D2 BELAMAF vs. NCRAS POMDEX		[redacted]		
D3 BELAMAF vs DREAM3 POMDEX		21.2 – 21.1 = 0.1		
Note: the populations in the three studies were not aligned with each other				

As far as medians are concerned the major difference between DREAMM-3 arms and the CS naïve comparison of DREAMM-2 [1, 2] versus NCRAS is that the former generates a meagre 0.1 months advantage for Belamaf but the latter generates a larger [redacted] months advantage.

No significant effect was observed for the primary outcome (HR [redacted]), possibly bringing into question EMA licensing and the FDA fast-track licencing of Belamaf for RRMM. PFS medians were reported as 11.28 and 7.0 months (Belamaf vs. PomDex respectively); this difference may reflect some unequal distribution of prognostic factors between arms. Similarly, barely differing OR rates of 41% and 36% (Belamaf vs. PomDex respectively) with “deeper response” for Belamaf may also reflect slightly unequal distribution of prognostic factors between arms. OS data was relatively immature with HR 1.14 (95% CI: 0.77, 1.68) and median survival of 21.2 months (Belamaf) and 21.1 months (PomDex), results that are consistent with those for PFS and OR.

3.5.3.1 Real world UK studies of 4L+ treatment

The EAG identified two recent real world studies[26, 27] which have reported outcomes for UK patients receiving 4L+ intervention, PanoBorDex[27] and IsaPomDex[26]. The former study provided median overall survival but no KM analysis; in this study patients were elderly (median 72 years) and had received a median of four prior therapies. Figure 12 shows the median survival reported together with KM plots for NCRAS. Note, all data was derived from single arm studies.

Figure 12 Median (95% CI) survival in the study of Maouche et al. together with the KM plots for NCRAS POMDEX.

Patients in the single arm study of Djebbari et al 2022 in UK patients who had previously received at least 3 lines of treatment including a PI and an ImiD, received anti-CD 38 treatment (IsaPomDex). Patients who progressed after anti-CD38 treatment and have completed 4 lines of treatment are now considered TCR. Following progression, patients are then TCR and in their 5L of treatment as are NCRAS PomDex and DREAMM-2 [1, 2] patients. This population might offer an alternative proxy-control group to that used in the CS; like the PomDex proxy control there will be differences between such a proxy population and that in DREAMM-2 [1, 2].

OS and PFS KM plots from Djebbari et al., are shown in Figure 13 (A) together with the OS KM for NCRAS POMDEX and Weibull models of these in Figure 13 (B, C). By coincidence, Weibull models for Djebbari PFS and NCRAS OS are almost identical. Survival after progression on anti-CD 38 therapy (i.e., of TCR patients in 5L therapy) can be estimated by the difference between the

Djebbari OS and PFS Weibull models and is shown in Figure 13 together with the Weibull model for NCRAS OS. Weibull models of 5L are very similar; post progression treatment in Djebbari et al was not mentioned; there may have been no further interventional treatment and thus no associated drug.

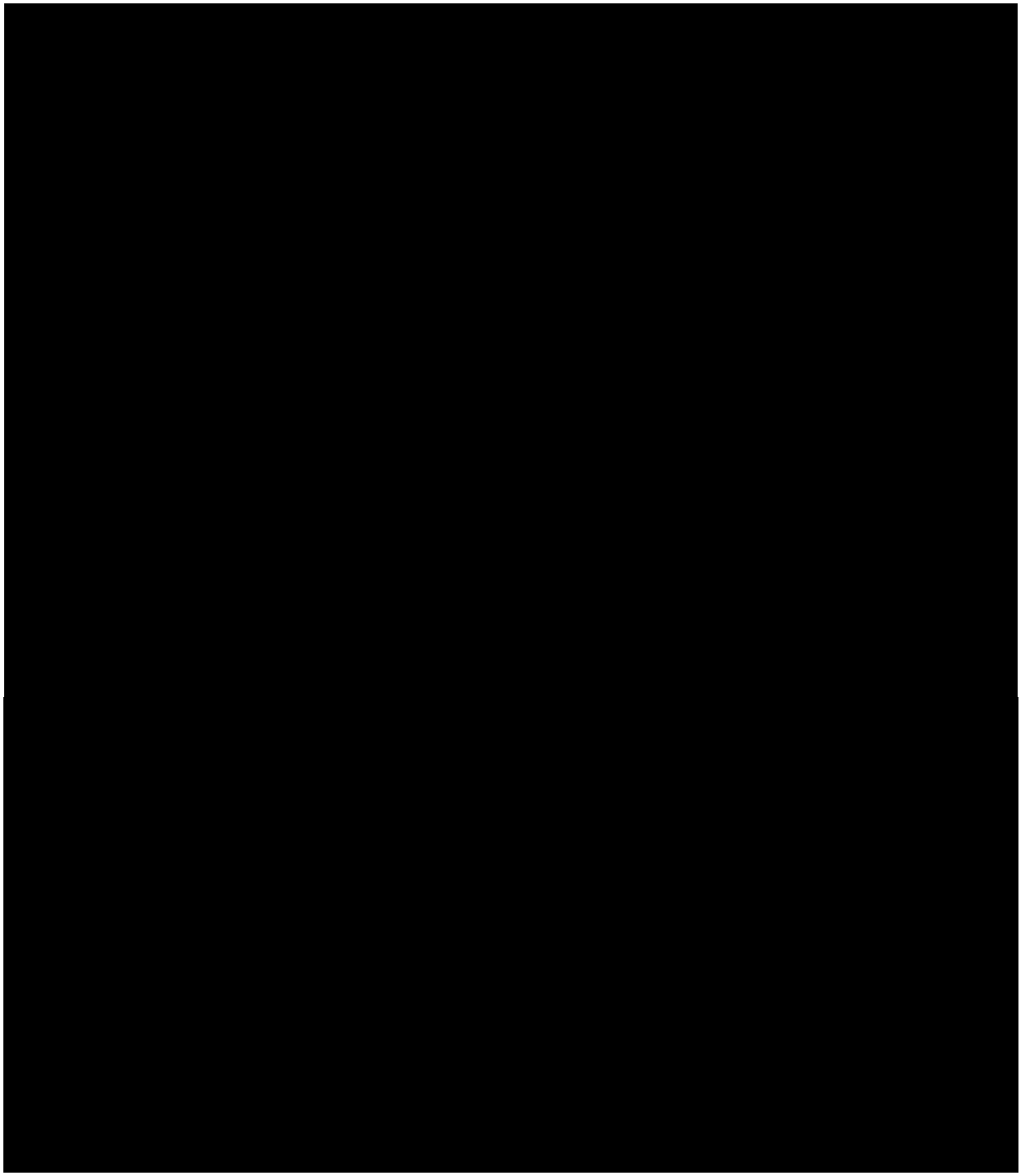


Figure 13 KM and Weibull models: NCRAS and Djebbari et al.

3.5.3.2 OS reported in POMDEX studies

Because the CS's NCRAS study of PomDex lacked a control arm it was not possible to reliably allocate the observed survival to an effect of PomDex. The EAG therefore, looked for studies in RRMM in which PomDex was compared with a placebo or a no treatment arm. The EAG was unable to identify any such study amongst those listed in the CS or amongst those included in Network Meta-Analyses of treatments for RRMM[28, 29]. Davies et al. 2022 list the studies included in the network (see Table 1 in Davies et al.) identifying intervention and comparators. Placebo was not a comparator in any included study; in all but two of the network studies, the comparator was dexamethasone in combination with another drug, in two bortezomib alone was the comparator. On the basis of this meta-analysis the EAG cannot conclude that PomDex is effective, because it has not been shown equivalent or better than a comparator known to be superior to no treatment / placebo.

Studies of PomDex were either: a) single arm (e.g.[32]), or b) compared different dose regimens of PomDex, (MM 030) or c) compared PomDex vs Pom alone,[31] or d) randomised studies in which drug D + PomDex was compared to PomDex alone. In these PomDex either delivered less survival than D + PomDex (e.g. as in the ICARIA MM RCT[33]) or more survival (as in Keynote 183

study[30]). In no studies, is it possible to reliably allocate an effect due to PomDex and what would have happened without PomDex. The largest PomDex study the EAG found was the MM 010 STRATUS single arm study with 682 RRMM patients,[32] the median number of priors was 5. Table 21 compares participant demographics in MM 010 STRATUS with those from CS Document B Table 11 for NCRAS.

The MM 010 STRATUS population is younger (46% < 65 years vs. [redacted]%, and 12.8% >75 vs. [redacted]%), and less ill (ISS I-II 60.7% vs. [redacted]%, and ECOG 0 to 1 90% vs. [redacted]%, and ECOG >1 10% vs [redacted]%). NCRAS patients were TCR while MM 010 likely dual refractory with no previous exposure to a CD 38 inhibitor.

Figure 14 shows the KM plot from MM 010 STRATUS and that for NCRAS. The 95% CIs largely overlap, and plot trajectories are similar with MM 010 delivering superior estimated survival. Like the NCRAS study there was no control arm in MM 010 STRATUS so that the proportion of survival that can be allocated to a specific effect of PomDex is uncertain. Figure 15 shows Weibull models fit to each.

Table 21. Demographic characteristics NCRAS POMDEX and MM 010 STRATUS studies

	NCRAS (N=[redacted])	**MM 010 Stratus (N=682)**
Male	[redacted]	59%
Age (years), n	[redacted]	66 (37-88)
Age Group (years), n (%)		
<18	[redacted]	
18 to <65	[redacted]	< 65 46%
65 to <75	[redacted]	65 to <75 41.2%
75	[redacted]	>75 12.8%
ISS staging system, n (%)		
I	[redacted]	
II	[redacted]	I II 60.7%
III	[redacted]	III 34%
Un-staged*	[redacted]	Missing 4.7%
ECOG performance status, n (%)		
0	[redacted]	
1	[redacted]	0- 1 90%
2	[redacted]	2- 3……10%
3-4	[redacted]	
Unknown*	[redacted]	
Prior therapy exposure, n (%)		
PI	[redacted]	PI 100%
IMiD	[redacted]	IMiD 100%

Len	[redacted]	Len 100%
Anti-CD38	[redacted]	Anti-CD38. NR/0%

…

Figure 14 KM plot OS NCRAS and reconstructd KM plot MM 010 STRATUS

…

Figure 15 Weibull models of OS in NCRAS and in MM 010 STRATUS

ICARIA MM RCT[33] compared Isatuximab + PomDex (vs. PomDex). Figure 16 shows the KM OS plots for the whole ICARIA PomDex population and for the 4L+ line subgroup, together with the OS KM plot for the NCRAS PomDex study. The 4L+ subgroup has poorer survival indicating an unsurprising strong relationship between line of therapy and survival. It should be noted that the 4L+ subgroup data is relatively immature and that naïve comparison with NCRAS would ignore prognostic differences between populations.

…

Figure 16 KM OS plots for the whole ICARIA POMDEX population and for the 4L+ subgroup

3.5.3.3 Estimation of "specific effect" of Belamaf and PomDex on OS and PFS

Although there is no evidence presented in the CS to determine the proportion of modelled OS that may be attributable to Belamaf or to PomDex, it is possible to explore the potential impact of assumed proportions based on DREAMM-2 [1, 2] and the NCRAS study. The EAG recognises that this is a naïve approach, but it seems acceptable in the context of the submission's naïve comparison between Belamaf and PomDex. The CS scale parameters of Weibull models for OS and for PFS were adjusted so that the AUC for survival curves was varied. This has allowed exploration of scenarios in the economic analysis (see Section 5.4).

3.5.4 Conclusion of EAG additional work and exploration

In summary, Section 3.5 has highlighted and reinforced several deficiencies in the CS which the EAG considers of prime importance for decision makers. These are summarised below:

1. **The submission fails to present evidence that demonstrates that Belamaf is a clinically effective intervention.** This is because:
    a. The DREAMM-2 trial lacks a control arm; so that it is unknown whether estimated outcomes are caused by the intervention or would have happened anyway in the absence of Belamaf intervention. Any assumptions regarding causation are associated with very considerable uncertainty.
    b. The DREAMM-3 trial is the only available randomised comparison of Belamaf and the proxy-comparator PomDex in a 3L + Len and PI exposed population. It indicates a lack of clinical superiority for Belamaf versus PomDex in any outcome.

2. **The proxy-comparator PomDex based on NCRAS data is not a valid comparator for Belamaf.** This is because:
    a. There are important differences between the two populations regarding prognostic factors. And data on multiple prognostic factors is missing from the NCRAS data base. Furthermore, population differences remain even after matching was undertaken (see Section 3.3.6).
    b. The lack of a control in the NCRAS database means that it is unknown to what extent outcomes are caused by intervention with PomDex and what would have happened without PomDex. Additional studies from outside the CS do not provide any convincing evidence that PomDex is clinically effective.
    c. The NCRAS data for PomDex appears unlikely to represent NHS practice because the intervention appears rarely used within the NHS at this stage of disease and because the sample used in the CS is unlikely to be representative of UK recipients of 5L therapy for TCR patients.

3. **The proxy-PFS (TTNT) is unlikely to have been equitably estimated for Belamaf and PomDex**.
    a. This because in the DREAMM-2 trial, only [redacted] UK patients received the 2.5 mg/kg regimen while the remaining patients were scattered through many jurisdictions where time to acquisition of next treatment is subject to different local exigencies, whereas all patients in the NCRAS data base were UK patients subject to UK exigencies.

In summary, the EAG consider that for the reasons described above, the naive comparison undertaken in the CS lacks validity and should not be used for an economic analysis. In particular, the two studies included as clinical evidence (DREAMM-2 and NCRAS) both lack a control, and their populations are likely to differ regarding prognostic factors. This is associated with very substantial uncertainties that are impossible to adjust for or calibrate in a meaningful way, this thereby likely invalidates the cost-effectiveness results presented by the company (see Section 5.1).

3.6 *Conclusions of the clinical effectiveness critique*

The CS decision problem generally matched the decision problem for the technology of interest, regarding the population, comparators, and outcomes as defined in the NICE's final scope. However, the EAG have concerns regarding the appropriateness of the comparators in the context of the NHS.

The CS clinical effectiveness section consists of an SLR (updated to August 2022) conducted by the company, IPD from the DREAMM-2[1, 2] randomised trial (Document B, Section B.2.3.1),[1, 2] and the NCRAS aggregate dataset (Document B, Section B.2.3.2 and Appendix O).[19] The clinical effectiveness evidence focuses on a single arm of DREAMM-2[1, 2] using IPD for Belamaf 2.5 mg/kg (the licensed dose of the technology of interest) and the company-conducted England-based RWE observational study of the eligible comparator intervention (PomDex, PanoBorDex) provided by the NCRAS aggregate dataset. Both sets of data sources were comprised of 5L+ TCR MM patients.

- Additional details of DREAMM-2[1, 2] and the NCRAS dataset studies are provided in Sections 3.2.1 and 3.2.2.
    - Briefly, DREAMM-2[1, 2] was a phase II, multicentre open-label randomised two-arm trial to investigate the efficacy and safety of two doses of Belamaf (2.5 mg/kg IV Q3W and 3.4 mg/kg IV Q3W) in patients with RRMM. DREAMM-2 was not designed to compare the two doses of Belamaf but to investigate efficacy and safety in the two different doses used.
    - Most domains of this trial were assessed to be rated as 'low risk of bias', although it should be noted that this trial did not have a relevant and appropriate comparator arm and was an open-label study. Therefore, knowledge of the treatment assignment could have influenced subjective outcome assessments (for example, response to treatment).
    - The NCRAS dataset has a number of uncertainties across methodological domains (no specific hypothesis, loss to follow up data, absence of efficacy response data, no safety data, and representativeness of a wider UK patient population).

The EAG did not identify any major concerns in regard to the methodology of the company's SLR searches and study screening process (i.e., inclusion/exclusion) which would alter the results of the SLR.

- The SLR concluded that DREAMM-2[1, 2] was the only experimental study that evaluated clinical efficacy and safety of Belamaf for the treatment of 5L+ TCR MM patients. However, the other arm of this trial (Belamaf 3.4 mg/kg) was not a relevant comparator.
- The SLR did not identify any experimental or observational study that would provide clinical efficacy/safety evidence for the eligible treatment comparator (PomDex or PanoBorDex) in 5L+ TCR MM patients.
- The company conducted an RWE study using the NCRAS dataset in order to generate the comparator clinical efficacy evidence.

In the absence of head-to-head comparison of Belamaf 2.5 mg/kg to the relevant comparator, the company considered ITC methodology to compare the efficacy of Belamaf 2.5 mg/kg from DREAMM-2[1, 2] IPD to that of PomDex (or PanoBorDex) from the NCRAS dataset. Since there was no common comparator (i.e., anchor) to connect the two treatments, the company chose to

conduct an unanchored MAIC analysis which would allow the adjustment for cross-study differences in the distribution of important patient baseline characteristics.

3.6.1 Interpretation of MAIC results

The MAIC indicated that Belamaf was associated with a statistically significant difference in TTD compared to PomDex (HR=[redacted] 95% CI[redacted]). Although there was no difference in OS (HR=[redacted] 95% CI: [redacted]) and TTNT (HR=[redacted] 95% CI: [redacted]) as these HR estimates had a high degree of uncertainty in terms of rather wide confidence intervals. Belamaf compared to PanoBorDex was associated with a statistically significant [redacted] in OS (HR=[redacted] 95% CI[redacted], TTNT (HR=[redacted] 95% CI: [redacted]), and TTD (HR=[redacted] 95% CI: [redacted]).

The ERG suggests that these MAIC HR estimates for OS, TTNT, and TTD should be interpreted with caution given the small samples and implausibly large magnitude of HRs in favour of Belamaf.

The EAG considers that the NCRAS dataset is an inappropriate source of comparator data given the incongruence/non-comparability of the DREAMM-2[1, 2] trial IPD and the NCRAS dataset regarding the following:

- Study design and study aims/purpose: DREAMM-2[1, 2] IPD is multicentre, randomised controlled trial-based, whereas the NCRAS dataset is an England-based, retrospective, non-interventional RWE study.
- There is little overlap between the two data sources with respect to the distributions of important patient baseline characteristics (treatment effect modifiers and/or prognostic factors).
    - This could be partially due to different inclusion/exclusion criteria used in the two data sources.
    - The cross-study differences in clinical factors persisted even after DREAMM-2[1, 2] IPD was adjusted and matched to NCRAS dataset as evidenced by the very low ESS=[redacted].

- The NCRAS dataset excluded [redacted] PomDex RRMM 5L + TCR patients treated with CDF-funded drugs at any time during their entire treatment history, leaving a rather small sample in the NCRAS dataset (PomDex n=[redacted] and PanoBorDex n=[redacted]) that could be analysed.
    - Therefore, the EAG conclude that this dataset is unlikely to provide a representative comparator relevant to the UK practice settings for this line of treatment.
- Unlike the DREAMM-2[1, 2] trial, the NCRAS dataset did not provide response rates. Thus, there is no evidence to confirm if PomDex induces any response at all (according to the International Myeloma Working Group) in RRMM 5L + TCR patients.
- The only efficacy data reported by the company (KM curves for OS, TTNT, and TTD) does not determine the comparator's efficacy response (for example on OS) relative to no intervention or placebo in this patient population.

In addition to the lack of overlap between the two datasets, missing values for some patients or completely unavailable data for the important baseline factors in NCRAS dataset, precluded adequate matching in the MAIC analysis for these factors. As a result, the unanchored MAIC was adjusted for only three factors (age, extramedullary disease, and number of prior lines of treatment). Furthermore, some outcome definitions were different across the two sources.

Finally, the EAG suggests that the feasibility of MAIC was undermined because the requirement to account for all effect modifiers and prognostic factors in an unanchored MAIC was not satisfied. Close location of the Belamaf and PomDex KM curves for OS and TTNT do not give strong support to the observed large magnitude of benefit of Belamaf over PomDex for OS (HR=[redacted]) and TTNT (HR=[redacted]) reported in the CS which appear implausible.

3.6.2 Overall limitations in evidence and uncertainties

- Given the CS, the evidence base is incomplete to allow an adequate comparative effectiveness assessment of the technology of interest.
    - Specifically, the SLR did not identify a head-to-head comparative study that compares Belamaf to an appropriate comparator treatment in RRMM 5L + TCR patients. The DREAMM-3 trial which evaluates safety/efficacy of Belamaf compared

to PomDex in 3L+ Len and PI exposed MM patients has recently reported null results (see Section 3.5.3).

- There is a lack of studies which demonstrate the effectiveness of the eligible treatment comparator (PomDex or PanoBorDex) in RRMM 5L + TCR patients.
- In the absence of connected networks (i.e., lack of common comparator), the company conducted an unanchored MAIC using the comparator data (PomDex or PanoBorDex) from NCRAS-based RWE study.
    - The feasibility of a valid MAIC was undermined from the outset given the limitations of NCRAS dataset, missing/unavailable data, and other important differences between the DREAMM-2[1, 2] IPD and NCRAS dataset.
    - The HRs for Belamaf vs. PomDex (or PanoBorDex) likely suggest overestimated clinical benefits in OS, TTNT, and TTD in favour of Belamaf.
- The MAIC analysis did not compare the safety profiles of Belamaf and PomDex (or PanoBorDex) in RRMM 5L + TCR patients, since the NCRAS dataset did not report adverse event data.

Taking all information into account, the EAG consider that both the MAIC analysis and the naive comparison of Belamaf versus PomDex undertaken in the CS lack validity for an economic analysis. The EAG suggests that all results reported in the cost-effectiveness section be interpreted with great caution as they are likely to be implausible.

4 COST EFFECTIVENESS

This section provides the EAG critique on the cost-effectiveness evidence submitted for this appraisal. Due to the limitations of the evidence presented in the CS (critiqued in the clinical effectiveness Section 3.6), the EAG do not present alternative scenario analysis to account for these limitations.

EAG preferred assumptions to the company base case are presented in Section 5.4.3 and impacts on the cost-effectiveness results (including the ICER) are presented in

Table 33.

4.1 *EAG comment on company's review of cost-effectiveness evidence*

The CS provided the details of three SLRs on Health-Related Quality of Life (HRQoL), resource utilisation and costs, and cost-effectiveness analysis for treating RRMM patients who received at least three prior lines of therapy (4L+ RRMM). The details of the SLR can be found in the CS appendices G (for cost-effectiveness evidence), H (HRQoL), and I (resource utilisation and cost).

The initial search strategy was conducted on July 23 2019, and was updated on August 10th 2022. Similar to the clinical effectiveness SLR (see Section 3.1.1), the original (2019) and updated (2022) SLRs are reported differently, across the different appendices, with the updated searches undertaken and reported alongside the clinical effectiveness update in CS Appendix D. It is, therefore, quite difficult for the EAG to track the process of searching and identification of relevant studies through the various SLRs.

4.1.1 Search strategies

The company's search includes retrieved evidence from MEDLINE, Embase and grey literature (encompassing both conferences and organisations/authorities). The CS provides the details of inclusion and exclusion criteria. The EAG has some concerns in terms of the search methodology. There are several features of the search strategies (CS Appendix G.2, Tables 4-10, and Appendix D.1.1, Table 7) that suggest the searches were not fully comprehensive. For example, MeSH/Emtree terms for relapsed and refractory are not used.

The economic evaluations, cost, and resource use searches (CS Tables 4 and 5) use filters for both outcomes and study design, which risks missing some studies by over-narrowing the search. The filter used for HRQoL outcomes (CS Tables 6 and 7) only searched title and abstract field of records and does not use any thesaurus (Emtree/MeSH) terms such as "Quality Adjusted Life Year", "Health Status Indicator". The EAG recommends using published and/or tested search filters such as those listed on the ISSG Search Filters Resource.[34] Additionally, the SLR update searches run in August 2022 is not a true update of the original searches reported in CS Appendix G.2, as Embase and MEDLINE are searched together via a different interface (Embase.com, rather than Ovid).

In conclusion, despite these methodological concerns, the EAG considers that the economic studies most relevant to the context of this appraisal have been identified and presented in the economic evaluation SLRs.

4.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

The company's economic evaluation is limited by two major uncertainties which are unlikely to be addressed in this appraisal and EAG report.

1) The lack of availability of an appropriate comparator for Belamaf either via well-designed head-to-head studies or by ITC. The EAG note that both comparators included in the CS (PomDex and PanoBorDex) were selected and aligned to the NICE Final Scope (see Table 4) and included in the treatment pathway (see Error! Reference source not found.) for 4L+ onward treatment.[7, 8]

   - As outlined in Section 3, (explored in detail in EAG additional analysis Section 3.5) the EAG conclude that there is no available evidence which determines the efficacy of PomDex or PanoBorDex.

   - The company's approach to using a proxy-control group through the NCRAS RWE study does not address the problem of determining the attributable effects of PomDex (detail provided in 3.4). This stems from the lack of availability of a control group in the NCRAS, and the variety of demographic and clinical characteristics of the patients which are not comparable between datasets (see Table 11).

   - The EAG agrees with the company, that the results of the CS unanchored MAIC analysis would further constrain the cost-effectiveness analysis in terms of the very low numbers of patients in the analysis ([redacted] patients) (see Section 3.3.4).

   - The EAG describe the problems of selecting PomDex as an effective drug for such highly pre-treated patients (5L of the treatment) (3.5.1.3). As supported by EAG clinical experts. Briefly, there is no direct evidence to suggest the comparator (PomDex) provides additional benefits for patients.

2) The second problem is related to the Belamaf source of data, which is the DREAMM-2 trial. The trial evaluates two different doses of the drug with no control group, therefore **the pure effect of Belamaf cannot be determined** (as discussed in detail in Section 3.2.1).

- The DREAMM-2 study is a small trial (n=[redacted]) and the response rate for Belamaf (considering the partial responses) is [redacted]. In addition, it appears that the patients in DREAMM-2 trial have unusually high level of quality of life for such a heavily pre-treated cohort (as confirmed by EAG clinical advice) (the utility value for the PFS equals [redacted]).

- Although the utility weight used is the same for the treatment regimens, the company has assumed that the utility would be independent of the treatment regimen. This assumption would prevent the analysis capturing the true effect of Belamaf, PomDex, and PanoBorDex. This would assume the difference between Belamaf and the comparators' effectiveness is only related to the survival differences. As previously mentioned, both PomDex and PanoBorDex are limited to very short-term benefits because these drugs are not assumed to be the SoC for patients requiring 5L of the treatment.

- The company attempted to explore the uncertainty around the utility values in the one-way sensitivity analysis (OWSA) (CS Figure 50, page 153). However, because of assuming independence of utility from the treatment regimen; the changes in OWSA in effect constitute a circular argument, reporting the same level of changes again, therefore, it seems not possible to observe a situation in the analysis where PomDex provides more QoL as compared to Belamaf.

For reasons 1 and 2 above, the EAG suggests that the results of the ICERs presented in this section should be interpreted with extreme caution, despite the statistical and computational approaches applied in the CS cost-effectiveness analysis which were otherwise appropriate

4.2.1 NICE reference case checklist

The EAG assessment against the NICE reference case checklist is presented in

Table 22. Key concerns are highlighted in BOLD.

Table 22 NICE reference case checklist

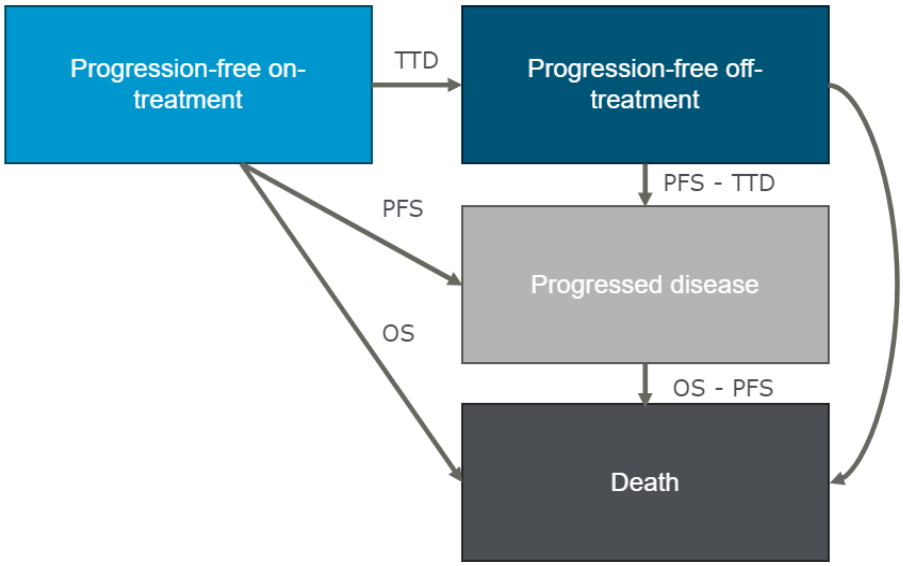
Element of HTA	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
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.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	**No.** **The source of the data for QoL of the comparators is DREAMM-2 which is a dose-response trial for comparing Belamaf 2.5 mg/kg with 3.4 mg/kg.** **The company assumes that QoL is the same for all strategies.**
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	**No.** **The company uses Proskorovsky's[35] mapping algorithm to convert the EORTC-QLQ-C30 and MY20 to EQ-5D. This study used the UK's value sets which were used to calculate health utility for all patients.** **However, the population used was a combination of people from Germany (n=65) and the UK(n=89). Therefore, has questionable representativeness to a UK sample.**
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes

Element of HTA	Reference case	EAG comment on company's submission
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
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 used a four-state cohort-based partitioned survival modelling approach. The health states are Progression Free Survival (PFS) on treatment (on- treatment), PFS off-treatment (off-treatment), Progressed Disease (PD), and Death. The off-treatment state is applied to patients who have withdrawn from treatment before the disease has progressed. The company also considered a four-state model structure which did not distinguish between on and off-treatment for the PFS health state. The company explored the structural uncertainty through a scenario analysis presented in the CS (CS Section B.3.2.2.).

Figure 32 in the CS presents the model structure (repeated in EAG Figure 17).



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

Figure 17. Diagram of model structure

The company uses the Area Under Curve (AUC) which is derived from the survival curve to capture the time spent in PFS and OS. The CS partitioned survival is summarised in CS Document B Figure 33. Although a pre-specified ITT analysis of ICR-assessed PFS in DREAMM-2[1, 2] was undertaken (CS Figure 11) this was not used in the economic model.

Rather than model ITT PFS, the economic model employs a proxy for PFS (proxy-PFS) termed "time to next treatment" (TTNT). Section 3.5.1.1 of this report presents detail on TTNT and the limitations of this approach. Briefly, the EAG argue that the use of proxy-PFS rather than PFS will tend to accumulate more QALYs for Belamaf as indicated in **Error! Reference source not found.** (EAG additional analysis).

In summary;

- A partitioned survival model is appropriate for modelling the decision problem.
- The model structure is consistent with models built in this disease area and aligns with the NICE recommendation.
- The use of TTNT as a proxy for PFS introduces uncertainty into the efficacy outcomes and consequently, cost-effectiveness estimates. TTNT was not directly measured within the DREAMM-2 trial and the definitions for TTD across the DREAMM-2 trial and NCRAS datasets differed (see Section 3.5.1).
- With the proxy-PFS (TTNT) (CS Figure 19) rather than PFS, the model will tend to accumulate more QALYs (described in additional EAG analyses see Section 3.5)

4.2.3 Population

The patient population considered in the model is in line with the NICE Final Scope: *adult patients with multiple refractory myeloma who have had at least four prior treatment regimens (are at the fifth line of the treatment) plus TCR* (see Section 2.2).

As described in Section 3.2, the CS mainly relies on data from two sources: (i) the DREAMM-2 trial[1, 2] and the NCRAS dataset. The population for Belamaf comes from the DREAMM-2 trial that includes 58 locations including the US, Australia, Canada, France, Germany, Italy, Spain, UK. The population for PomDex used a real-world evidence study solely from England – the NCRAS study.

The company used a naïve (unadjusted) approach to estimate relative efficacy and cost-effectiveness of Belamaf versus PomDex in its base case analysis rather than a matched-adjusted comparison. As described in Section 3.3.2, the CS explored anchored and unanchored MAIC in an attempt to resolve the differences between the two data sources. The details on the populations' characteristics of both data sources and the comparability of each can be found in the EAG's report Sections 3.3.3.1 and 3.3.5.

- The EAG note that there are differences between the characteristics of the DREAMM-2 and NCRAS populations which could not be resolved through matching and adjusting. Although relaxing the matching procedure would be helpful to have a larger population (from n=[redacted] for MAIC to n=[redacted] for naïve/unadjusted) there are considerable differences between the populations that cannot be ignored, for example in terms of the average age and race of proportions, unavailability of weight (which is an important factor in Belamaf drug administration), unavailability of High-risk cytogenetics (% with), and also Prior stem cell transplant (% with) in the NCRAS study.

Therefore, the EAG cannot confirm the suitability of the data for the modeled population as inputs for the economic analysis. In addition, because of the absence of a control group in the DREAMM-2 trial, or in the NCRAS study, the EAG cannot quantify the benefits of Belamaf.

4.2.4 Interventions and comparators

The intervention is Belamaf, as per NICE Final scope (Table 4). Belamaf is available as a 100 mg powder for concentration solution. The recommended dose in the CS is 2.5 mg/kg administered as an intravenous infusion once every three weeks.

The company's base case compares Belamaf with PomDex, and PanoBorDex, but considers PomDex the most relevant comparator; which partly reflects the description of comparators in the NICE Final scope (see Table 4 and 3.5.1.3 for more detail). The recommended dose of pomalidomide is 4mg orally administered once daily for three weeks, followed by a week's break every four-week cycle. Dexamethasone is available in 20 mg tablets. In the CS, chemotherapy alone or combination with a steroid or thalidomide was not included as a comparator. The EAG clinical advisors agree with this exclusion (see Table 4).

The EAG argues that PomDex is unlikely to be an appropriate comparator for Belamaf. There is no direct/indirect evidence to suggest that PomDex provides additional benefits for patients. The EAG's clinical advisors suggest that PomDex is rarely prescribed in the 4L+ patients and its use is "vanishingly rare" in the 5L. Further stating "Those who have had PomDex may have been excluded from further pomalidomide treatment because of refractory disease which at this stage of the disease is going to be high, in the region of 75-80%". It appears, from EAG clinical advice, that using PomDex at the 5L of treatment is likely given as a last attempt at active treatment for patients rather than moving them onto a palliative care pathway.

In NHS practice, it seems that the effectiveness of PomDex for such heavily pretreated patients is not confirmed. As PomDex is rarely prescribed for 4L and onward. It seems that using, or not using PomDex, may not meaningfully change QoL or survival estimates, however PomDex is associated with incurred costs for treatment and administration and will therefore impact the base case ICER. Thus, in terms of the CEA, the health system incurs cumulative costs for a drug that appears ineffective for the patients at the fourth or beyond (4L+) level of treatment. In summary, the EAG cannot mitigate the uncertainty around the base-case ICER or confirm the suitability of the comparators, due to a lack of head-to-head evidence demonstrating efficacy for PomDex (as summarised in Section 3.2.3.1)

The EAG appreciates the NICE recommendations regarding inclusion of CDF reviews for other possible comparators (see **Error! Reference source not found.**); however, the Company has not presented any other valid comparator.

4.2.5 Perspective, time horizon, and discounting

The CS uses an NHS Personal and Social Services, with £30,000 willingness-to-pay (WTP), and 3.5% discount rates in line with the NICE reference case. The company applies a lifetime analysis of 25 years which is sufficient to capture extrapolated survival curves, given the modelled cohort's age. The EAG consider this appropriate.

4.2.6 Treatment effectiveness and extrapolation

The company has used the time to next treatment (TTNT) as a proxy for PFS. The EAG present critique of this proxy in Section 3.5.2. Due to the absence of head-to-head trials, and the use of

NCRAS, PFS is not reported (e.g., not included in the RWE dataset). However, the company has applied a naïve analysis based on NCRAS for conducting the cost-effectiveness analysis. PFS, progressed disease (PD), survival parameters alongside death have been traced for the time horizon (25 years). This is the same for both three and four health states in the partitioned survival analysis.

The EAG argues the company's extrapolation method by applying proxy-PFS measures does have limitations that can lead to unreliable results for ICER. Detailed critiques of the company's extrapolation method and its implications for the economic analysis can be seen in Section 3.5.

4.2.7 Health-related quality of life

The company used DREAMM-2[1, 2] utility values for capturing HRQoL and has assumed the utility values are identical between Belamaf, PomDex, and PanoBorDex.

The utility values from DREAMM-2[1, 2] have been captured by EORTC-QLQ-C30 and QLQ-MY20 and then mapped to the EQ-5D measure by applying Proskorovsky et al. 2014 trimmed version.[35] The EAG suggest that the full version of the mapping equation may provide a more realistic estimation for QoL, though the company, in response to clarification question B14, stated that based on the mapping study conclusion there is a high level of correlation between the trimmed version results and full version. However, it is not clear to the EAG, if this statement can be generalised to patients with such a high pre-treatment profile, as is the case with this patient population.

The company's utility values by health states [redacted] for on-treatment patients in the PFS state, [redacted] for off-treatment patients in the PFS state, and [redacted] for patients in the PD state. These QoL quantities have been applied in the company's base-case analysis regardless of the treatment regimen.

The disutility values associated with AE have come from NICE TA510,[36] TA 369[37] and Milne RJ (2006).[38] The company also has applied a utility decrement related to age. The company disutility weights for patients who are on-treatment with Belamaf were estimated at [redacted], for PomDex [redacted], and PanoBorDex [redacted].

The company calculated the utility weights at the utility for the general population. The EAG argues such an assumption may be optimistic for heavily pre-treated patients (those with at least four prior treatment regimens). A more plausible assumption is to cap the QoL for these patients at the QoL level for patients who have experienced one relapse/refractory treatment. This was confirmed by the EAG clinical experts.

4.2.7.1 Severity modifier

In the absence of adequate data collection on HRQoL, the company used a severity modifier of 1.7x to the incremental QALYs, based on the proportional and QALY shortfall analysis (see Table 23). The company applied a severity modifier of 1.7x to the incremental QALYs, based on the proportional and QALY shortfall analysis (see Table 23). However, the weighting applied seems inconsistent with the NICE recommendations and the company's base case analysis, which is deterministic. According to NICE recommendations[39] the QALY weightings for severity should be based on the absolute and proportional shortfall, whichever implies the greater severity level (see Table 24).

Table 23 Summary of average QALY shortfall analysis (source CS Table 86)

Factor	Mean QALY in expectation	Absolute shortfall	Proportional shortfall
No disease	[redacted]	[redacted]	[redacted]
PomDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
PanoBorDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
Weighted average of real-world usage of PomDex and PanoBorDex	[redacted]	[redacted]	[redacted]

Table 24 QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
X1.2	0.85 to 0.95	12 to 18
X1.7	At least 0.95	At least 18

For the company's QALY shortfall analysis, the absolute shortfall implies that a QALY weighting of 1x should be applied, whilst the EAG considers a proportional QALY shortfall of [redacted] implies that a QALY weighting of 1.2x should be applied. As proportional QALY shortfall implies a greater severity level, the appropriate severity weighting is 1.2x. However, the company chose the highest

severity weight and justified the decision on two grounds: (i) that the 95% confidence interval [i.e., [redacted] includes both the 1.2x and 1.7x multiplier; and (ii) PSA results showed that 1.7x severity modifier could be applied to approximately [redacted]% of patients.

The EAG argues that for the company's deterministic base case analysis, the correct weighting (for severity weighted QALYs) should be based on the point estimate ([redacted] rather than 95% CI or results of the PSA. Applying severity weighting to a deterministic analysis based on confidence intervals will bias QALY gains in favour of the intervention, particularly when results are highly uncertain and confidence intervals wide.

The EAG applies a severity weight of 1.2x to incremental QALY gains (see preferred assumptions

Table 33). However, this change does not impact the base case ICERs derived from unadjusted (non-severity weighted) QALYs.

4.2.8 Resources and costs

The company adopted an NHS and PSS perspective for costing, which is in line with the NICE reference case (

Table 22). A variety of sources were used to identify and measure the costs. The company also conducted a purposive SLR of cost and healthcare resource utilisation (see Section 4.1). The company used the currency codes from the NHS reference cost, uplifted costs from the previous NICE TAs[7, 40], the British National Formulary (BNF),[41] and Personal Social Services Research Unit (PSSRU) 2021 costs.[42] If data for resources use and attributed costs were not available, the company used assumptions following consultation with their clinical advisors.

In clarification, the EAG raised concerns about the sources of costs and how the company has captured the costs, when there are multiple currency codes for a health condition. The company provided reasonable citations and explanations to clarification questions and made some updates in the costs. The company applied revised costs in their updated analysis (post-clarification) which can be found in the CS Appendix A which accompanies the company's clarification responses. The EAG confirm that these changes did not have a meaningful impact on the base-case ICER results.

The cost components in the CS and the EAG critique are provided below:

4.2.8.1 Drug acquisition costs

The company used the BNF and the Summary of Product Characteristics (SmPC) for calculating acquisition costs of Belamaf and PomDex. The recommended dose of Belamaf is 2.5 mg/kg which is administered by intravenous infusion once every three weeks. The company has offered a [redacted] confidential simple Patient Access Scheme (PAS) discount. At a list price of £5,707.83 for 1 vial of 100 mg powder for concentration solution. This results in a PAS price of [redacted]. The PAS price per dose calculated according to the DREAMM-2 trial[43] with dose delay, modeled through the company's relative dose intensity value is [redacted]. The company assumes 50% wastage in a scenario analysis. The company states that due to current NHS practice and their clinical advisors' opinion, this is clinically plausible. The current acquisition costs for Belamaf at the list price is £[redacted], which at the PAS price will be £[redacted].

For PomDex, the EAG agrees with the company's calculations for acquisition costs, at a dose of 4 mg for Pomalidomide and 20 mg for Dexamethasone, and the administration form of both drugs.

In the absence of information on the dose received in NCRAS, the company used the data from the MM-010 trial.[32] The acquisition costs for PomDex are based on the list price of Pomalidomide as the company was not aware of the PAS price, therefore, the weekly acquisition cost for Pomalidomide used was £2,668.16 (3 weeks on, 1-week break) and £3.60 for Dexamethasone.

4.2.8.2 Administration costs

The company applied no administration cost for the PomDex and used the appropriate calculation for the administration costs for Belamaf. The EAG agrees with the administration cost calculations. The administration cost for Belamaf was split into two parts: the first infusion at week one with a price of £[redacted], and the subsequent administration cost (applied for week 4+) for £[redacted].

4.2.8.3 Routine monitoring unit costs

The company assumed that routine monitoring costs are the same for all strategies and applied unit resource use and subsequent unit cost for each health state. The company states that this is the approach in the NICE TA510.[36] For each health state, unit costs have been computed for a physician visit, complete blood count test, and blood chemistry. The EAG agrees with the source and calculations that the company used.

4.2.8.4 Adverse reaction unit costs and resource use

The company applies the attributed costs to the AEs only for those AEs at Grade ≥3 as it expects only AEs at this grade to incur costs. The company uses the DREAMM-2 trial as the source of AEs for Belamaf and MM-010 for PomDex.

The main AE experienced by patients taking Belamaf is keratopathy which can be mild, moderate, or severe. Patients with mild/moderate keratopathy are assumed to visit an ophthalmologist (including an ophthalmic examination with visual acuity and slit lamp examination) every 3 weeks during an event. In contrast, patients with more severe keratopathy are expected to visit an ophthalmologist every week until the resolution of the event (assumed to take up to 5 weeks). Furthermore, those with mild/moderate keratopathy are assumed to need 1 pack of 10 ml eye drops (4 drops [0.05 ml] per eye per day) whereas patients with severe keratopathy are assumed to need 5 packs of 10 ml eye drops (1 drop [0.05 ml] in each eye every two hours during the event).

Unit costs for all other AEs were sourced from the 2020/21 NHS Reference Costs. The total costs of keratopathy are £170.22 for mild and moderate, and £851.10 for severe conditions. The EAG agrees with the costing sources and methods.

4.2.8.5 End of Life costs

The end-of-life cost has been calculated based on the approach in NICE TA427.[7] The calculation was uplifted according to the Personal and Social Service Research Unit (PSSRU) 2021[42] The company has reached an end-of-life care cost of £6,834. The EAG agrees with these cost and uplifting methods which have been used in the company's submission.

4.2.8.6 Concomitant therapies and supportive care

The company included the costs of granulocyte stimulating factor (GCSF), red blood cells, and platelet transfusions. The company states that their approach to this draws on NICE TA510 and TA783.[36, 40] The proportion of patients receiving transfusions and GCSF treatments for Belamaf and PomDex was based on expert clinical opinion and the MM-010 trial, respectively.[32]

The one-off costs for the supportive care were £[redacted] and £[redacted] for Belamaf and PomDex, respectively.

Estimated costs for concomitant therapies were £[redacted] and £[redacted] for the first year and subsequent years respectively, in the Belamaf strategy. This amount was £141.33 for the PomDex strategy. The EAG were unable to confirm whether the proportion of patients receiving each subsequent regimen is reflective of NHS clinical practice, as practice is not standardized. The EAG welcome clinical opinion during Technical Engagement/committee meeting.

4.2.8.7 Subsequent therapies

The company has used two lists of subsequent therapies for Belamaf and PomDex. These are presented in Table 25 and Table 26 below.

Table 25. Subsequent therapies Belamaf

Subsequent regimen	Proportion of Belamaf patients switching, re-weighted (%)
Chemotherapy	[redacted]

Steroids	[redacted]
Bortezomib (IV)	[redacted]
Pomalidomide	[redacted]
Lenalidomide	[redacted]
Thalidomide (oral)	[redacted]
Other	[redacted]

Table 26 Subsequent therapies PomDex

Regimen	**6L – Following PomDex treatment**
Bortezomib Panobinostat	[redacted]
Melphalan Thalidomide	[redacted]
Cyclophosphamide	[redacted]
Melphalan	[redacted]
Bortezomib	[redacted]

The summary of one-off subsequent treatment is presented in

Table 27.

Table 27 on-off subsequent treatment

Index treatment	Subsequent treatments received	Subsequent treatment one-off cost (£)
Belamaf	[redacted]	[redacted]
PomDex	[redacted]	[redacted]

The proportion of patients receiving transfusions and GCSF treatments for Belamaf and PomDex was based on company expert clinical opinion. The EAG's clinical advisor agrees that the proportions used for costing are reasonable.

5 COST-EFFECTIVENESS RESULTS

5.1 *Company's cost-effectiveness results*

The results for the company's base case deterministic cost-effectiveness analysis are presented below (CS appendix A for the clarification responses table 3) EAG Table 28. Note, this table presents the company's revised base case deterministic cost-effectiveness results (post-clarification stage).

Table 28 Deterministic base-case results for Belamaf versus PomDex

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs without Severity	Incremental QALYs with Severity	With ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
PomDex	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**	**Dominating**
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years									

The baseline QALYs and severity weighted QALYs were [redacted] and [redacted] respectively. Since Belamaf, is cost-saving, the resulting ICERs suggest that Belamaf is the dominant strategy compared to PomDex.

5.2 *Company's sensitivity analyses*

The company presented both One Way Sensitivity Analysis (OWSA) and PSA.

5.2.1.1 OWSA Company one way sensitivity analysis

The OWSA results have been presented only for PomDex against Belamaf (PanoBorDex against Belamaf in CS appendices). The OWSA demonstrates that the main drivers of the ICER results are:

- relative dose intensity for both Belamaf and PomDex,
- Overall Survival (OS) for both Belamaf and PomDex,
- and time to discontinuation (TTD) for both Belamaf and PomDex

However, the ICER seems not to have changed in favor of the comparator (PomDex) in all those sensitivity analyses. The tabulated form of the sensitivity analysis after the clarification stage (post-clarification) can be found in the CS clarification response, Appendix A document, table 3 (and also in the EAG Table 29). The OWSA results show a positive net monetary benefit (NMB) in favour of Belamaf versus PomDex in all included parameters. The tornado graph for Belamaf vs PomDex after the clarification stage can be found in the CS clarification responses, Appendix A, figure 4 (

Figure 18 in the EAG report). For the other comparator (PanoBorDex), the OWSA shows that by changing the parameters in PanoBorDex the NMB remains constant at £[redacted].

Table 29. Tabulated OWSA results for Belamaf versus PomDex

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Pomalidomide relative dose intensity	[redacted]	[redacted]	[redacted]
Belamaf relative dose intensity	[redacted]	[redacted]	[redacted]
Belamaf - OS	[redacted]	[redacted]	[redacted]
PomDex - OS	[redacted]	[redacted]	[redacted]
PomDex - TTD	[redacted]	[redacted]	[redacted]
Belamaf - TTD	[redacted]	[redacted]	[redacted]
Utility: PD on-tx	[redacted]	[redacted]	[redacted]
Utility: PFS on-tx	[redacted]	[redacted]	[redacted]
PomDex concomitant therapies/supportive additional cost per cycle	[redacted]	[redacted]	[redacted]
PomDex - PFS	[redacted]	[redacted]	[redacted]

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis, OS, overall survival; PD, progressed disease; PFS, progression free survival; TTD, time to treatment discontinuation.

Figure 18 Tornado diagram (source CS Figure 4 Appendix A)

5.2.2 Company probabilistic sensitivity analysis

The PSA results are presented in CS table 94, which are replicated in EAG **Error! Reference source not found.**. Incremental QALYs without severity adjustments were [redacted], with severity adjustments applied, this changed to [redacted].

Additional PSA results were generated post clarification in the company's responses to clarifications, Appendix A, table 4. These are replicated below in Table 30.

Table 30. PSA base-case results for Belamaf versus PomDex

Tech.	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs Without Severity	Incremental QALYs With Severity	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
PomDex	[redacted]	[redacted]	[redacted]	-	-	-	--		
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

The related cost-effectiveness scatter plot after clarification phase for the severity modifier can be seen in the company's clarification responses Appendix A, figure 1, EAG Figure 19.

[redacted]

Abbreviations: PSA, probability sensitivity analysis; QALYs, quality-adjusted life years

Figure 19. Incremental cost-effectiveness plane for Belamaf versus PomDex before clarification stage

The company's Appendix A for the clarification responses presents the Cost-Effectiveness Acceptability Curve (CEAC) where the probabilities of cost-effectiveness of Belamaf are [redacted] to

[redacted] at £20,000 to £30,000 as the Willingness to Pay (WTP) thresholds. (See the company's responses to clarifications; Appendix A Figures 2) replicated as EAG Figure 20.

Figure 20. Company CEAC Belamaf versus PomDex

5.3 *Model validation and face validity check*

The company's model structure is based on a Partitioned Survival Analysis that includes four health states (as per Abbreviations: OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

Figure 17). The model outputs are consistent with the model's inputs and assumptions and the EAG agrees with the model facial validity.

However, in the absence of direct evidence from head-to-head trials, the company uses proxy-PFS which is termed "time to next treatment" (TTNT). The limitations of the proxy-PFS are

described in Section 3.5.1.2. In short, whereas TSNT (and therefore, TTNT) in the PomDex arm is likely to reflect experience for UK patients via the NCRAS database, the EAG considers it unlikely this is the case for the Belamaf arm of DREAMM-2. In the EAG's opinion the development of TSNT is unlikely to have been equitable across the two arms. Detail of EAG exploratory extrapolation of proxy-PFS across health states can be found in Section 3.5 of this report. However, limitations of the data presented in the CS prevent alternative/more informative EAG analysis.

5.4 *EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES*

5.4.1 Exploratory and sensitivity analyses undertaken by the EAG

Given the limitations of the submission, which have been described in the economic evaluation critique, and the EAG's preferred assumptions resulting in the base-case ICER sections; the EAG conclude that it would be implausible to run exploratory analysis and trace the related results through respective uncertainty analyses.

The EAG has provided its preferred assumptions (Section 5.4.3) which only seek to correct issues in the key parameters of the company economic model/base case.

5.4.2 Impact on the ICER of additional clinical and economic exploratory analyses undertaken by the EAG:

Using the data presented in the CS, it is difficult to determine whether what has been presented in the submission reliably reflects the costs and effects of Belamaf.

This mainly stems from the uncertainty around the sources of data (DREAMM-2 for Belamaf, and NCRAS naïve analysis for PomDex). The outcomes for both PFS and OS in both Belamaf and PomDex are uncertain. The EAG consider that the OS and PFS estimations are at risk of overestimation for Belamaf and underestimation for the PomDex.

To explore this further, the EAG undertook additional analyses. The reported results for DREAMM 3 supply the only head-to-head comparison of Belamaf and PomDex in a 3L+ Len and PI exposed population, and indicate no survival advantage for Belamaf relative to POM DEX. The EAG therefore explored the impact of assuming equal OS models for each arm. This was done in three ways: a] Assuming OS PomDex Weibull model delivered the same LYG was as the Belamaf

model (“levelling up”); b] Assuming OS Belamaf Weibull model delivered the same LYG was as the PomDex model (“levelling down”); c] assuming the Weibull model for both PomDex and Belamaf delivered LYG intermediate between the base cases for Belamaf and PomDex (“compromise levelling”).

Unsurprisingly the resulting incremental QALYs were extremely small ([redacted]) so that ICERs are best described as unstable and dependent on what the EAG believe are likely inequitable estimates of PROXY PFS differences.

5.4.3 EAG’s preferred assumptions

The EAG has identified some limitations in the submission’s cost-effectiveness analysis which limits the interpretation of the results (see 5.4.3.1). The EAG preferred assumptions do not change the superiority of the Belamaf strategy.

5.4.3.1 Inappropriateness of the comparators

Because the CS NCRAS study of PomDex lacked a control arm, it was not possible to ascribe (or attribute) any change in OS to an effect of PomDex. The ERG searched for additional evidence in RRMM in which PomDex was compared with a placebo or any standard treatment arm (EAG consider 'no treatment' an implausible option for this patient population). The EAG could not identify any such study amongst those listed in the CS and other newly published relevant studies or reviews not captured by the company SLR searches.

Any changes in the company’s key parameters and assumptions do not lead to a change in the base-case ICER in favor of the PomDex strategy.

EAG preferred assumptions 1- 2 are presented below with justification.

5.4.3.2 Calculated utility weights

1) The company calculated the utility weights at the general population's quality of life. The EAG argues that this is very optimistic for patients in such a heavily pre-treated population. In addition, the company fed the model with data for QoL from the DREAMM-2 trial which has substantial missing data.

The EAG suggests a cap of QoL for patients with one prior treatment. Terpos et al. (2022)[3] applied 0.647 QoL at the baseline for the PFS state. This is applied in agreement with the company's other assumption about the independence of QoL from treatment regimen.

The base case ICER is £[redacted]; by applying the EAG's suggested utility weights, the ICERs results change with considering the severity modifier is £[redacted], and without severity modifier is £[redacted].

Table 31. EAG preferred assumption for utility cap on the company base case ICER

	Incremental costs	Incremental QALYs	ICER	Changes (±) in ICER (without severity modifier)
Company's base-case	£[redacted]	[redacted]	£[redacted]	-
EAG's assumption	£[redacted]	[redacted]	£[redacted]	£[redacted] £[redacted]

5.4.3.3 Severity modifier choice

2) The company used a severity modifier at 1.7 for incremental QALYs. The EAG argues that this is higher than as recommended in the NICE technology appraisal guide, and a value of 1.2 would be more suitable. The base-case ICER at 1.7 is £[redacted]; by using 1.2 as the EAG's preferred severity modifier, the base-case ICER changes to £[redacted]. Changes are presented in Table 32.

Table 32 EAG preferred assumption for 1.2x severity modifier for Belamaf on the company base case ICER

	Incremental costs	Incremental QALYs	ICER	Changes (±) in ICER
Company's base-case	[redacted]	[redacted]	[redacted]	-
EAG's assumption	[redacted]	[redacted]	[redacted]	[redacted]

The EAG summarises the impact of these preferred assumptions on the company cost-effectiveness results in

Table 33.

Table 33 Summary of EAG preferred assumption on company base case

Scenario	Incremental cost	Incremental QALYs	ICERs
Company's base case: The company applies a utility weight of [redacted] for patients on the treatment at the PFS state with a severity modifier of 1.7	£[redacted]	[redacted]	£[redacted]
The EAG's assumed a utility of 0.647 for patients on the treatment at the PFS state with a severity modifier of 1.7	£[redacted]	[redacted]	£[redacted]
Changes after the EAG's preferred assumptions (without the severity modifier)	**£[redacted]**	[redacted]	**£[redacted]**
Company's base-case: **The company applied a 1.7 severity modifier on incremental QALYs**	£[redacted]	[redacted]	£[redacted]
The EAG assumes the appropriate severity modifier is 1.2	£[redacted]	[redacted]	[redacted]
Changes after the EAG's preferred assumptions	£[redacted]	[redacted]	£[redacted]

In summary, the EAG preferred assumptions do not change the company's base case ICER, and should be viewed as addressing issues in the company analysis. All ICERs presented in the EAG report should be interpreted with caution however, as the EAG question the appropriateness and validity of key model efficacy inputs (See Section 3.3.7). It should be noted that the EAG consider the ICER presented in the CS implausible.

5.5 *Conclusions of the cost-effectiveness section*

The company presented an appropriate model structure to model the cost-effectiveness of Belamaf versus PomDex.

5.5.1 Summary of company results

- The company's deterministic results suggest that for Belamaf (intervention): Total costs were £[redacted] Total life years gain (LYG) were [redacted], total QALYs were [redacted]. For PomDex (comparator), total costs were £[redacted], total LYG were [redacted], and total QALYs were [redacted]. This resulted in £[redacted] in cost savings; [redacted] added LYG and [redacted] added QALYs. These results indicate that Belamaf is dominating (since it gives a greater QALY gain versus PomDex, at reduced cost). The resulting cost is £[redacted] per QALY. **Table 34** shows the

company base-case ICER for Belamaf against PomDex (including both with and without considering the severity modifier)

Table 34 company base-case ICER for Belamaf against PomDex (including both with and without considering the severity modifier)

Treatment	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus severity modified incremental (QALYs)
PomDex	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	Dominating

- The company PSA results suggest that for Belamaf (intervention): Total costs were £[redacted] Total LYG were [redacted], total QALYs were [redacted]. For PomDex (comparator), total costs were £[redacted], total LYG were [redacted], and total QALYs were [redacted]. This results in £[redacted] cost savings; [redacted] added LYG and [redacted] added QALYs. Again, this indicates that Belamaf is dominating at a cost per QALY of £[redacted].

- The company OWSA results suggest that the base-case Net Monetary Benefit (NMB) changes within a range of £[redacted] to £[redacted] if the Pomalidomide relative dose intensity changes at 20% unit.
  - The OWSA also presents a variation between £[redacted] to £[redacted] for changes to the relative dose intensity of Belamaf.
  - Changing Belamaf OS gives a difference ranging between £[redacted] to £[redacted].
  - Changing the PomDex Time to treatment discontinuation (TTD) parameter varies NMB between £[redacted] to £[redacted].
  - Variation of TTD for Belamaf gives values of £[redacted] to £[redacted] in NMB.
  - For the PomDex strategy on-treatment if the utility changes among patients who are in a PFS state, the ICER changes between £[redacted] to £[redacted], and changes in the utilities for the Belamaf strategy on-treatment, gives NMB changes between £[redacted] to £[redacted].

The company OWSA results demonstrate that the main drivers of the ICER results are.

1- Relative dose intensity for PoM and Belamaf
2- Overall Survival (OS), for PoM and Belamaf
3- Time to discontinuation (TTD) for both strategies.

The company CEAC presented in Figure 20 suggests that the probabilities of cost-effectiveness for Belamaf range between [redacted] to [redacted] at the £20,000 to £30,000 WTP thresholds.

5.5.2 Overall key issues

The evidence base in the CS is incomplete thus not allowing an adequate comparative effectiveness assessment of the technology of interest.

The company uses the clinical effectiveness data from the DREAMM-2[1, 2] trial and the NCRAS RWE study by applying a naïve unadjusted comparison to conduct the economic evaluation. Whilst the EAG, generally agree with the appropriateness of statistical and computational approaches applied in the CS cost-effectiveness analysis, the results of the ICERs presented in Section 5.1 should be interpreted with extreme caution.

Additional issues include;

- The SLR did not identify a head-to-head comparative study that compares Belamaf to an appropriate comparator treatment in RRMM 5L + TCR patients. The DREAMM-3 trial that evaluates safety/efficacy of Belamaf compared to PomDex in 3L + Len and PI exposed patients is unpublished, so its findings were not included in this CS
- There was a lack of studies of the eligible treatment comparator (PomDex or PanoBorDex) in RRMM 5L + TCR patients and this which could not be resolved by ITC (company MAIC)
- The MAIC analysis did not compare the safety profiles of Belamaf and PomDex (or PanoBorDex) in RRMM 5L + TCR patients, since the NCRAS dataset did not report adverse event data.
- The company's calculated utility weights for patients with such a heavily pre-treated profile seems to be very optimistic. The EAG's clinical advisor believed this is very optimistic. Due

to the toxicity of multiple lines of treatment and the clinical condition of these patients, it is difficult to consider that such levels of QoL are valid for these patients.

- The CS (table 60) shows that twenty-five ([redacted]%) patients had utility observations at both baseline and (End-of-Treatment) (EOT) visits.[1, 2]The Company has not applied multiple imputation methods for addressing the missing values for QoL. The EAG considers that it is difficult to consider these utility values as used in the submission as representative for all patients.

- The company used the trimmed edition of the mapping equation for transforming the QoL from QLQ30 to EQ 5D rather than the full edition as used by Proskorovsky et al.[35] This means the patients' clinical and demographical backgrounds which have interactive impacts on the QoL have been removed. This may be another reason for such high level of QoL for the participants and a further cause an increased uncertainty around the base case ICER. The EAG argues that for these patients with a heavily pre-treated profile, it is inappropriate to use the trimmed version of the Proskorovsky QoL tool.[35]

The company also has used a variety of data sources as model inputs and utilised largely appropriate resources and costing (EAG preferred assumptions are listed below). The impact on the ICER for these changes combined is presented in

- Table 33 which includes the changes for both with and without considering the severity modifier.

1- Inappropriateness of the comparators
2- Calculated utility weights– ICER: [redacted] (Impact on the ICER £[redacted]).
3- Severity modifier choice– ICER: [redacted] (Impact on the ICER the £[redacted])

The company presented a four-health state partitioned survival analysis to run the economic model. In the absence of a head-to-head trial for the comparator, the company used proxy parameters of TTNT for the PFS, as the health state of interest for the cost-effectiveness analysis. The EAG question the validity of this proxy parameter (see Section 3.5.1).

In summary, the EAG are unable to confirm the suitability of PomDex as the main comparator for Belamaf or provide a superior alternative. The EAG cannot confirm the reliability of the sources of efficacy data for either strategies in the economic model.

- The DREAMM-2 trial evaluates two different doses of the drug, with no control group and a small sample size (n=90),
- The NCRAS study, has no control group, and a relatively small sample size.
- Given this, the true effectiveness of Belamaf against PomDex is unknown.

The EAG consider that the use of PomDex for the heavily pre-treated patients considered in this CS, appears to translate into excessive costs to the NHS. This means that the assumptions and calculations of costs in the CS do not change the ICER in favour of PomDex.

However, as stated throughout the report, the EAG suggest that all results presented in this section be interpreted with caution due to the severe limitations in the clinical effectiveness evidence for this technology.

6 SEVERITY MODIFIERS

The company applied a severity modifier of 1.7x to the incremental QALYs, based on the proportional and QALY shortfall analysis (see Table 23). However, the weighting applied seems

inconsistent with the NICE recommendations and the company's base case analysis, which is deterministic. The EAG note that applying the modifier will not change the dominating status of Belamaf, however, the EAG argues that the change in modifier will provide more plausible results. Described in detail in Section 4.2.7.1.

REFERENCES

1. Lonial S, Lee HC, Badros A. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol* 2020;**21**:207-21. http://dx.doi.org/10.1016/S1470-2045(19)30788-0
2. Lonial S, Lee HC, Badros A. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer* 2021;**127**:4198-212. http://dx.doi.org/10.1002/cncr.33809
3. Terpos E, Dimopoulos MA, Boccadoro M, Delimpasi S, Beksac M, Katodritou E*, et al.* Health-related quality of life in patients with relapsed/refractory multiple myeloma treated with pomalidomide and dexamethasone ± subcutaneous daratumumab: patient-reported outcomes from the APOLLO trial. *Am J Hematol* 2022;**97**(4):481-90. http://dx.doi.org/10.1002/ajh.26480
4. Nikolaou A, Ambavane A, Shah A. Belantamab mafodotin for the treatment of relapsed/refractory multiple myeloma in heavily pretreated patients: a US cost-effectiveness analysis. *Expert Rev Hematol* 2021;**14**(12):1137-45. http://dx.doi.org/10.1080/17474086.2021.1970522
5. European Medicines Agency. *Assessment report: Blenrep*. 2020. URL: https://www.ema.europa.eu/en/documents/assessment-report/blenrep-epar-public-assessment-report_en-0.pdf (Accessed 6 December 2020).
6. *BLENREP 100 mg powder for concentrate for solution for infusion: Summary of Product Characteristics*. EMC; 2022. URL: https://www.medicines.org.uk/emc/product/12545/smpc#gref (Accessed 30 November 2022).
7. National Institute for Health and Care Excellence. *Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib [TA427]*. 2017. URL: https://www.nice.org.uk/guidance/ta427/ (Accessed 28 November 2022).
8. National Institute for Health and Care Excellence. *Panobinostat for treating multiple myeloma after at least 2 previous treatments [TA380]*. 2016. URL: https://www.nice.org.uk/Guidance/TA380 (Accessed 29 November 2022).
9. Dimopoulos MA, Moreau P, Terpos E. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2021;**32**:309-22.
10. National Comprehensive Cancer Network. *NCCN guidelines for patients: multiple myeloma*. 2022. URL: https://www.nccn.org/patients/guidelines/content/PDF/myeloma-patient.pdf (Accessed 30 November 2022).
11. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia* 2009;**23**:3-9.
12. Michels TC, Peterson KE. Multiple myeloma: diagnosis and treatment. *Am Fam Physician* 2017;**95**:373-83.
13. Kurtin S, Faiman B. The changing landscape of multiple myeloma: implications for oncology nurses. *Clin J Oncol Nurs* 2013;**17**:7-11.
14. Da Via MC, Ziccheddu B, Maeda A. A journey through myeloma evolution: from the normal plasma cell to disease complexity. *Hemasphere* 2020;**4**(6):e502. http://dx.doi.org/10.1097/HS9.0000000000000502
15. Ferlay J, Colombet M, Soerjomataram I. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019;**144**:1941-53.
16. Su CT, Ye JC. Emerging therapies for relapsed/refractory multiple myeloma: CAR-T and beyond. *J Hematol Oncol* 2021;**14**:115.

17. 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**:377-84. http://dx.doi.org/10.1136/jech.52.6.377
18. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. http://dx.doi.org/10.1136/bmj.d5928
19. GlaxoSmithKline. *Non-interventional study protocol: RWE study on patient characteristics, treatment patterns and outcomes of RRMM patients in England (NCRAS study) [unpublished; supplied by company]*; 2022.
20. Nice Decision Support Unit. *Population-adjusted indirect comparisons (MAIC and STC)*. University of Sheffield; 2016. URL: https://www.sheffield.ac.uk/nice-dsu/tsds/population-adjusted (Accessed 29 November 2022).
21. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, *et al.* Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010;**28**(10):935-45. http://dx.doi.org/10.2165/11538370-000000000-00000
22. GlaxoSmithKline. *Protocol: a phase II, single-arm study to investigate the efficacy and safety of the antibody drug conjugate GSK2857916 in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody (DREAMM 2). Protocol number: 205678 [company submission]*; 2018.
23. 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. http://dx.doi.org/10.1016/s1470-2045(16)30206-6
24. Woods BS, Sideris E, Palmer S, Latimer N, Soares M. Partitioned survival and state transition models for healthcare decision making in oncology: where are we now? *Value Health* 2020;**23**(12):1613-21. http://dx.doi.org/10.1016/j.jval.2020.08.2094
25. Anderson KC, Kyle RA, V RS. Clinically relevant end points and new drug approvals for myeloma. *Leukemia* 2008;**22**:231-9. http://dx.doi.org/10.1038/sj.leu.2405016
26. Djebbari F, Rampotas A, Vallance G, Panitsas F, Basker N, Sangha G, *et al.* Efficacy of isatuximab with pomalidomide and dexamethasone in relapsed myeloma: results of a UK-wide real-world dataset. *Hemasphere* 2022;**6**(6):e738. http://dx.doi.org/10.1097/hs9.0000000000000738
27. Maouche N, Kishore B, Bhatti Z. Panobinostat in combination with bortezomib and dexamethasone in multiply relapsed and refractory myeloma; UK routine care cohort. *PLoS One* 2022;**17**(7):e0270854. http://dx.doi.org/10.1371/journal.pone.0270854
28. Davies FE, Saunders E, Bourhis F, Guyot P. Re: Arcuri and Americo "Treatment of relapsed/refractory multiple myeloma in the bortezomib and lenalidomide era: a systematic review and network meta-analysis". *Ann Hematol* 2022;**101**(7):1599-601. http://dx.doi.org/10.1007/s00277-022-04792-0
29. Arcuri LJ, Americo AD. Treatment of relapsed/refractory multiple myeloma in the bortezomib and lenalidomide era: a systematic review and network meta-analysis. *Ann Hematol* 2021;**100**(3):725-34. http://dx.doi.org/10.1007/s00277-021-04404-3
30. Mateos MV, Blacklock H, Schjesvold F, Oriol A, Simpson D, George A, *et al.* Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial. *Lancet Haematol* 2019;**6**(9):e459-e69. http://dx.doi.org/10.1016/s2352-3026(19)30110-3
31. Richardson PG, Ds S, Vij R. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood* 2014;**123**:1826-32. http://dx.doi.org/10.1182/blood-2013-11-538835

32. Dimopoulos MA, Palumbo A, Corradini P. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. *Blood* 2016;**128**:497-503. http://dx.doi.org/10.1182/blood-2016-02-700872
33. 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. *Lancet Oncol* 2022;**23**(3):416-27. http://dx.doi.org/10.1016/s1470-2045(22)00019-5
34. Glanville J, Lefebvre C, Manson P, Robinson S, Shaw N, editors. *The ISSG search filter resource*. York (UK): The InterTASC Information Specialists' Sub-Group; 2022. URL: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/ (Accessed 23 November 2022).
35. Proskorovsky I, Lewis P, Williams CD. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes* 2014;**12**:35. http://dx.doi.org/10.1186/1477-7525-12-35
36. National Institute for Health and Care Excellence. *Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]: committee papers*. 2017. URL: https://www.nice.org.uk/guidance/ta783/evidence/appraisal-consultation-committee-papers-ta510-pdf-11016892909 (Accessed 28 November 2022).
37. National Institute for Health and Care Excellence. *Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears [TA369]*. 2015. URL: https://www.nice.org.uk/guidance/ta369 (Accessed 28 November 2022).
38. Milne RJ, Heaton-Brown KH, Hansen P, Thomas D, Harvey V, Cubitt A. Quality-of-life valuations of advanced breast cancer by New Zealand women. *Pharmacoeconomics* 2006;**24**(3):281-92. http://dx.doi.org/10.2165/00019053-200624030-00007
39. National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual [PMG36]*. 2022. URL: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (Accessed 28 November 2022).
40. National Institute for Health and Care Excellence. *Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [TA783]*. 2022. URL: https://www.nice.org.uk/guidance/ta783 (Accessed 28 November 2022).
41. National Institute for Health and Care Excellence. *British National Formulary (BNF)*. 2022. URL: https://bnf.nice.org.uk/ (Accessed 28 November 2022).
42. Personal Social Services Research Unit. *Unit costs of health and social care*. 2022. URL: https://www.pssru.ac.uk/project-pages/unit-costs/ (Accessed 28 November 2022).
43. GlaxoSmithKline. *Clinical study report for DREAMM-2 13-month follow-up [company submission]*; 2020.

7 APPENDIX

GSK's Blenrep: 15 Days From Confirmatory Trial Failure To Withdrawal Announcement

The Pink Sheet

November 28, 2022 Monday 6:07 PM GMT

Length: 1862 words

GSK plc's announcement of a planned US withdrawal of the multiple myeloma drug **Blenrep** (belantamab mafodotin-blmf) a mere 15 days after disclosing that the DREAMM-3 trial was unsuccessful appears to set a new standard for speed of voluntary removal following a confirmatory trial failure.

The company's action seemingly also reflects the FDA Oncology Center of Excellence's push to remove "dangling" accelerated approval drugs more quickly, especially when other therapeutic alternatives exist, rather than letting them linger on the market for an extended period of time absent confirmation of clinical benefit.

On 22 November, GSK announced it has begun the process for withdrawing **Blenrep**'s biologics license application "following the request" of the FDA based on the outcome of the DREAMM-3 confirmatory trial.

In DREAMM-3, the efficacy and safety of single-agent **Blenrep** was compared to Celgene Corporation's Pomalyst (pomalidomide) in combination with low-dose dexamethasone (PomDex) in 325 patients with relapsed or refractory multiple myeloma (RRMM).

On 7 November, GSK disclosed that DREAMM-3 failed to meet its primary endpoint of progression-free survival (HR 1.03 [95% CI: 0.72, 1.47]), although the observed median PFS was longer for belantamab versus PomDex (11.2 months vs 7 months). The overall response rate was 41% for belantamab and 36% for PomDex, and duration of response rates at 12 months were 76.8% and 48.4%, respectively. (*"GSKs **Blenrep** Hit By Trial Failure Raising Questions About Its Future In The Myeloma Market" "Scrip"*)

The FDA likely was concerned not only about the failed PFS primary endpoint but also with an adverse survival trend.

At the time of the primary analysis, the overall survival data had achieved 37.5% maturity. The median OS was 21.2 and 21.1 months for belantamab and PomDex, respectively, with an HR of 1.14 (95% CI: 0.77, 1.68).

First BCMA-Targeting Agent

Blenrep was approved on 5 August 2020, making it the first B-cell maturation antigen-directed (BCMA) antibody to receive regulatory clearance. (*"Keeping Track Four Novel Agents Clear US FDA Including Evrysdi **Blenrep**" "**Pink Sheet**"*)

The approved indication was for treatment of adult patients with RRMM who have received least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

The FDA granted accelerated approval based on response rate in the open-label DREAMM-2 study of patients who had previously received three or more prior therapies. A total of 97 patients received **Blenrep** at a dose of 2.5 mg/kg administered intravenously once every three weeks, and the overall response rate was 31%. The median time to first response was 1.4 months, and 73% of responders had a duration of response >=6 months.

In briefing documents for a July 2020 advisory committee meeting, agency reviewers raised no major concerns about the drug's efficacy based on the ORR rate in DREAMM-2, saying that belantamab may be beneficial in a heavily pretreated patient population.

Rather, the agency focused its concerns on the drug's ocular toxicity, including the high incidence of keratopathy, which was sometimes severe, and reports of a clinically significant decline in visual acuity, including severe vision loss. (*"US FDA Eyes Ocular Risks With GlaxoSmithKlines Myeloma Drug Belantamab" "**Pink Sheet**"*)

The belantamab review was the first major advisory committee meeting to take place virtually due to the COVID-19 pandemic, and the proceeding was a rocky one, marked by a host of technical problems and delays. The Oncologic Drugs Advisory Committee ultimately voted 12-0 that the drug's benefits outweighed its risks in the proposed population. (*"GlaxoSmithKline Survives Technical Woes To Win US FDA Panel Nod For Belantamab" "**Pink Sheet**"*)

Furthermore, panelists said GSK's proposed Risk Evaluation and Mitigation Strategy, which included ophthalmic exams prior to each dose and an algorithm for dose modifications, provided some reassurance that any ocular issues would be caught early and could be addressed through dose reductions or interruptions.

Although **Blenrep** was the first BCMA-targeting agent to gain approval in myeloma, it never became the blockbuster for which GSK had hoped, and the ocular safety concerns contributed to a modest launch trajectory. The product's third quarter revenues were £36m ($42.8m), with more than half of that coming from the US.

Blenrep also is facing competition from three other BCMA-targeting advanced biologics recently approved for heavily pretreated multiple myeloma: two chimeric antigen receptor T-cell (CAR-T) therapies - *Janssen Biotech Inc.*'s Carvykti (ciltacabtagene autoleucel) and *bluebird bio*/*Bristol Myers Squibb Company*'s Abecma (idecabtagene vicleucel) - and Janssen's first-in-class "off-the-shelf" T-cell redirecting bispecific antibody Tecvayli (teclistamab).

Belief In Benefit-Risk Profile

GSK said patients already enrolled in the **Blenrep** REMS would have the option to enroll in a compassionate use program to continue to access treatment, and further information on how to enroll patients into the compassionate use program would be provided directly to REMS-enrolled prescribers.

GSK said it continues to believe, based on the totality of data available from the DREAMM clinical program, that belantamab's benefit-risk profile remains favorable in a hard-to-treat RRMM patient population.

Nevertheless, "we respect the agency's approach to the accelerated approval regulations and associated process," chief medical officer Sabine Luik said. "Multiple myeloma is a challenging disease, with poor outcomes for patients whose disease has become resistant to standard-of-care treatments. We will continue the DREAMM clinical trial programme and work with the US FDA on a path forward for this important treatment option for patients with multiple myeloma."

Additional DREAMM trials are continuing and are designed to determine the benefit of **Blenrep** in combination treatment with novel therapies and standard-of-care treatments in earlier lines of therapy, and dosing optimization to maintain efficacy while reducing corneal events, GSK said.

DREAMM-7 is evaluating the safety and efficacy of belantamab in combination with bortezomib and dexamethasone versus daratumumab in combination with bortezomib and dexamethasone in patients previously treated with at least one prior line of therapy.

In DREAMM-8, belantamab is being studied in combination with pomalidomide and dexamethasone compared with a combination of pomalidomide, bortezomib and dexamethasone in RRMM patients previously treated with at least one prior line of therapy, including a lenalidomide-containing regimen.

Data from the DREAMM-7 and DREAMM-8 Phase III trials are anticipated in the first half of 2023. "Results of these trials will be shared with health authorities and will inform future regulatory pathways," GSK said.

840 Days On Market

GSK's announcement of **Blenrep**'s withdrawal came 840 days after the drug's accelerated approval, marking one of the shorter commercial intervals for an accelerated approval drug before withdrawal. (See chart at end of story.)

DREAMM-3 was initiated in April 2020, four months prior to the drug's accelerated approval. This is notable given OCE's increasing emphasis on the need to have confirmatory trials underway, and ideally fully enrolled, at the time of accelerated approval to ensure that clinical benefit is confirmed as quickly as possible.

By announcing **Blenrep**'s withdrawal just 15 days after the press release on the failed DREAMM-3 study, GSK bested the speed of *Eli Lilly and Company*'s withdrawal announcement for the soft tissue sarcoma drug Lartruvo (olaratumab) following a failed confirmatory trial.

In January 2019, Lilly said the ANNOUNCE trial failed its PFS primary endpoint. A little over three months later, in April 2019, Lilly said it would withdraw Lartruvo worldwide. (*"A Successful Failure Lartruvos Speedy Withdrawal Sets New Bar For Accelerated Approval Drugs" "**Pink Sheet**"*) Lartruvo's NDA's officially was withdrawn in February 2020.

Zejula's Indication Narrowed

The **Blenrep** withdrawal is the second major setback for GSK's marketed oncology drugs in a matter of days. On 11 November, the company said that, at the FDA's request, it would restrict the second-line maintenance indication for the ovarian cancer drug Zejula (niraparib) to only the patient population with deleterious or suspected deleterious germline BRCA mutations (gBRCAmut).

This decision follows an FDA review of the final overall survival analysis of the ENGOT-OV16/NOVA Phase III trial, which served as the basis for regular approval of the second-line maintenance indication. In the final OS results, there was an adverse survival trend in the non-gBRCAmut cohort (HR 1.06 [95% CI: 0.81-1.37]).

ODAC had been scheduled to discuss the OS data on 22 November, but that public session was cancelled in October, with the FDA saying it was no longer needed. (*"Zejula Revatio Advisory Committee Meetings Cancelled Palovarotene Panel Postponed" "**Pink Sheet**"*)

Zejula's first-line indication remains unchanged for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have a complete or partial response to platinum-based chemotherapy.

In September, GSK withdrew a different ovarian cancer indication for Zejula based on a potential detrimental effect on OS observed with other PARP inhibitors. (*"Its The Overall Survival Sponsors Ovarian Cancer Indications Withdrawn For Three PARP Inhibitors" "**Pink Sheet**"*)

Other Potential Withdrawal Decisions Pending

The final verdicts are not yet in for two non-GSK cancer agents that have been the recent focus of FDA regulatory scrutiny due to adverse survival trends in postmarketing studies.

On 22 September, ODAC voted 14-2 that the benefit-risk profile of *Oncopeptides AB*'s Pepaxto (melflufen) is unfavorable in the current accelerated approval indication for fifth-line treatment of multiple myeloma. (*"Oncopeptides Pepaxto Needs New Study To Identify Population That Will Benefit FDA Panel Says"* ***"Pink Sheet"***)

Pepaxto has not been marketed in the US since Oncopeptides informed the FDA in October 2021 it would withdraw the agent due to an adverse survival trend in the OCEAN confirmatory trial. However, the company rescinded that withdrawal in January.

Oncopeptides said it has an ongoing discussion with the FDA regarding the regulatory path forward for Pepaxto in the US, and the FDA has not requested the company withdraw the drug from the US market.

On 23 September, ODAC voted 8-4 that the benefits of *Secura Bio, Inc.*'s Copiktra (duvelisib) do not outweigh its risks in the drug's current indications for third-line treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma. The indications hold regular approval, but the FDA said a re-examination was warranted in light of final survival data from the DUO trial, which showed a higher rate of death in the duvelisib arm relative to a comparator group. (*"Securas Copiktra Trial Design Shifting Standard Of Care Could Spell The End For ThirdLine CLLSLL"* ***"Pink Sheet"***)

By *Sue Sutter*

Load-Date: November 28, 2022

End of Document

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

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 4 January 2023** 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.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Table 1: List of priority issues

Issue 1 Appropriateness of pomalidomide plus dexamethasone (PomDex) as a valid comparator to Belamaf in the NHS context.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 86, Section 3.5.4: "The DREAMM-3 trial is the only available randomised comparison of Belamaf and the proxy-comparator PomDex. It indicates a lack of clinical superiority for Belamaf versus PomDex in any outcome. The two interventions may be equally harmful, or equally beneficial, or both might be null in their effect."	The Company requests that the text be amended to the following: "The DREAMM-3 trial is the only available randomised comparison of Belamaf and the proxy-comparator PomDex. In a 3L+ Len and PI exposed population, it indicates a lack of clinical superiority for Belamaf versus PomDex in any outcome. The two interventions may be equally beneficial, or both might be null in their effect."	Results for the ITT population (3L+ Len and PI exposed population) of DREAMM-3 have been reported to date, and they cannot be extrapolated to the population considered for this appraisal, 5L+ TCR patients. Only efficacy outcomes are mentioned in this section and thus, any conclusion on safety ("*The two interventions may be equally harmful*") is not appropriate in this paragraph.	We are happy to amend the sentences to add "*In a 3L+ Len and PI exposed population*" improve clarity. **Changes made on page 86 and 111.**

Page 111, Section 5.4.2: "The reported results for DREAMM 3 supply the only head-to-head comparison of Belamaf and PomDex and indicate no survival advantage for Belamaf relative to POM DEX."	"The reported results for DREAMM-3 provide the only head-to-head comparison of Belamaf and PomDex. In a 3L+ Len and PI exposed population, results indicate no survival advantage for Belamaf relative to POM DEX."		
Page 98, Section 4.2.4: "The EAG's clinical advisors suggest that PomDex is rarely prescribed in the 4L patients and its use is "vanishingly rare" in the 5L." **Page 99, Section 4.2.4:** "In NHS practice, it seems	Please could the accuracy of these statements be checked.	These comments are inconsistent with previous comments concerning the use of PomDex in the NICE pathway. For example, on page 13 it is stated that "The EAG clinical advisors suggest that PomDex is very rarely used in this patient population as it would have already been used earlier in the pathway (from 4L), and	The EAG note that these are the opinion of two independent clinical advisers in reference to their views of clinical practice (not the NICE pathway) As such, they can differ in their opinion. As stated on page 105 the EAG welcome additional clinical opinion during Technical Engagement/committee meeting.

that the effectiveness of PomDex for such heavily pretreated patients is not confirmed. As PomDex is rarely prescribed for 4L and onward."		therefore, patients are considered refractory."	No change made.
Page 67, Section 3.5.1.3: "The database contained [redacted] TCR patients receiving 5L+ therapies (CS Document B Figure 7). Of these [redacted] were identified as receiving "index" PomDex, and this population was used as proxy-comparator to Belamaf.	The Company requests that the text be amended to the following: "The database contained [redacted] TCR patients receiving 5L+ therapies (CS Document B Figure 7). Of these [redacted] were CDF-excluded patients and [redacted] were not CDF-excluded patients. Of the [redacted], [redacted] were identified as receiving "index" PomDex, and this population was used as a proxy-comparator to Belamaf."	The incorrect denominator has been used to calculate the use of PomDex. The denominator should be [redacted] (the [redacted] 5L+ TCR MM patients minus the [redacted] CDF-excluded patients), resulting in PomDex being used in [redacted] of patients in the 5L+ TCR cohort.	The company excluded [redacted] CDF drug recipient patients. This is a concern for external validity. How do we know that these [redacted] excluded patients did not receive PomDex? The true ideal denominator in this case is not known. Therefore, **we have removed the percentage altogether and mention only the number:** "Out of the [redacted] patients, [redacted] were identified receiving PomDex.

The EAG consider that because only [redacted] of UK 5L TCR patients received PomDex, this implies its infrequent use in the NHS and questions whether that treatment can be representative of NHS practice and provide a relevant comparator.”	The Company requests that the subsequent statement is deleted: “The EAG consider that because only [redacted] of UK 5L TCR patients received PomDex, this implies its infrequent use in the NHS and questions whether that treatment can be representative of NHS practice and provide a relevant comparator.”		In accordance with above, this **sentence has been removed.**
Page 67, Section 3.5.1.3: “The CS quotes clinical opinion as follows: “…when clinicians are up against a patient who is multiply relapsed and refractory and there are no reasonable	The company request that this statement be deleted.	This comment from the CS is taken out of context; this feedback gained by the company from a clinical expert is specific to PanoBorDex use only.	Whilst this quote does not specifically reference PanoBorDex (it is added in brackets by the company), the company have placed it under the PanoBorDex heading in their report. **The sentence has been deleted on page 67.**

therapies, clinicians are wondering what would I be allowed to use?...” (CS Document B page 20).”			
Page 67, Section 3.5.1.3: “Since PomDex is recommended by NICE as 4L treatment, the CS posits that, in absence of an alternative, PomDex represents “the only source” of “comparative efficacy evidence” (CS Document B page 67) for a proxy-comparator to Belamaf”.	The Company requests that the text be amended to the following: “Since PomDex is recommended by NICE as 4L+ treatment and was identified in the NICE final scope, the CS posits that PomDex represents the most appropriate comparator and the NCRAS study represents “the only source” of “comparative efficacy evidence” (CS Document B page 67) reporting efficacy outcomes for PomDex”.	In line with NICE published guidance for TA427, PomDex is recommended *‘as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib’*	**We have added “and was identified in the NICE final scope” to page 67 to improve clarity.** Statements regarding appropriateness of comparators are opinion not factual errors. **No further change made.**

Page 99, Section 4.2.4: "The EAG appreciates the NICE recommendations regarding inclusion of CDF reviews for other possible comparators (see Figure 1); however, the Company has not presented any other valid comparator."		Please could the EAG revise this wording, in light of previous comments made by the EAG regarding comparators? For example, on page 26, it is stated 'the EAG accept that there are no alternative comparators available for consideration in this appraisal (see **Error! Reference source not found.Error! Reference source not found.**).'	**No change made.** Statement is not factually inaccurate.

Issue 2 Inappropriate source data presented as evidence for efficacy of Belamaf and PomDex

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32, Section 3.2.1: "The efficacy endpoints evaluated in DREAMM-2 trial included response rates (overall, partial, very good partial, complete, stringent complete), overall survival	The Company requests that the text be amended to the following: "The efficacy endpoints evaluated in DREAMM-2 trial included overall response rate (ORR), (partial, very good partial, complete, stringent complete), overall survival (OS),	The current list is inaccurate and does not present all endpoints as reported in the CS.	**time to response (TTR),** **and** **minimal residual disease (MRD),**

(OS), progression-free survival (PFS), time to treatment discontinuation (TTD), time to start of next treatment (TSNT), clinical benefit rate (CBR), time to progression (TTP), duration of response (DOR), and health-related quality of life (HRQOL)."	progression-free survival (PFS), time to treatment discontinuation (TTD), time to next treatment (TTNT), clinical benefit rate (CBR), time to response (TTR), time to progression (TTP), duration of response (DoR), minimal residual disease (MRD), and health-related quality of life (HRQoL)."		**have been added to page 32**
Page 35, Section 3.2.2: "Although PanoBorDex was considered a relevant comparator to Belamaf in the NICE Final Scope, (see Table 3 Section 2.3) the company only included the PomDex arm as the source of comparative efficacy evidence".	The Company requests that the text be amended to the following: "PanoBorDex was considered a comparator to Belamaf in the NICE Final Scope, (see Table 3 Section 2.3) and although the company did not consider PanoBorDex as the most relevant comparator, a comparison was included in an appendix for completeness".	The Company included PomDex as the main comparator but acknowledged there is some use of PanoBorDex in this setting. To account for this limited use, an analysis of Belamaf vs PanoBorDex was presented in the appendix.	Not a factual inaccuracy. **No change made.**
Page 38, Section 3.2.2.1, Table 7: "Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was	The Company requests that the text be amended to the following: In the row "Was the randomised intervention assignment concealed from both patients and health care staff	To maintain consistency with the rest of the table.	**Happy to change for consistency in Table 7.**

complete and irrevocable?", "NA"	until recruitment was complete and irrevocable?", "Not applicable".		
Page 38, Section 3.2.2.2: "To remedy lack of data for PFS the company undertook post-hoc analyses to generate a "proxy-PFS" outcome for the NCRAS study"	The Company requests that the text be amended to the following: "To remedy lack of data for PFS the company used TTNT as a "proxy-PFS" outcome for the NCRAS study"	The NCRAS study collected TTNT as part of the primary objectives. In addition, the NCRAS database is updated regularly and is thus ongoing, therefore no post-hoc analyses were required.	**Text changed to** To remedy lack of data for PFS the company to generate a "proxy-PFS" outcome for the NCRAS study On page 38

Issue 3 Misrepresentations of company analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Wastage			

Page 20, Section 1.2, and Page 112, Section 5.4.3: “Assuming a 50% increase in £[redacted] as the baseline amount for Belamaf wastage costs can increase the base-case ICER by £[redacted] with a severity modifier of 1.7 (from £[redacted] as the company current base-case ICER to £[redacted] as the EAG’s preferred assumption). Without severity modifier the base-case ICER will be increased by £[redacted] (from £[redacted] as the company current base-case ICER to £[redacted] as the EAG’s preferred assumption).”	The Company requests that the text be amended to the following: "The EAG's assumption of 50% wastage cost differs from the Company's calculation. The EAG methodology applies a further 50% cost to the price of Belamaf when a 100% wastage cost is considered (100% wastage cost: [redacted]). This results in a 150% wastage cost. Under the EAG’s methodology, assuming a 50% increase in the baseline amount for 100% Belamaf wastage cost of £[redacted] can increase the base-case ICER by [redacted] with a severity modifier of 1.7 (from [redacted] as the company current base-case ICER to £[redacted] as the EAG’s preferred assumption). Without severity modifier the base-case ICER will be increased by [redacted] ([redacted] as the company current base-case ICER to [redacted] as the EAG’s preferred assumption). In contrast, based on the company's approach to wastage, 50% of Belamaf's total wastage costs (100% wastage: [redacted]) are added together with 50% of Belamaf's total cost without	The current text is misleading and does not provide sufficient detail into the methodology used to calculate wastage. An error in the calculation of the wastage cost was identified in the EAG’s economic model. The EAG’s approach applies an additional 50% wastage cost on top of the cost of Belamaf when wastage is included, thereby overestimating wastage (resulting in a 150% wastage cost). Furthermore, the EAG's report fails to include results of the Company's preferred methodology for this scenario, which indicates the cost effectiveness of Belamaf remains dominating. As such, the Company request that the text presents both approaches to allow for a more balanced argument.	The EAG are happy with this amendment. **The EAG removed this assumption as this adds an excess wastage cost to the Company’s 100% wastage costs for Belamaf.** **revision has been made throughout the report.**

	wastage (100% no wastage: [redacted]) to arrive at a cost of [redacted] per cycle. When considering the Company's approach to wastage, the cost effectiveness of Belamaf remains dominating."		

Page 113, Section 5.4.3.3: **Page 116, Section 5.4.3.3, Table 35:** "If wastage costs equal to £[redacted] are applied, the base case ICER changes to £[redacted], and Belamaf is still dominating. However, if the wastage cost is increased by 50%, which means a cost of £[redacted], then the base case ICER changes substantially to £[redacted]."	The Company requests that the text be amended to the following: "If 100% wastage costs equal to £[redacted] are applied, the base case ICER changes to £[redacted], and Belamaf is still dominating. However, if the wastage cost is increased by 50%, which means a cost of £[redacted], then the base case ICER changes substantially to £[redacted]."	The Company calculated the cost of 100% wastage as [redacted]. The current text is misleading as it does not provide sufficient detail into the methodology used to calculate wastage. The EAG's approach applies an additional 50% wastage cost on top of the cost of Belamaf when wastage is included, thereby overestimating wastage (resulting in a 150% wastage cost).	**Text removed**
Page 119, Section 5.5.2: 2- "Capped the utility weights– impact on the ICER £[redacted]. 3- Inclusion of wastage costs – impact on the ICER £[redacted] 4- Severity modifier choice– impact on the ICER the £[redacted].	The Company requests that the text be amended to the following: 2- "Capped the utility weights– ICER: [redacted] (Impact on the ICER £[redacted]). 3- Inclusion of wastage costs using the EAGs wastage methodology – ICER: [redacted] (Impact on the ICER £[redacted])	The Company request that the ICERs are reported as the current text reporting changes in the ICER is misleading.	**Although not factually inaccurate, this change has been made on page 119 to improve clarity.**

5- Relative dose intensity – impact on the ICER £[redacted]."	4- Severity modifier choice– ICER: [redacted] (Impact on the ICER the £[redacted]) 5- Relative dose intensity – ICER : £[redacted] – (Impact on the ICER £[redacted])."		
Page 120, Section 5.5.2: "The EAG preferred assumption regarding wastage costs changes the cost effectiveness of Belamaf from being dominating to a positive value."	The Company requests that the text be amended to the following: "The EAG preferred assumption regarding wastage costs changes the cost effectiveness of Belamaf from being dominating to a positive value. In contrast, under the Company's assumption of wastage, Belamaf remains dominant."	The current text is misleading and does not take into account results of the Company's wastage scenario.	**The EAG has removed this assumption.**
Capped utilities			
Page 17, Section 1.6, **Page 19, Section 1.7,** **Page 100 Section 4.2.7,** **Page 113, Section 5.4.3.2,** **and Page 119, Section 5.5.2:**	The Company requests that the text be removed.	This statement is incorrect. The Company did not cap the utility weights at the general population's quality of life. The company applied age-related adjustments to DREAMM-2 utility data using adjustments from Ara &	The EAG agree that the company has used the age-related adjustments to decrement the utility weights and also agree with the calculations, but the EAG argue considering the general

“The company capped the utility weights at the general population's quality of life. The EAG argues that this is very optimistic for patients in such a heavily pre-treated population.”		Brazier et al. 2010, thereby reflecting the NICE Reference Case.	population Quality of Life level as the threshold which cannot be exceeded is very optimistic, as for patients with such a heavily pre-treated profile the best condition is to consider the maximum utility at utility for patients at the first line of the treatment. **Capped change to calculated throughout.**

Issue 4 Company proxy measure for progression free survival (PFS) termed timed to next treatment (TTNT)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 46, Section 3.3.2: **“**Data on TTD and time to start of next treatment (TSNT) available for DREAMM-2 was used to	The Company requests that the text be amended to the following: “TTNT is defined as the time from randomisation until the date of start of	In response to clarification questions the company confirmed that TTNT was not generated as a combination of TTD and	The CS Document B 2.5.1.9 page 55 stated: “*TTNT was not a pre-specified outcome in the DREAMM-2 trial. To allow a comparison with PomDex TTNT data from*

calculate TTNT by combining the two parameters." **Page 49, Section 3.3.3.4:** "Moreover, TTNT which was not directly measured for the DREAMM-2 IPD, was derived by combining TTD and TSNT" **Page 62, Section 3.4.2, Table 17:** "TTNT was derived by combining TTD and TSNT from discontinuation" **Page 97, Section 4.2.2:** "TTNT was not directly measured within the DREAMM-2 trial"	follow-up anti-cancer treatment or death due to any cause." "Moreover, TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause." "TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause." "TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause in the DREAMM-2 trial."	TSNT. TTNT was generated in a post-hoc analysis of the DREAMM-2 trial and is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause.	*the NCRAS study, this outcome was reconstructed by combining TTD to TSNT".* In clarification response A9 the company corrected their original description of how TTNT was derived. We have not carried over this correction into our final report. The EAG text has been changed to the following *"..in clarification the company explained that TTNT was not derived as originally described (i.e. from TTD and TSNT) but*

			was generated by direct post hoc analysis." **Text regarding TTNT has been removed or changed throughout.**
Page 66, Section 3.5.1.2: "Time to start of next treatment (TSNT) is used to estimate proxy-PFS (TTNT) for intervention and comparator."	The Company requests that the text be amended to the following: "TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause."	The Company would like to clarify that TTNT is defined in DREAMM-2 as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. In NCRAS, TTNT is defined as the time from the start of the first cohort-eligible line of	**As above. Text changed.**

		therapy until failure (the earliest of all-cause death or the start of a new line of treatment).	
Page 49, Section 3.3.3.4: "Given these procedures, the definitions of TTNT across the datasets differed, because the TTNT definition in the NCRAS dataset is not based on TTD, but instead incorporates either 'time to all-cause death' or 'time to start of a new treatment'."	The company request that this statement be deleted.	As per the justification above, the two data sets do not differ in the manner described. DREAMM-2 TTNT: Defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause. NCRAS TTNT: Defined as the time from the start of the first cohort-eligible line of therapy until failure (the earliest of all-cause death or the start of a new line of treatment).	As above. **Text removed**
Page 51, Section 3.3.4: "Treatment effects were estimated using a robust sandwich estimator and expressed as weighted	The Company requests that the text be amended to the following: "Treatment effects were estimated using a robust sandwich estimator and	No PFS data was available in the NCRAS dataset.	***PFS* has been deleted on page 51.**

HRs (for OS, PFS, TTNT, and TTD)"	expressed as weighted HRs (for OS, TTNT, and TTD)"		
Page 65, Section 3.5.1.1, Page 97, Section 4.2.2, and Page 110, Section 5.3: "TTNT was re-constructed post-hoc using two post-hoc analyses, time to treatment discontinuation (TTD) and time to start of next treatment (TSNT). "	The Company requests that the text be amended to the following: "For DREAMM-2, TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause."	The Company would like to add clarification that post-hoc analyses was only performed for DREAMM-2 and not for NCRAS.	**Text removed.**
Page 97, Section 4.2.2: "Briefly, the EAG argue that the use of proxy-PFS rather than PFS will tend to accumulate more QALYs for Belamaf as indicated in Figure 4 (EAG additional analysis)."	The Company requests that the text be amended to the following: "Briefly, the EAG argue that the use of proxy-PFS rather than PFS will tend to accumulate more QALYs for Belamaf and PomDex as indicated in Figure 4 (EAG additional analysis)."	This would lead to more QALYs for both treatments, not just Belamaf.	Not factually inaccurate no change made.

Issue 5 Typographical errors and other factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect reports			
Page 20, Section 1.2, Page 21, Section 1.2, Table 2 and Page 112, Section 5.4.3: "The EAG applies a 50% wastage costs on £[redacted] (this is identical to the company's spreadsheet amounts for the situation that there is a wastage cost: ICER: £[redacted]"	The Company requests that the text be amended to the following: "The EAG applies a 50% wastage costs on £[redacted] (ICER: £[redacted])"	Typographical error - numerical	**Text removed**
Page 21, Table 2 **and Page 116, Section 5.4.3.5, Table 35:** Several of the entries in the ICER column, specifically those in rows titled are changes from the base-case ICER and	The Company requests that the formatting of the table be updated "Changes after the EAG's preferred assumptions"	Misrepresentation The current formatting misrepresents ICERs from updated analysis by the EAG.	The company analyses are based on two states: with and without severity modifier, the EAG's tables present the changes from the company's ICERs after applying the preferred assumptions. The EAG believe the current format would provide a broader view to the readers to understand what the changes would be after applying the EAG's preferred assumptions.

not the ICERs themselves.	£[redacted] (£[redacted]), £[redacted] (£[redacted]) and £[redacted] £[redacted] should not be labelled as ICERs, the format of the table needs updating to reflect this.		
Page 30, Section 3.1.3: "… with the number of participants randomised or enrolled ranging from 32- 304"	To update the text as follows: "… with the number of participants randomised or enrolled ranging from 32-455."	Typographical error - numerical	**Typo corrected.**
Page 34, Section 3.2.2: "It comprised of [redacted] English patients who were "closely aligned" with the DREAMM-2 population"	"It comprised of [redacted] English patients who were "closely aligned" with the DREAMM-2 licensed population"	Typographical error – missing information	**Not a factual error no change made.**
No Page 69, Section 3.5.1.4, Figure 4 and Page 72, Section 3.5.2, Figure 6a:	The Company requests that the text be amended to the following:	Typographical error – spelling	**Typo corrected.**

The legend states “OS = overall survival; proxy PMS = time to next treatment (TNTT); TTD = time to discontinuation”	“OS = overall survival; proxy PFS = time to next treatment (TTNT); TTD = time to discontinuation”		
Page 65, Section 3.5.1.1, Figure 2: The legend states “Distribution of patients in progression-free and on treatment, progression-free and off-treatment, progressed and death health states.”	The Company requests that the text be amended to the following: **“**Distribution of patients in progression-free, progressed and death health states.”	Misrepresentation – the figure is not split into on/ off-treatment health states	**Legend changed.**
Page 70, Section 3.5.1.4, Figure 5 and Page 73, Section 3.5.2, Figure 6b: The legend states “…proxy PFS = time to next treatment (TNTT)”	The Company requests that the text be amended to the following: “…proxy PFS = time to next treatment (TTNT)”	Typographical error – spelling	**Typo changed.**
Page 74, Section 3.5.2.1, Figure 7 and Page 78, Section 3.5.2.2, Figure 11:	Please add legends to both figures	Misrepresentation	**Legend added to Figure 7 and Figure 11.**

Neither figure has a legend			
Page 107, Section 5.2.1.1, Table 29	This table should be amended to Table 5 of Appendix A in the post-submission version of the CS.	Misrepresentation This set of OWSA results have been taken from the original CS and not the post-submission version.	The EAG is happy with this amendment.
Page 112, Section 5.4.3: "Increasing the RDI from [redacted]% to [redacted]% which leads to.."	The Company requests that the text be amended to the following: **"**Increasing the RDI from [redacted]**%** to [redacted]% which leads to..."	Typographical error – numerical	The RDI assumption is no longer available in the EAG report, subsequently this was **removed from the EAG's report.**
Page 115, Section 5.4.3.5, Table 34: "..which can be translated to a base-case ICER of [redacted]**"**	The Company requests that the text be amended to the following: "..which can be translated to a base-case ICER of [redacted]"	Typographical error – numerical	**The related assumption was removed**, subsequently this is no longer in the EAG report.
Page 116, Section 5.4.3.3, Table 35:	To update the text as follows:	Typographical error - numerical	**This was removed.**

"The EAG applies a 50% wastage costs on £[redacted] (this is identical to the company's spreadsheet amounts for the situation that there is a wastage cost: ICER: £[redacted]"	"The EAG applies a 50% wastage costs on £[redacted] (this is identical to the company's spreadsheet amounts for the situation that there is a wastage cost: ICER: £[redacted]"		
Page 116, Section 5.4.3.5, Table 35: "The EAG's assumed a utility of 0.647 for patients on the treatment at the PFS state with a severity modifier of 1.7 : ICER £[redacted]"	To update the text as follows: The EAG's assumed a utility of 0.647 for patients on the treatment at the PFS state with a severity modifier of 1.7 : ICER £[redacted]	Typographical error – numerical	**Table 33 amended.**
Page 116, Section 5.4.3, Table 35: "The company applies a RDI at [redacted]%-for Belamaf. "	The Company requests that the text be amended to the following: "The company applies a RDI at [redacted]% for Belamaf."	Typographical error – numerical	**Text removed.**

Page 117, Section 5.5.1: "This resulted in £[redacted] in cost savings; [redacted] added LYG and [redacted] added QALYs."	The Company requests that the text be amended to the following: "This resulted in £[redacted] in cost savings; [redacted] added LYG [redacted] added QALYs."	Typographical error – numerical The base-case added QALY should be [redacted]. The value of [redacted] refers to the added QALYs without a severity modifier.	**Typo changed.**
Page 117, Section 5.5.1: "The OWSA also presents a variation between £[redacted] to £[redacted] for changes to the relative dose intensity of Belamaf"	The Company requests that the text be amended to the following: "The OWSA also presents a variation between £[redacted] to £[redacted] for changes to the relative dose intensity of Belamaf"	Typographical error – numerical	**Typo changed.**
Spelling and grammar issues			
Page 11, Section 1.1: "Section **Error! Reference source not found.** provides an overview of the key issues. Section **Error!**	The Company requests that the text be amended to the following:	Typographical error – wrong cross reference	**Cross referenced changed.**

Reference source not found. provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 0 to **Error! Reference source not found.** explain the key issues in more detail."	"Section **Error! Reference source not found.** provides an overview of the key issues. Section **Error! Reference source not found.** provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to **Error! Reference source not found.** explain the key issues in more detail."		
Page 17, Section 1.6, Issue 3: "one refractory MMA treatment"	The Company requests that the text be amended to the following: "one refractory MM treatment"	Typographical error – spelling MM is the abbreviation for multiple myeloma, not MMA	**Typo changed.**
Page 18, Section 1.6, Issue 4: "TNT was re-constructed post-hoc using two post-	The Company requests that the text be amended to the following:	Typographical error – spelling	**Typo changed. Text removed.**

hoc analyses, time to treatment discontinuation (TTD) and time to start of next treatment (TSNT)."	"TTNT is defined in DREAMM-2 as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause."	TTNT is the acronym for Time to Next Treatment The definition of TTNT is also incorrect which has been noted in Issue 4	
Page 31, Section 3.2, **Page 31, Section 3.2.1,** **Page 32, Section 3.2.1,** **and Page 32, Section 3.2.1:** "mg/Kg"	The Company requests that the text be amended to the following: "mg/kg."	Typographical error – grammar Typo in units occurs on four occasions.	**Typo changed.**
Page 31-32, Section 3.2.1: "The EAG note that there was no control arm, and the 2.5 regimen outcomes were used as evidence in the CS"	The Company requests that the text be amended to the following: "The EAG note that there was no control arm, and the 2.5 mg/kg regimen outcomes were used as evidence in the CS."	Missing information 2.5 should be 2.5 mg/kg	**Typo changed.**

Page 32, Section 3.2.1: "…the patient characteristics of the ITT population were compared with the 2.5mg/Kg dose arm"	The Company requests that the text be amended to the following: "…the patient characteristics of the ITT population were compared with the 5L+ TCR patients (i.e. ITT minus the [redacted] patients who received three prior lines)."	Missing information	**Changed for clarity not a factual inaccuracy.**
Page 33, Section 3.2.1.1, Table 4: "However, the EAG point out that this information is irrelevant for this appraisal, because the 3.4Kg dosage is not further considered by the company".	The Company requests that the text be amended to the following: "However, the EAG point out that this information is irrelevant for this appraisal, because the 3.4 mg/kg dosage is not further considered by the company".	Typographical error – spelling	**Typo changed.**
Page 34, Section 3.2.1.2, and Page 68, Section 3.5.1:	The Company requests that the text be amended to the following:	Typographical error – spelling	**Typo changed.**

"The primary outcome of the DREAMM-2 (ITT population) was overall response rate (ORR) by IMW standard criteria." "DREAMM-2 reported favourable ORR (according to IMW standard criteria) for some patients following intervention with Belamaf."	"… IMWG standard criteria…"		
Page 44, Section 3.3.3.1, Table 7, Page 62, Section 3.4.2, Table 17 and Page 97, Section 4.2.3 : DREAMM-2 was not conducted in 59 centres/ locations as stated on several occasions	The Company requests that the text be amended to the following: "…58 centres/ locations…"	Typographical error – numerical	**Typo changed.**
Page 57, Section 3.3.7: "….with no improvement in median f OS.."	The Company requests that the text be amended to the following:	Typographical error – spelling	**Typo changed.**

	"…with no improvement in median OS.."		
Page 59, Section 3.3.7: "…compared with pre-matched data (unadjusted Belamaf) or PomDex/PanoBorDex"	The Company requests that the text be amended to the following: "…compared with pre-matched data (unadjusted Belamaf) for PomDex/PanoBorDex"	Typographical error – spelling	**Typo changed.**
Page 62, Section 3.4.2, Table 17: "DREAM-2 trial (59 centers in North America, Australia, France, Germany, Italy, and UK) vs. NCRAS (UK, England)." "Dexamethazone dose was not reported. No dose was reported for the PanoBorDex cohort."	The Company requests that the text be amended to the following: "DREAMM-2 trial (58 centers in North America, Australia, France, Germany, Italy, and UK) vs. NCRAS (UK, England)." "Dexamethasone dose was not reported. No dose was reported for the PanoBorDex cohort."	Typographical error – numerical Typographical error – spelling	**Typos changed.**

Page 77, Section 3.5.2.2, **Page 78, Section 3.5.2.2, Figure 11:** "PanoBorTex"	The Company requests that the text be amended to the following: "PanoBorDex"	Typographical error – spelling	**Typos changed.**
Page 80, Section 3.5.3.1: "…a PI and an ImID, received anti CD 38 treatment…"	The Company requests that the text be amended to the following: "…IMiD…" "…anti-CD38…"	Typographical error – spelling	**Typo changed.**
Page 82, Section 3.5.3.2: "dexamethosone"	The Company requests that the text be amended to the following: "dexamethasone"	Typographical error – spelling	**Typo changed.**
Page 84, Section 3.5.3.2, Figures 14, 15, and 16: "NSCAR"	The Company requests that the text be amended to the following: "NCRAS"	Typographical error – spelling	**Typo changed.**
Page 86, Section 3.5.4: "Additional studies from outside the CS do not provide any convincing evidence that PomDex is a clinically effective"	The Company requests that the text be amended to the following: "Additional studies from outside the CS do not	Typographical error – grammar	**Typo changed.**

	provide any convincing evidence that PomDex is clinically effective”		
Page 95, Section 4.2.1, Table 22: “Source of data for measurement of health-related quality of life”, “comparing Belamaf 2 mg with 4 mg”	The Company requests that the text be amended to the following: “Source of data for measurement of health-related quality of life”, “comparing Belamaf 2.5 mg/kg with 3.4 mg/kg.”	Typographical error – spelling	**Typo changed.**
Page 100, Section 4.2.7: “QLQ-MMY20”	The Company requests that the text be amended to the following: “QLQ-MY20”	Typographical error – grammar	**Typo changed.**
Page 107, Section 5.2.1.1: “Belmaf”	The Company requests that the text be amended to the following: “Belamaf”	Typographical error – spelling	**Typo changed.**
Page 108, Section 5.2.2: “The PSA results are presented in CS table 94, which are replicated in EAG Table 31 Incremental QALYs	The Company requests that the text be amended to the following: “The PSA results are presented in CS table 94,	Typographical error – spelling	**Typo changed.**

without severity adjustments were [redacted], with severity adjustments applied, this changed to [redacted].”	which are replicated in EAG Table 31**.** Incremental QALYs without severity adjustments were [redacted], with severity adjustments applied, this changed to [redacted].”		
Misspecification			
Page 17, Section 1.6, Issue 3: “4. RDI of [redacted] from Nikolaou et al. study for the base-case analysis.”	Remove any reference to this alternate assumption, and replace with a note that the company’s RDI calculations are accurate	Misrepresentation. The publication from Nikolaou et al. reports the **mean** dose intensity not the **relative** dose intensity (i.e. dose delays are not accounted for in Nikolaou et al.). It is incorrect to use the mean dose intensity as a proxy for the relative dose intensity, and the	**The EAG is happy with the Company’s RDI and revised it in the EAG’s report accordingly.**

		company figure of [redacted]% should be used since it is based on relative dose intensity.	
Page 79, Section 3.5.3, Table 20	In all the cells with DREAMM-3 and D3, the ITT population, 3L+ Len and PI exposed, should be specified. PFS for this population is 11.2 months not 11.28 months as stated.	Only results for the ITT population of DREAMM-3 have been reported. Also, to note that the ITT population from DREAMM-3, 3L+ Len and PI exposed, is different to the population under appraisal (5L+ TCR), and as such the two populations are not comparable.	**We have added a footnote to Table 20 as follows** ***"Note: the populations in the three studies were not aligned with each other"*** **11.28 typo changed to 11.2.**
Page 11, Table 1: Issue 5 is mislabelled.	Issue 5 should be Issue 4.	Misspecification	**Typo changed.**

Page 11, Table 1: Issue 3 is not accompanied by an entry in the Report Section column.	A section should be added for reference.	Missing information This will allow the company to better understand the issue being raised by the EAG	**Information has been added.**
Page 13/14, Issue 1: "Inappropriate/unavailable comparator options for 5L patients. The EAG consider that there is no evidence available to demonstrate that PomDex is an active treatment for the patient group. The EAG remain unconvinced that PomDex is an appropriate comparison for this population (patients with MM, who had received 3 or more prior lines of treatment, are refractory to a PI, an	The Company requests that the text be amended to the following: "Inappropriate/unavailable comparator options for 5L+ TCR MM patients. The EAG remain unconvinced that PomDex is an appropriate comparison for this population (patients with MM, who had received 4 or more prior lines of treatment, are refractory to a PI, an IMiD and who had failed an anti-CD38 mAb)."	Misrepresentation 5L+ TCR MM patients are considered in the submission. PomDex is recommended in patients with MM, who have received 4 or more prior lines of treatment, are refractory to a PI, an IMiD and who had failed an anti-CD38 mAb.	***'+ TCR MM'* added to Page 13.** **'*4 or more prior*' changed.** No further changed made, these are points of opinion not factual errors.

IMiD and who had failed an anti-CD38 mAb).” “DREAMM-2 was the only study available to compare Belamaf to PomDex”	“DREAMM-2 was the only clinical trial available to compare Belamaf to PomDex”	Other studies such as the NCRAS studies are available and have been used to inform the comparison of Belamaf to PomDex.	
Page 15, Issue 2: **“**The EAG agree with the company that the estimates produced via the unanchored MAIC (adjusted data) are implausible and contribute to further uncertainty in the economic analysis due to low patient numbers (see Section 3.4).”	The Company requests that the text be amended to the following: “The EAG agree with the company that the estimates produced via the unanchored MAIC (adjusted data) are uncertain and contribute to further uncertainty in the economic analysis due to low patient numbers (see Section 3.4).”	Misrepresentation The results of the MAIC are uncertain but do not lead to implausible numerical estimates.	**No change made**, these are points of opinion not factual errors.

Page 16, Section 1.5: **"**Due to the limitations of the clinical effectiveness evidence (Issue 1 and Issue 2) the EAG consider the cost-effectiveness results presented in the CS implausible.**"**	The Company requests that the text be amended to the following: "Due to the limitations of the clinical effectiveness evidence (Issue 1 and Issue 2) the EAG consider the cost-effectiveness results presented in the CS uncertain."	Misrepresentation The results of the cost-effectiveness analysis are uncertain but do not lead to implausible numerical estimates.	**No change made**, these are points of opinion not factual errors.
Page 18, Section 1.6, Issue 4: "TNT was re-constructed post-hoc using two post-hoc analyses, time to treatment discontinuation (TTD) and time to start of next treatment (TSNT)."	The Company requests that the text be amended to the following: "TTNT is defined in DREAMM-2 as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause."	Misrepresentation The definition of TTNT is misleading and not accurately described.	See comments above regarding TTNT. **Issue 4 changed**
Page 22, Section 2.1: "In the UK, the treatment options are limited for the patients categorised as	The Company requests that the text be amended to the following:	Misrepresentation RRMM patients are not necessarily also	**Changed to 'categorised as RRMM *particularly*, patients' on page 22**

RRMM i.e., patients who have had four previous lines of therapies and/or triple-class refractory (TCR) (i.e., refractory to a PI, an IMiD and an anti-CD38 mAb)."	"In the UK, the treatment options are limited for the patients who have had four previous lines of therapies and who are triple-class refractory (TCR) (i.e., refractory to a PI, an IMiD and an anti-CD38 mAb)."	5L+ TCR as is currently implied in the text.	
Page 26, Section 2.3, Table 3: In the 'Outcomes' row, "Time to start of next therapy (TSNT) (from discontinuation) was used in combination with TTD to estimate TTNT for Belamaf."	The Company requests that the text be amended to the following: "TTNT is defined as the time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause."	Misrepresentation Incorrect definition of TTNT.	See comments above regarding TTNT. **Table 3 changed.**
Page 30, Section 3.1.3.1: "The EAG was unable to ascertain why this information was only provided for four studies."	The Company requests that the text be amended to the following: "The company provided information only for the four studies relevant to	Misrepresentation The company provided rationale as to why information on the four studies was provided, namely	**No change made,** these are points of opinion not factual errors.

	the population in the decision problem."	that they were the only relevant studies for the target population (CS Appendix D, section D.1.4, Page 26).	
Page 30, Section 3.1.3.2: "The EAG was unable to ascertain why information was only provided for 17 publications"	The Company requests that the text be amended to the following: "The company provided information only on the 17 unique studies."	Misrepresentation The company provided rationale for there being 55 relevant clinical publications describing 17 unique studies, and this is what is detailed in Table 13 CS Appendix D, section D.1.4, Page 30.	**No change made**, these are points of opinion not factual errors.
Page 31, Section 3.1.3.2: "The EAG could not ascertain why the company conclude that DREAMM-2 was the "only identified trial" (CS	The Company requests that the text be amended to the following: "The company concluded that DREAMM-2 was the only clinical trial to evaluate the clinical	Misrepresentation Rationale is given in Table 10 CS Appendix D (page 26) and Table 13 CS Appendix D (page 31-37),	**No change made,** these are points of opinion not factual errors.

Document B, B.2.2 page 24) to evaluate the clinical efficacy and safety of Belamaf for the treatment of 5L+ patients.”	efficacy and safety of Belamaf for the treatment of 5L+ patients.”	where other RWE studies reported on Belamaf, but no other studies apart from DREAMM-2 were 'trials'.	
Page 31, Section 3.1.1: “In summary, the clinical SLR is of poor quality. It contains errors in the search, study selection and reasons for exclusion of studies.”	The Company requests that the EAG provide detail on the errors the EAG has identified.	The Company feels this is unclear based on the lack of details on specific errors identified by the EAG. In addition, the Company note that a rationale was provided for the selected publications being presented (CS Appendix D page 26, page 30, page 31-37) and full reasoning for exclusion of studies (for the original SLR - Appendix B	Errors are listed in EAG report Section 3.1 ‘critique of the methods of review’ **No change made**

		Response to Clarification Question A1a, page 1-124 and for the SLR update - CS Appendix D, section D.1.4, page 38-64). Finally, there are no material errors in the search terms.	
Page 31, Section 3.2: "DREAMM-2 trial Individual Patient Data (IPD). DREAMM-2 was an open label, one dose 2.5mg/Kg arm phase II, randomised trial,"	The Company requests that the text be amended to the following: "DREAMM-2 trial Individual Patient Data (IPD). DREAMM-2 was an open label, two arms (2.5 mg/kg and 3.4 mg/kg), phase II, randomised trial,"	Misrepresentation The DREAMM-2 trial evaluate two doses of Belamaf: 2.5 mg/kg and 3.4 mg/kg	**Changed as requested to page 31.**
Page 33, Section 3.2.1.1, Table 4: In the row "Blinding of outcome assessment", "Unclear	The Company requests that the text be amended to the following:	Misrepresentation	**Typo changed.**

risk" should be "Unclear risk of bias".	"Unclear risk of bias"		
Page 33, Section 3.2.1, Table 4: "Blinding of participants and personnel" is labelled as a "high risk of bias"	Suggest changing the assessment to "some concerns"	The DREAMM-2 CSR denotes that the data from the study were not summarised at any time point except the pre-defined analyses. This is therefore not a high risk of bias.	**No change made**, these are points of opinion not factual errors.
Page 33, Section 3.2.1.1, Table 4: In the row "Other sources of bias", "Unclear risk of bias" should be "Low risk of bias".	The Company requests that the text be amended to the following: "Low risk of bias"	"No other type of bias specified" does not pose a risk to the submission.	**No change made,** these are points of opinion not factual errors.
Page 38, Section 3.2.2.2: "No results for quality of life, for PFS or for OR were collected or reported in the CS." **Page 78, Section 3.5.3**: "The primary outcome was PFS with a primary	The Company requests that the text be amended to the following: "No results for quality of life, for PFS or for ORR were collected or reported in the CS."	Misrepresentation	**Typos corrected.**

completion date of September 2022; secondary outcomes included OS and OR."	"The primary outcome was PFS with a primary completion date of September 2022; secondary outcomes included OS and ORR."		
Page 39, Section 3.2.3: "The company also present efficacy outcomes results for PanoBorDex but reiterate that they do not consider it a main comparator in this appraisal (see Table 3)."	"The company also present efficacy outcomes results for PanoBorDex but reiterate that they do not consider it a main comparator in this appraisal (see Table 2)."	Misrepresentation	**Typo changed.**
Page 40, Section 3.2.3, Table 6, **Page 52, Section 3.3.5, Table 11,** **Page 58, Section 3.3.7, Table 14,** **Page 58, Section 3.3.7, Table 15** **and Page 59, Section 3.3.7, Table 16**	Add definition of superscript £ which appears in column headings	Misrepresentation	£ is a footnote to inform that ITT sample includes [redacted] patients ([redacted] who received only three prior lines of therapy which is outside of the population considered in this appraisal **Now included where missing in Tables 6 11 14 15 16**
Page 42, Section 3.3.1.2: "Patients became eligible for inclusion into the cohort if	The Company requests that the text be amended to the following:	Misrepresentation	**Typo changed on page 42.**

they had received 5L+ (5th or more lines of treatment and TCR)."	"Patients became eligible for inclusion into the cohort if they were 5L+ (4 or more prior lines of treatment) and TCR."	5L+ patients have received 4 prior lines of therapy	
Page 46, Section 3.3.3.2, Table 8: "Although PFS was measured in DREAMM-2 it was not reported for the NCRAS study, so TTNT was calculated instead)."	The Company requests that the text be amended to the following: "Although PFS was measured in DREAMM-2 it was not reported for the NCRAS study, so TTNT was used instead)."	Misrepresentation of TTNT outcome	See above comment regarding TTNT. **Calculated changed to used**
Page 52, Section 3.3.5, Table 11	Add space so that column heading reads "NCRAS AD PanoBorDex (n=[redacted])"	Typographical error – grammar	**Typo changed.**
Page 55, Section 3.3.6.1, Table 12	The sample size of 97 for DREAMM-2 does not need to be marked as AIC.		**AIC removed.**
Pages 65 – 78, Section 3.5 **Pages 80 – 85, Section 3.5.3**	All in-text cross-references to figures are misaligned; the figure is	Misrepresentation Unclear which figure is being	**Figure cross references have been checked and changed throughout the EAG report.**

	n, the in-text reference is n+1. Figure headings are also below the figures.	referred to in the text unless the ctrl + click function is performed to check	
Page 67, Section 3.5.1.3: "After literature search and SLR, the submission was unable to find any study that presented useful results for a suitable comparator to Belamaf in 5L treatment for a TCR population." "Consequently, the CS conducted the "NCRAS-study" (National Cancer Registration and Analysis Service -study) aiming to identify 5L PomDex patients who were TCR."	The Company requests that the text be amended to the following: "After literature search and SLR, the submission was unable to find any study that presented useful results for a suitable comparator to Belamaf in 5L+ treatment for a TCR population." "Consequently, the CS conducted the "NCRAS-study" (National Cancer Registration and Analysis Service -study) aiming to identify 5L+ PomDex patients who were TCR."	Misrepresentation The population of interest is 5L+ TCR MM patients, not 5L	**Typos changed.**

Page 67, Section 3.5.1.3: "Consequently, the CS conducted the "NCRAS-study" (National Cancer Registration and Analysis Service -study) aiming to identify 5L PomDex patients who were TCR."	The Company requests that the text be amended to the following: "Consequently, the CS conducted the "NCRAS-study" (National Cancer Registration and Analysis Service -study) aiming to identify 5L+ patients who were TCR."	Misrepresentation The NCRAS dataset considered a 5L+ cohort overall and not just those patients who received PomDex.	**Typo changed.**
Page 71, Section 3.5.1.4: "The CS points out that in TA427 NICE recommends PomDex for 4L therapy"	The Company requests that the text be amended to the following: "The CS points out that in TA427 NICE recommends PomDex for 4L+ therapy"	Misrepresentation	**Typo changed.**
Page 71, Section 3.5.1.4: "The NCRAS study, like DREAMM-2, is a single arm study so that the proportion of observed OS that can be specifically attributed to the influence of PomDex is uncertain."	The Company requests that the text be amended to the following: "The NCRAS study is a retrospective study evaluating multiple therapies, so the proportion of observed OS that can be	Misrepresentation DREAMM-2 is a two-arm trial with no comparator arm, NCRAS is a retrospective study evaluating multiple therapies.	**'two-arm trial with no comparator arm' added to page 71**

	specifically attributed to the influence of PomDex is uncertain."		
Page 77, Section 3.5.2.2: "Within the economic model, the EAG was unable to find KM data corresponding to the adjusted BELAMAF plot and so the EAG could not test this"	To remove text.	Misrepresentation This data can be found on the NCRAS MAIC - KM sheet in the economic model.	This is not a factual error. The EAG were unable to find the information. We have checked again and: The KM data in "NCRAS MAIC - KM sheet in the economic model" does **not** correspond to the plot shown in CS Fig 29; the plot in Fig 29 has numerous steps not seen in the data in the economic model sheet. **No change made.**
Page 77, Section 3.5.2.2: "The "observed Belamaf" plot is calculated rather than observed."	The Company requests that the text be amended to the following: "The "observed Belamaf" plot is observed."	Misrepresentation The data in this plot is observed	Note this was changed in clarification response A9. **Changed in the EAG report page 77.**

Page 82, Section 3.5.3.2: "On the basis of this meta-analysis the EAG cannot conclude that PomDex is effective, because it has been shown equivalent or better than a comparator known to be superior to no treatment / placebo"	The Company requests that the text be amended to the following: "On the basis of this meta-analysis the EAG cannot conclude that PomDex is effective, because it has not been shown equivalent or better than a comparator known to be superior to no treatment / placebo"	Misrepresentation	**Typo changed.**
Page 86, Section 3.5.4: "The DREAMM-3 trial is the only available randomised comparison of Belamaf and the proxy-comparator PomDex.**"**	The Company requests that the text be amended to the following: "The DREAMM-3 trial, in a 3L+ Len and PI exposed population, is the only available randomised comparison of Belamaf and the proxy-comparator PomDex."	Misrepresentation Population of the DREAMM-3 trial needs to be specified to avoid any confusion with the DREAMM-2 trial population	Already changed in line with previous comment. **No further change made.**
Page 90, Section 3.6.2: "The DREAMM-3 trial which evaluates safety/efficacy of	The Company requests that the text be amended to the following:	Misrepresentation Null results have only been	**"In 3L+ Len and PI exposed MM patients" added**

Belamaf compared to PomDex in RRMM 5L + TCR patients has recently reported null results (see Section 3.5.3).”	“The DREAMM-3 trial, which evaluates safety/efficacy of Belamaf compared to PomDex in 3L+ Len and PI exposed MM patients, has recently reported null results (see Section 3.5.3).”	reported for the ITT population of DREAMM-3 (3L+ Len and PI exposed), not the 5L+ TCR subgroup	
Page 92, Section 4.1.1: “For example, MeSH/Emtree terms for relapsed and refractory are not used.”	Text to be deleted.	Misrepresentation This is inaccurate and the tables referred to by the EAG state as part of the population search terms: "relaps*" or "refract*" or "recurren*" or "resistant" or "prior treatment" or "prior treatments" or "prior therapy" or "prior therapies" or "previously treated" or "third line" or "3rd line"	The full search line in the tables is: “(relaps* or refract* or recurren* or 'resistant' or 'prior treatment' or 'prior treatments' or 'prior therapy' or 'prior therapies' or 'previously treated' or 'second line' or 'third line' or '2nd line' or '3rd line' or 'fourth line' or '4th line')**.ti,ab.**”. The **ti, ab** field codes indicate that only the titles and abstracts of database records are being searched, not the MeSH/EMTREE headings. It is best practice to use both approaches. See ‘4.4.4 Controlled vocabulary and text words’ in the Cochrane Handbook for Systematic Reviews of Interventions: https://training.cochrane.org/handbook/current/chapter-04#section-4-4-4 **No change made.**

		or "fourth line" or "4th line".	
Page 93, Section 4.2: "The trial is a dose-response study"	The Company requests that the text be amended to the following: "The trial evaluates two different doses of the drug"	Misrepresentation Inaccurate description of DREAMM-2	**"evaluates two different doses of the drug" added to page 93 and on page 121**
Page 94, Section 4.2: "The DREAMM-2 study is a small trial (n=92) and the response rate for Belamaf (considering the partial responses) is [redacted]."	The Company requests that the text be amended to reflect the final analysis for the 2.5 mg/kg (n=97) ITT population, to: "The DREAMM-2 study is a small trial and the overall response rate (≥PR) for Belamaf in the 2.5 mg/kg ITT population (n=97) according to the final analysis is [redacted]."	Misrepresentation	**Typo changed**
Page 107, Section 5.2.1.1: "The OWSA results have been presented only for	The Company requests that the text be amended to the following: "The OWSA results have been presented for	Missing information	**"(PanoBorDex against Belamaf in CS appendices)."** **Added to page 107 for clarity.**

PomDex against Belamaf.”	PomDex against Belamaf in the core of the submission, and for PanoBorDex against Belamaf in the appendices”.		
Page 118, Section 5.5.2: “The DREAMM-3 trial that evaluates safety/efficacy of Belamaf compared to PomDex in RRMM 5L+ TCR patients unpublished, so its findings were not included in this CS”	The Company requests that the text be amended to the following: “The DREAMM-3 trial that evaluates safety/efficacy of Belamaf compared to PomDex in 3L + Len and PI exposed patients is unpublished, so its findings were not included in this CS”	Misrepresentation of the DREAMM-3 ITT population.	**“3L + Len and PI exposed patients” added to page 118**
Page 120, Section 5.5.2: “The company presented a three-health state partitioned survival analysis to run the economic model.”	The Company requests that the text be amended to the following: “The company presented a four-health state partitioned survival analysis to run the economic model.”	Misspecification The company base-case model was a four-state partitioned survival model	**Change made to page 120.**

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13 February 2023**. 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 received during engagement, 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 during engagement 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.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	GlaxoSmithKline
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Appropriateness of pomalidomide plus dexamethasone as a valid comparator to belantamab mafodotin in the NHS context (section 3.5.1.3, Table 3)	Yes (new feedback from the Company's clinical experts and new analyses of the NCRAS dataset)	Pomalidomide in combination with dexamethasone (PomDex) was identified by NICE as a comparator in the final scope and therefore was considered when determining the most appropriate comparator for the population under evaluation in this appraisal (5L+ TCR MM). The EAG remain unconvinced that PomDex is an appropriate comparator for this population (5L+ TCR MM), as most patients in this setting will have received isatuximab in combination with pomalidomide and dexamethasone (IsaPomDex) at 4L and therefore they will be refractory to Pomalidomide on relapse. During the technical engagement call the Company requested clarification on whether the EAG consulted clinical experts had considered IsaPomDex (currently recommended in the Cancer Drugs Fund [CDF]) when defining the MM pathway and informing the most appropriate comparator. Response from two clinical experts was shared with the Company: • First EAG consulted expert: "*Most people will use Isa+POM in 4th line if they had no exposure to CD38 immunotherapy prior.*" • Second EAG consulted expert: "*Isa Pom Dex is fixed at 4th line/ 3rd relapse from the CDF access point of view. In addition, as Daratumumab monotherapy is NICE approved at 4th Line and given until progression so patients with CD38 refractory disease will be able to access Pom Dex at 5th line/ 4th relapse if they have not received it in a prior line of therapy. At late relapse only a small number of patients will be fit enough to proceed to further*

		treatment dependent upon 1. drug class refractoriness, 2. patient frailty and 3. accumulative co-morbidities and adverse effects from prior treatments. So, in conclusion I would suggest, that most patients at 5L/4th relapse are either unsuitable for further treatment or will have received prior Pomalidomide and despite triplet therapy being the preferred option, at this stage Pomalidomide will be given with dexamethasone alone." The first EAG consulted expert feedback suggests that CDF-funded option IsaPomDex was considered when defining the MM pathway and consequently PomDex was not deemed appropriate as a comparator. The conclusions on the appropriateness of PomDex as a comparator in 5L+ TCR MM remains unclear from the second EAG consulted expert. Clinical experts consulted by the Company have described two situations that could influence the perception of the MM pathway: • In a world where CDF options are available, IsaPomDex is the most frequently used option at 4L [TA658, CDF] and consequently, patients at 5L are likely to be Pom-refractory limiting the use of PomDex in the 5L+ TCR setting. • In a world where CDF-options are not considered, patients would typically receive Dara monotherapy or PomDex at 4L [TA783/TA427]. Patients who receive PomDex at 4L and progress are typically not refractory to an anti-CD38 therapy and therefore they are not considered to be at 5L+ and TCR. It should be noted that some patients receiving PomDex at 4L may be exposed to an anti-CD38 therapy as part of the DaraVTD 1L quadruplet, however, NICE has recommended 4 induction and 2 consolidation cycles of Dara which therefore is unlikely to result in anti-CD38 refractoriness [TA763].(1) Thus, when considering the 5L+ TCR population, most patients receive Dara monotherapy at 4L, and they would then typically receive PomDex in the 5L+ setting. The NICE HTA guidelines stipulates in section 2.2.15 that "*Technologies that NICE has recommended with managed access are not considered established practice in the NHS […]*".(2) Hence, the 'world without CDF-options' was considered by the Company when defining the UK MM pathway and to confirm the selection of PomDex as the most relevant comparator. This approach is consistent with how NICE has defined the MM pathway in previous appraisals. For example, in the recent appraisal reviewing the additional evidence collected as part of the CDF managed access agreement for Dara monotherapy [TA783, April 2022], the final appraisal document

		did not consider CDF approved triplet IsaPomDex as a relevant comparator at 4L [TA658, November 2020], stating in section 3.3 that *"The clinical expert at the meeting explained that daratumumab monotherapy or pomalidomide plus dexamethasone are the most commonly used options after 3 previous lines of treatment."*(1) In addition, the NCRAS dataset reflects the MM pathway in a world without CDF-options (an embargo is in place as part of an agreement between NCRAS and NHS England, to prevent release of data relating to CDF evaluations prior to a decision from NICE) and demonstrates that in this situation, PomDex is the main comparator for 5L+ TCR patients with [redacted]% use (Figure 1). **Figure 1. NCRAS treatment patterns for 5L+ TCR MM**  Abbreviations: NCRAS: National cancer registration and analysis service; 5L+: Fifth line plus; TCR: Triple class refractory; Pom: Pomalidomide; Dex: Dexamethasone; Pano: Panobinostat; Bor:

		Bortezomib; NICE: National institute for health and care excellence; Cyclo: Cyclophosphamide; RRMM: Relapsed refractory multiple myeloma **Altogether, the NICE final scope, feedback derived from the clinical experts consulted by the Company and the NCRAS treatment pattern data confirm that PomDex is the most relevant comparator for this appraisal.**
Key issue 2: Inappropriate source data presented as evidence for efficacy of belantamab mafodotin and pomalidomide plus dexamethasone (section 3.2.1, 3.2.2)	Yes	***1. New evidence provided in an addendum to the submission*** The Company acknowledge some of the limitations and uncertainty associated with the cost-analyses presented in the original submission. However, the original submission included data from the final analysis of the DREAMM-2 trial which is a key source of evidence providing a robust demonstration of the clinical effectiveness of Belamaf in a population of 5L+ TCR MM patients. The DREAMM-2 trial underpins the current GB license for Belamaf in the population under evaluation. ***2. UK RWE study of Belamaf efficacy from the [redacted]*** Since the original submission, additional evidence has become available, namely a non-GSK RWE study reporting efficacy and safety data for Belamaf in a population of UK patients with 5L+ TCR MM who have received Belamaf as part of the [redacted]. Details on study methodology and results are provided in Section 2.1 and Section 3.1 of the submission addendum. In this real-world cohort of [redacted] heavily pre-treated 5L+ TCR MM patients, clinically meaningful and deep responses were achieved with single agent Belamaf evidenced by an overall response rate of [redacted]% and [redacted]% of responders achieved VGPR or better. A median OS of [redacted] months and a median PFS was [redacted] months were reported in this analysis, demonstrating the high potential for Belamaf to provide significant clinical benefits to patients with 5L+ TCR MM in the UK who are otherwise left with extremely limited efficacious options. The feasibility of an unanchored MAIC vs PomDex using data from the NCRAS dataset (presented in the original submission) was explored. However, in both datasets some baseline characteristics were incomplete or missing and therefore a MAIC was deemed unfeasible.

		As an alternative, a naïve comparison of Belamaf ([redacted]) vs PomDex (NCRAS) was selected to inform the new base-case in the cost-effectiveness analysis (CEA) as described in the response form. ***3. <u>Subgroup of 5L+ TCR MM patients from the DREAMM-3 trial</u>*** In addition, since the original submission, top line data for the DREAMM-3 trial was reported in November 2022.(3) The DREAMM-3 trial compares Belamaf to PomDex (2:1 randomisation, Belamaf:PomDex respectively) in patients with 3L+ relapsed refractory multiple myeloma who are exposed to both lenalidomide and a proteasome inhibitor. Study methodology and results are described in Section 2.2 and Section 3.2 of the submission addendum. The trial includes a subset of patients with 5L+ TCR MM including [redacted] and [redacted] patients in the PomDex and Belamaf arms, respectively, although the study was not powered to report on this subgroup. Due to the [redacted] number of PomDex patients in this subgroup, [redacted] can be made regarding the efficacy of PomDex and the comparative efficacy of Belamaf vs PomDex. The uncertainty is evidenced by the [redacted] associated with medians and hazard ratios and [redacted]. Considering the very high degree of uncertainty associated with this data, the inclusion in a cost-effectiveness scenario analysis was deemed inappropriate. ***4. <u>Use of single arm trial data in previous NICE technology appraisals</u>*** The EAG questioned whether the use of a single arm trial was appropriate and sufficient to demonstrate the clinical efficacy of Belamaf given the absence of a control arm. In NICE appraisals TA510 and TA783 (daratumumab monotherapy in 4L RRMM initial submission and CDF-exit re-appraisal) the key source of efficacy evidence for Dara monotherapy was the single arm trial MMY2002. While this was identified by the Committee as a limitation, it was deemed sufficient to inform the MAIC vs PomDex and PanoBorDex used as the base case cost-effectiveness analysis supporting both the CDF-entry and the routine commissioning of Dara monotherapy in the CDF-exit re-appraisal. Similarly, in NICE appraisal TA586 (lenalidomide plus dexamethasone after one prior therapy in MM), a single-arm trial of melphalan plus prednisolone was used to inform the efficacy of this

comparator, using the study to derive a hazard ratio for overall survival of lenalidomide compared with melphalan plus prednisolone.

The use of single-arm trials in oncology is common and widely accepted as they allow patients with high unmet need expedited access to novel therapies. They are primarily conducted in relapsed/refractory patient populations,(4) and are common at phase 1 and 2. DREAMM-2 is absent of a comparator arm as there is not a clearly defined standard of care (SOC) for triple-class exposed/refractory patients in real world practice, as evidenced by the 92 combinations of SOC treatments received by patients in the LocoMMotion study.(5) Finally, due to small patient numbers in this late stage of the disease, it can be challenging to obtain data sources with sufficient patient numbers and with similar baseline characteristics for both Belamaf and PomDex.

5. Unadjusted HRs for the efficacy outcome measures

As requested by the EAG, the unadjusted HRs for the efficacy outcome measures from the naïve comparison of Belamaf (DREAMM-2) and PomDex (NCRAS) are provided below.

Table 1: Unadjusted DREAMM-2 vs NCRAS naïve comparison hazard ratios

Outcome	HR Belamaf (DREAMM-2) vs PomDex (NCRAS)
OS	[redacted]
TTNT	[redacted]
TTD	[redacted]

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Other issue 3: Minor changes to the economic model which include EAG preferred assumptions on: - calculated utility weights - severity modifier choice	Section 5.4.3, Table 2	Yes	***1. Utility weights*** The EAG propose a cap on the QoL for 5L+ TCR MM patients at a level consistent with patients who have experienced one relapse/refractory treatment. They propose that the PFS health state utility is set at 0.647, taken from the APOLLO trial.(6) The Company note that other RRMM NICE appraisals have used health state utility values higher than this cap and have been accepted. In TA658 (1) for IsaPomDex in 4L RRMM, the utility values accepted for decision-making for the “PF: on-tx” health state was 0.731 for IsaPomDex and 0.717 for PomDex, respectively. The Company’s model in TA427 (7) for pomalidomide in 3L+ RRMM patients used a utility value accepted for decision-making of 0.76 for the “PF: on-tx” health state.

			The utility value used for the PFS: on-tx in the Company's base case model in the original submission was 0.759. In line with TA658 and TA427, the Company suggests that the cap on the utility value of the PFS health state is not applied. In addition, the EAG utility scenario implies that the health state utility value for the PD health state is larger than that for the PFS: on-tx health state. As referenced above, both TA427 and TA658 use utility values for PFS that are greater than those for PD, which in both cases were accepted. In addition, the Company would like to point out that such utility values are consistent with the course of disease progression in MM. HRQoL is expected to worsen over time such that overall prognosis in PF health states is better than PD.(8) Therefore, the EAG's assumption is considered by the Company to be unrealistic and thus this scenario does not hold face validity. The Company would also like clarify that in the base-case there are 4-health states; PFS: on-treatment, PFS: off-treatment, PD, and death. The utility values used in the Company model were from the 13-month follow-up analysis of DREAMM-2, based on mapping patient reported outcomes (PROs) from the EORTC-QLQ-C30 and EORTC-QLQ-MY20 to EQ-5D-3L using an algorithm by Proskorovsky et al,(9) as outlined in Section B.3.4 of the CS. Utility analysis has now been performed on the final data cut (40 months follow-up) from DREAMM-2 to provide the most up to date estimates for the health state utility values in the base-case 4-health state model. The methods for calculating the updated health state utility values remain the same as described in Section B.3.4 of the CS. Due to missing data, the updated analysis utilises PROs from Week 7 and at the end of treatment in the fitted models, and is based on [redacted] patients, compared to [redacted] in the primary analysis. The updated health state utility values are [redacted] (95% CI [redacted]) for PFS: on-tx (was [redacted]), [redacted] (95% CI [redacted]) for PFS: off-tx (was [redacted]) and [redacted] (95% CI [redacted]) for PD (was [redacted]).

			These values remain aligned with previous TAs outlined above, and PFS utility values have decreased from those previously used in the Company's model, helping to alleviate the EAGs concerns. Upon using these values in the cost-effectiveness model in the Company's preferred base case following technical engagement, incremental costs are [redacted], and incremental QALYs [redacted], meaning Belamaf still dominates and the incremental cost-effectiveness ratio (ICER) goes from [redacted] in the base-case, to [redacted]. The Company suggest that these health state utility values are used in the revised base-case. ***2. Severity modifier*** In addition to the above issues, the EAG also suggest that the QALY weighting applied in the Company model seems inconsistent with the NICE recommendations and the Company's deterministic base-case analysis.(2) The EAG argue that for QALY weighting to align with the deterministic base case analysis, the QALY weighting should not be based on 95% CIs or results of the PSA. However, the Company note that NICE methods do not specify that deterministic base cases are required for calculating severity weighting. Furthermore, in the revised health technology evaluations manual NICE indicates that probabilistic approaches should be preferred when presenting the base case cost-effectiveness results which supports the approach considered. In the Company's view, the New Methods assume a probabilistic approach to severity. The Company would like to emphasise that we therefore do not agree with the EAG's interpretation of the New Methods and would value the opportunity to put this point to the Committee if there is time to do so. On this basis, the Company would like to reiterate the appropriate use of a 1.7x multiplier.
Other issue 4: Inappropriate selection of	Sections 3.5.1.1, 3.5.1.2	No	***1. TTNT selected as a proxy for PFS***

proxy progression-free survival (PFS) measure			The EAG disagree with the selection of a proxy for PFS in the economic model indicating that time to start of next treatment (TSNT) is used to estimate proxy-PFS (TTNT) for intervention and comparator. Furthermore, the EAG indicates that the proxy-PFS (TTNT) is unlikely to have been fairly estimated for Belamaf and PomDex. This issue was discussed during the technical engagement call, where the Company clarified the definition of TTNT in DREAMM-2 which is independent of TSNT. TTNT was not a pre-specified outcome in the DREAMM-2 study protocol (10) , however TTNT data was generated in a post-hoc analysis and was defined as “time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause”, which is consistent with the definition of TTNT in NCRAS. While both PFS and TTNT were available in the DREAMM-2 trial, PFS was not reported in the NCRAS dataset for PomDex. Therefore, to allow a fair comparison of Belamaf vs PomDex and reduce the risk of bias, a comparison of Belamaf vs PomDex for TTNT was selected and used as a proxy for PFS in the cost-effectiveness model. The Company acknowledges that using TTNT as a proxy for PFS could lead to the accumulation of more QALYs than what could be observed with PFS hence, TTNT was selected as a proxy-PFS consistently for both treatment arms to limit the risk of bias in favour of the arm for which TTNT would be used and compared with PFS for the other arm. ***2. Setting difference may impact the comparability of TTNT*** The EAG also questioned the healthcare systems differences between DREAMM-2 trial and NCRAS study, in terms of treatment pathways and availability of technologies and the resulting impact on outcomes comparability, for instance on TTNT. In the DREAMM-2 trial, disease response assessment (including progressive disease and relapse) must be conducted Q3W according to the IMWG Uniform Response Criteria for Multiple Myeloma 2016,(11)

			which is consistent with clinical feedback received stating that in the UK patients attend hospital approx. Q3W for routine blood tests to assess disease response (including progressive disease and relapse). Thus, it is expected that PFS recording is consistent across both settings. A '*watch and wait*' period may be observed between progression and initiation of the next line of therapy to allow for the resolution of toxicities or for a decision to be made on next treatment, this would be observed regardless of the setting. In conclusion, while differences in healthcare systems may exist between the DREAMM-2 trial centres and the NCRAS NHS setting, this is unlikely to impact the comparability of outcomes such as TTNT. ***3. <u>The use of a proxy-PFS is common in oncology appraisals</u>*** In context where limited data for PFS is available, the use of proxy is typically observed. In the context of MM, proxies for PFS have been used in previous TAs such as TA763 (12) (daratumumab with bortezomib, thalidomide and dexamethasone for untreated MM) and TA783 (13) (daratumumab monotherapy for treating RRMM). Both appraisals included RWE collected from the SACT dataset which did not report PFS. In TA763 (12), the Company used TTNT (defined as the time from initiation of first therapy to death, censoring or the start of a new treatment) from the SACT dataset as a proxy for PFS while in TA783 (13), TTD was selected as the proxy PFS in a naïve comparison of daratumumab (SACT dataset) and PanoBorDex (PANORAMA trial). In both instances, the use of a proxy for PFS was accepted by the EAG and the Committee.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)*
The Company's preferred base case following technical engagement. This includes all changes in the subsequent rows of this table:			Belamaf was associated with higher average QALYs ([redacted]) and lower average costs ([redacted] cost savings) when compared to PomDex suggesting that Belamaf is dominant vs PomDex over a 25-year horizon, with an ICER of [redacted] and an NMB of [redacted]. The difference from the base-case ICER in response to the technical engagement is: [redacted]
Issue 2: Inappropriate source data presented as evidence for efficacy of belantamab mafodotin and pomalidomide plus dexamethasone	The Company performed a naïve (unadjusted) comparison of clinical outcomes from the DREAMM-2 trial and NCRAS study. The Company used TTNT as	The Company has updated their base case to incorporate the [redacted] data using a naïve (unadjusted) comparison of clinical outcomes from the [redacted] study and NCRAS study. The comparison uses TTNT data from NCRAS as before, compared to Belamaf PFS data from the [redacted] dataset.	The difference from the base-case ICER in response to the technical engagement is: [redacted] (Belamaf remains dominant vs PomDex with an ICER of [redacted])

Issue 4: Inappropriate selection of proxy progression-free survival (PFS) measure	a proxy for PFS, using data from DREAMM-2 generated in a post-hoc analysis defined as “time from randomisation until the date of start of follow-up anti-cancer treatment or death due to any cause”, which is consistent with the definition of TTNT in NCRAS.	To ensure the analysis did not overestimate the clinical effectiveness of Belamaf, Belamaf PFS was capped at 2 years, thereby better reflecting [redacted] data presented in the [redacted] abstract. This cap was also applied to PomDex PFS. A 50% waning was applied to PFS to adjust the proportion of patients in PFS after 1-year in both arms. To reflect the Belamaf dosing information in the [redacted] dataset, RDI was calculated to be [redacted]%. Use of subsequent therapy data for Belamaf from the [redacted] dataset was attempted, however gave very low numbers. Therefore, the NCRAS subsequent therapy data were assumed for Belamaf. The updated efficacy data impacts the total routine monitoring costs and one-off concomitant therapy and subsequent treatment costs used in the base case analysis, however the methodology used to calculate these costs remains as in the original submission. Please see Section 2.1 of the submission addendum document for a description of the [redacted] study and Section 4.1.2 for a description of the parametric survival modelling.	

Issue 3: Calculated utility weights	The utility values used in the Company model were from the 13-month follow-up analysis of DREAMM-2	The Company has updated their base case to incorporate utilities based on the final data cut (40 months follow-up) from DREAMM-2. Please see Issue 3 under Additional issues for further information on this.	The difference from the base-case ICER in response to the technical engagement is: [redacted] (Belamaf remains dominant vs PomDex with an ICER of [redacted])
N/A		[redacted]. Please see section 4.2.1 of the submission addendum document.	The difference from the base-case ICER in response to the technical engagement is: [redacted] (Belamaf remains dominant vs PomDex with an ICER of [redacted])

*Severity modified

Summary of cost-effectiveness results

- The deterministic results demonstrate that Belamaf is dominant when compared to PomDex, with higher average QALYs ([redacted]) and lower average costs ([redacted] cost savings) resulting in a positive net monetary benefit of [redacted].
- The results from the scenario analyses show that the cost-effectiveness results are robust to changes in model structure and inputs, with Belamaf continuing to dominate PomDex in all deterministic and probabilistic scenarios. The scenarios with the greatest impact on incremental results are assuming 15% wastage and the PFS utility value proposed by the EAG. In addition, the probabilistic base-case analysis is consistent with the deterministic base-case results.
- Overall, and mindful of NHS resources, these results demonstrate that Belamaf, a much-needed new mechanism of action, would be a valuable addition to the treatment pathway for patients with 5L+ TCR MM in England and Wales who are currently faced with very limited treatment alternatives towards the end stages of their disease.

Sensitivity analyses around revised base case

Probabilistic total costs, life years gained (LYG), quality-adjusted life years (QALYs) and the ICER for Belamaf versus PomDex are presented in Table 2. An incremental cost-effectiveness plane (ICEP) scatter plot, cost-effectiveness acceptability curve (CEAC), and cost-effectiveness acceptability frontier (CEAF) were produced to graphically illustrate the level of variability and uncertainty in the results, as shown in Figure 2, Figure 3, and Figure 4, respectively.

In the base-case probabilistic sensitivity analysis, on average Belamaf generates [redacted] incremental QALYs with cost savings of [redacted] over a 25-year horizon, dominating PomDex (Table 2).

The ICEP (Figure 2) shows that [redacted]% of results are in the southeast quadrant (i.e. Belamaf is less costly and more effective), [redacted]% are in the northeast quadrant (i.e. Belamaf is more costly and more effective), [redacted]% are in the southwest quadrant (i.e. Belamaf is less costly and less effective) and [redacted]% are in the northwest quadrant (i.e. Belamaf is more costly and more effective).

The CEAC and CEAF show that at a willingness-to-pay (WTP) threshold of £30,000, Belamaf has a [redacted]% chance of being cost effective (Figure 3 and Figure 4).

Table 2. PSA base-case results for Belamaf versus PomDex

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYs	Severity modified incremental QALYs	ICER versus severity modified incremental QALYs (£/QALY)
PomDex	[redacted]	[redacted]	[redacted]	-	-	-	-
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

Figure 2. Incremental cost-effectiveness plane for Belamaf versus PomDex

[redacted]

Figure 3. Cost-effectiveness acceptability curve Belamaf versus PomDex

[redacted]

Figure 4. Cost-effectiveness acceptability frontier for Belamaf versus PomDex

Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) tornado diagram presenting the top 10 most sensitive parameters is given in Figure 5, with tabulated results presented in

Table 3. Results are shown in terms of net monetary benefit (NMB) using a WTP threshold of £30,000. Across all parameters varied there was a positive net monetary benefit. The model was most sensitive to RDI for Belamaf and pomalidomide, followed by OS and TTD for PomDex.

Figure 5. OWSA tornado diagram for Belamaf versus PomDex using NMB

Table 3. Tabulated OWSA results for Belamaf versus PomDex using NMB

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pomalidamide relative dose intensity	[redacted]	[redacted]	[redacted]
Belamaf relative dose intensity	[redacted]	[redacted]	[redacted]

PomDex - TTD	[redacted]	[redacted]	[redacted]
PomDex - OS	[redacted]	[redacted]	[redacted]
Utility: PFS on-tx	[redacted]	[redacted]	[redacted]
Utility: PD on-tx	[redacted]	[redacted]	[redacted]
Belamaf subsequent treatment cost	[redacted]	[redacted]	[redacted]
Belamaf subsequent treatment % patients	[redacted]	[redacted]	[redacted]
PomDex concomitant therapies/supportive additional cost per cycle	[redacted]	[redacted]	[redacted]
PomDex subsequent treatment cost	[redacted]	[redacted]	[redacted]

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis, OS, overall survival; PD, progressed disease; PFS, progression free survival; TTD, time to treatment discontinuation.

A number of scenarios were explored to investigate the impact of using different assumptions, values, and data sources for model inputs. These are outlined in full below and summarised in Table 4.

Table 4. Scenarios explored in the cost-effectiveness analysis

#	Category	Base-case	Scenario	
		Value	Value	Rationale
1	Survival curves	PFS: Exponential OS and TTD: Weibull	PFS: Weibull OS and TTD: Exponential	Base-case and scenario analysis models selected following guidance in TSD 14. Alternative next best fitting curves tested in a scenario.
2	Number of health states	Four health states	Three health states	Four health states represent the time spent off-treatment by DREAMM-2 patients while progression-free which also aligned with previous NICE TA783 (13). Three health state model scenario performed to test structural uncertainty.
3	Wastage	No wastage	15% wastage	Vial sharing is expected to be prevalent in clinical practice during Belamaf administration. To test this assumption, a scenario explores the impact that vial sharing is only applicable in 15% of Belamaf administrations based on clinical feedback that wastage may be between 0% and 15%.
4	Utilities	DREAMM-2 final analysis (40 months)	DREAMM-2 primary analysis (13 months)	DREAMM-2 primary analysis values were used in the original submission.
5			EAG utilities	To reflect EAG preferences for utilities.
6	Subsequent treatment	43% of patients on Belamaf receive subsequent treatment (based on NCRAS)	5% decrement applied to proportion of Belamaf patients receiving subsequent treatment (38%)	NCRAS has been used for subsequent treatments in the base case based on a large proportion of missing subsequent treatments in the [redacted] dataset. The [redacted] data that are available suggest that the proportion of patients receiving

#	Category	Base-case	Scenario	
		Value	Value	Rationale
				subsequent treatments may be lower. Therefore an arbitrary decrement of 5% is considered.
7			Distribution of subsequent treatments received informed by clinical opinion	As [redacted] data are incomplete, there remains uncertainty surrounding subsequent treatment costs. This scenario explores using different resource use estimates based on clinical opinion.

Table 5. Results for scenario analyses

#	Category	Base-case	Scenario	Deterministic				Probabilistic
				Inc. costs (£)	Inc. LYs	Inc. QALYs*	ICER (£)*	ICER (£)*
1	Survival curves	PFS: Exponential OS and TTD: Weibull	PFS: Weibull OS and TTD: Exponential	[redacted]	[redacted]	[redacted]	Dominating	Dominating
2	Number of health states	Four health states	Three health states	[redacted]	[redacted]	[redacted]	Dominating	Dominating
3	Wastage	No wastage	15% wastage	[redacted]	[redacted]	[redacted]	Dominating	Dominating
4	Utilities	DREAMM-2 final analysis (40 months)	DREAMM-2 primary analysis (13 months)	[redacted]	[redacted]	[redacted]	Dominating	Dominating
5	Utilities		EAG utilities	[redacted]	[redacted]	[redacted]	Dominating	Dominating
6	Subsequent treatment	43% of patients on Belamaf receive subsequent treatment (based on DREAMM-2)	5% decrement applied to proportion of Belamaf patients receiving subsequent treatment (38%)	[redacted]	[redacted]	[redacted]	Dominating	Dominating
7	Subsequent treatment		Subsequent treatment mix informed by UK clinical opinion	[redacted]	[redacted]	[redacted]	Dominating	Dominating

*Severity modified. **Abbreviations**: AE: adverse events; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LY, life year, MAIC, matching adjusted indirect comparison; NCRAS, National Cancer Registration and Analysis Service, OS: overall survival; PD, progressed disease: PF, progression-free: QALY, quality-adjusted life year; TTD, time to treatment discontinuation; TTNT, time to next treatment; Tx, treatment.

Conclusions

The results of the updated economic analysis using UK RWE efficacy data demonstrate that Belamaf is not only an effective treatment option for patients with 5L+ TCR MM but also represents a cost-effective use of NHS resources when compared to PomDex at a WTP threshold of £30,000 per QALY gained.

The results of sensitivity and scenario analyses support the robustness of the conclusions and indicate a [redacted]% probability of being cost-effective at the £30,000 per QALY gained threshold.

For patients with 5L+ TCR MM, Belamaf represents a step change in the clinical management of this condition and this analysis demonstrates that Belamaf is a cost-effective use of NHS resources for these patients who are currently left to feel abandoned and to face an extremely poor prognosis.

References

1. National Institute for Health and Care Excellence. NICE TA658: Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [Internet]. Available from: https://www.nice.org.uk/guidance/ta658/documents/committee-papers-2

2. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual [Internet]. 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

3. GSK. GSK provides update on DREAMM-3 phase III trial for Blenrep in relapsed/refractory multiple myeloma [Internet]. 2022. Available from: https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-dreamm-3-phase-iii-trial-for-blenrep/

4. Single-Arm Trials Using Real-World Evidence For Rare Disease Product Development | Premier Consulting [Internet]. 2020 [cited 2023 Feb 7]. Available from: https://premierconsulting.com/resources/blog/single-arm-trials-using-real-world-evidence-for-rare-disease-product-development/

5. Mateos MV, 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 May;36(5):1371–6.

6. Terpos E, Dimopoulos M, Boccadoro M, Delimpasi S, Beksac M, Katodritou E, et al. Health-related quality of life (HRQoL) in patients with relapsed/refractory multiple myeloma (RRMM) treated with pomalidamide and dexamethasone ± subcutaneous daratumumab: patient-reported outcomes (PROs) in APOLLO. Journal of clinical oncology [Internet]. 2021;39(15 SUPPL). Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02305538/full

7. National Institute for Health and Care Excellence. Overview | Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib | Guidance | NICE [Internet]. Available from: https://www.nice.org.uk/guidance/ta427

8. 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 Jul 7;16(1):427.

9. Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health Qual Life Outcomes. 2014 Mar 11;12:35.

10. GSK. Trial Protocol for DREAMM-2.

11. 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 oncology. 2016;17:328–46.

12. Overview | Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable | Guidance | NICE [Internet]. NICE; [cited 2022 Sep 23]. Available from: https://www.nice.org.uk/guidance/ta763

13. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (CDF review of TA510)| Guidance | NICE [Internet]. NICE; [cited 2022 Jul 28]. Available from: https://www.nice.org.uk/guidance/ta783

Calculations of severity weighting

Introduction

This Appendix lists technical details the update of the proportional shortfall modifier reflecting the utility estimates from the final DREAMM-2 data-cut and the characteristics of the [redacted] considered in the revised base case.

The overall impact of updating the severity modifier estimates is minimal, although the direction of the change is slightly in favour of the company's position which indicates that a 1.7x severity modifier is appropriate for this appraisal.

The calculated proportional severity modifier is [redacted], which is slightly higher than the original calculation of [redacted]. The 95% confidence interval around this point estimate is [redacted], which is again slightly higher than the original calculation of [redacted]. The NICE Methods state that for the proportional shortfall above 85% but below 95% the 1.2x threshold should be used, whereas above 95% a 1.7x threshold should be applied. The point estimate and confidence interval calculated imply that for approximately [redacted] of patients, the 1.7x threshold is applicable. Thus, the most appropriate estimate of the proportional QALY shortfall falls on the cut-off between thresholds. The NICE Methods state that in this situation the higher modifier should be applied: "*If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply*". For this reason, a 1.7x modifier should be applied in the submission.

The methods considered to calculate these modifiers are described below.

Data inputs

The data considered to calculate QALY shortfall are the age at which patients initiate treatment, the sex distribution in the patient population, the discount rate, and the remaining QALYs with standard of care. These have been updated to reflect changes made from the original submission in response to technical engagement.

Age distribution

The distribution of patient ages was taken from the abstract for the RWE study describing outcome data collected from the Belamaf UK [redacted] which has been submitted for publication to British Society for Haematology (BSH) 2023 [1]. Specifically, the mean age is [redacted] years, with an interquartile range of [redacted]. This indicates the standard deviation is [redacted], which is slightly greater than the standard deviation in the original submission (that is, there is slightly more heterogeneity with respect to age in the UK patient population than in the DREAMM-2 patient population).

Sex distribution

The sex distribution in the patient population is [redacted]% male in line with the [redacted] study cohort [1]. This is a slightly greater proportion of males than in the DREAMM-2 cohort described in Appendix P.2 of the original submission. While the sex of the patient adds a small amount of heterogeneity to the overall analysis, the effect is marginal compared to the age at which patients are treated and the remaining undiscounted QALYs and therefore only the mean sex distribution is used in the calculations as a simplification.

Discount rate

A 3.5% discount rate is considered in line with the NICE Reference Case.

Remaining QALYs with standard of care

There is uncertainty regarding the remaining QALYs for patients with 5L+ TCR MM receiving standard of care. This uncertainty is of both of a structural and parametric kind. The updated base case does not alter the nature of this uncertainty.

The structural uncertainty arises from the unclear definition of the 'standard of care' in 5L+ TCR MM as further described in Section B.1.3 of the submission. The NICE Methods define standard of care as "other available treatments, diagnostics, or best supportive care", but it should be noted that there is effectively no established clinical practice for the management of patients with this condition. The following calculations reflect the observations from the NCRAS study used to define the relevant comparators in the population of interest for the appraisal. PomDex represents the most relevant comparator in this population and PanoBorDex was also considered for these calculations in acknowledgement of its use, albeit limited in the 5L+ TCR setting.

The following calculations are based on the interventions which reflect the treatment options available for patients with 5L+ TCR MM in the UK, PomDex and PanoBorDex and using the proportion reported in the NCRAS dataset and summarised in Table 1.

Table 1. Proportions of different treatments used to calculate severity modifier

Treatment	% usage in NCRAS dataset	Weighted usage in severity modifier
PomDex	[redacted]	[redacted]
PanoBorDex	[redacted]	[redacted]

The parametric uncertainty arises from the fact that the data source used to estimate PFS and OS for comparator treatments is itself subject to uncertainty. This uncertainty is described in Section B.2.6 of the original submission and in section 3.5 of the submission addendum.

Deterministic calculations

Table 2 describes the model outputs for the QALY gain of the three relevant scenarios, based on the data inputs described above. The weighted average of the PomDex and PanoBorDex is weighted as per the scenario in Table 1.

Table 2. Summary of model outputs for proportional shortfall

Factor	Mean QALY in expectation	Absolute shortfall	Proportional shortfall
No disease	[redacted]	[redacted]	[redacted]
PomDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
PanoBorDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
Weighted average of real-world usage of PomDex and PanoBorDex	[redacted]	[redacted]	[redacted]

Probabilistic calculations

As described above, the NICE Methods state that, “If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply”. Consequently, a probabilistic analysis may be the preferred approach in this case, since the underlying parameter uncertainty (regarding age and background care QALYs) is such that a considerable proportion of patients would be eligible to the 1.7x multiplier. Similarly, in the NICE guidelines, probabilistic analyses are preferred to inform base case cost-effectiveness analysis.

The mechanism by which this heterogeneity affects the severity modifier calculations is depicted in Figure 1. The red bell curve represents the total number of QALYs generated by one of the comparators across 1000 scenarios varying age, using the same values used in the PSA base case in the main submission. The blue line represents the age which a patient would have to be for an age-matched member of the general population to have sufficient QALYs remaining that their proportional shortfall is 95%. This demonstrates that at the extreme left of the bell curve almost any patient will be young enough to have a 95% proportional shortfall, whereas at the extreme right end of the bell curve almost nobody would be.

Figure 1. Demonstration of mechanism by which heterogeneity impacts the severity modifier calculations

Figure 2 identifies how frequently these criteria are met in practice, based on the data inputs described above. The exact distribution of datapoints given in Figure 2 is taken from the PSA base case run in the main submission, but sensitivity analysis has demonstrated it is robust to stochastic uncertainty. 95% confidence intervals can be calculated from this analysis, as demonstrated in Table 3.

Figure 2. Graphical demonstration of heterogeneity in the 5L+ TCR MM population, and related severity modifiers

Table 3. Detailed results of plausible severity modifier scenario analysis

Background treatment	Age	Remaining QALY for healthy population	Absolute QALY shortfall	Proportional QALY shortfall	Severity modifier
PanoBorDex	[redacted]	[redacted]	[redacted]	[redacted]	1.7x
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	1.2x
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	1.7x
PanoBorDex	[redacted]	[redacted]	[redacted]	[redacted]	1.7x
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	1.2x

From this analysis, we see that approximately [redacted] of outputs lie above the 95% proportional shortfall modifier which represents the proportion of patients that would qualify for the 1.7x severity modifier. The improved case for a 1.7x modifier comes from the patient population in the UK real-world NPP study being slightly younger than the population of the DREAMM-2 trial ([redacted] years old at baseline) and from the age distribution being more heterogenous in the UK than in the DREAMM-2 study, leading to slightly more patients benefitting from the 1.7x modifier in the UK than anticipated from DREAMM-2. On the other hand, the higher proportion of men in the UK sample than the DREAMM-2 trial brings the proportional shortfall down slightly. Overall, the new data leads to a directionally higher proportion of patients who qualify for the 1.7x modifier now than under the original calculations (around [redacted] vs around [redacted]), but the difference is not substantial.

It should be noted that this is a relatively conservative analysis and including additional interventions patients may receive in 5L+ TCR MM such as palliative care could decrease the rate at which patients with the condition accrue QALYs.

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Technical engagement – 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.

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.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Minor outstanding factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment
Not all instances of the % of PomDex from NCRAS has been removed as agreed: "However, only [redacted] patients who received the recommended dose of PomDex were considered as a comparison." **Page 33, Section 3.2.2**	The Company requests the percentage value removed as per other updates agreed and performed by EAG.	Misrepresentation The incorrect denominator was used to calculate the percentage as identified during the Factual Accuracy Check.
Following sentence not updated as requested: "The NCRAS study, like DREAMM-2[1, 2], is a two-arm trial with no comparator arm study so that the proportion of observed OS that can be specifically attributed to the influence of PomDex is uncertain." **Page 74, Section 3.5.1.4**	The Company requests that the text be amended to the following: "The NCRAS study is a retrospective study evaluating multiple therapies, so the proportion of observed OS that can be specifically attributed to the influence of PomDex is uncertain." With reference to DREAMM-2 removed as DREAMM-2 was a two-arm trial with no comparator and NCRAS is a retrospective study evaluating multiple therapies.	Misrepresentation DREAMM-2 is a two-arm trial with no comparator arm, NCRAS is a retrospective study evaluating multiple therapies as identified during the Factual Accuracy Check.
Figure 4, 5, 8 and 13 formatting has led to the KM data not being presented **Pages 72 & 73, Section 3.5.1.4** **Page 78, Section 3.5.2.1** **Page 85, Section 3.5.3.1**	The company requests that the figures be updated.	Misrepresentation
Figure 16 has the label "NSCAR" instead of "NCRAS" **Page 89, Section 3.5.3.2**	The Company requests that the label be fixed.	Typographical error

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

NICE National Institute for Health and Care Excellence

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13 February 2023.** 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.

Clinical expert statement

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

NICE National Institute for Health and Care Excellence

We reserve the right to summarise and edit comments received during engagement, 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 during engagement 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.

Clinical expert statement

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

NICE National Institute for Health and Care Excellence

Part 1: Treating relapsed or refractory multiple myeloma after 4 or more therapies and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Karthik Ramasamy
2. Name of organisation	Oxford University Hospitals/ University of Oxford/ UK Myeloma Society
3. Job title or position	Consultant Haematologist/ Associate Professor/ Executive Member
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory multiple myeloma after 4 or more therapies? ☒ A specialist in the clinical evidence base for relapsed or refractory multiple myeloma after 4 or more therapies or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes discussed with Dr Rakesh Popat the main submitter
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil

8. What is the main aim of treatment for relapsed or refractory multiple myeloma after 4 or more therapies? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma after 4 or more therapies?	
11. How is relapsed or refractory multiple myeloma after 4 or more therapies currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care? • What proportion of this population have treatment with panobinostat with bortezomib and dexamethasone in clinical practice?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. 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 affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	

17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA427 and TA380?	
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. 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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	

Please consider whether these issues are different from issues with current care and why. 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.	

NICE National Institute for Health and Care Excellence

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Appropriateness of pomalidomide plus dexamethasone as a valid comparator to belantamab mafodotin in the NHS context (section 3.5.1.3, Table 3)	
Key issue 2: Inappropriate source data presented as evidence for efficacy of belantamab mafodotin and pomalidomide plus dexamethasone (section 3.2.1, 3.2.2)	

Other issue 3: Minor changes to the economic model which include EAG preferred assumptions on: - calculated utility weights - severity modifier choice (section 5.4.3, Table 2)	
Other issue 4: Inappropriate selection of proxy progression-free survival (PFS) measure (section 3.5.1.1, 3.5.1.2)	
Are there any important issues that have been missed in EAR?	

NICE National Institute for Health and Care Excellence

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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 our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

NICE National Institute for Health and Care Excellence

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13 February 2023.** 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.

Clinical expert statement

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

NICE National Institute for Health and Care Excellence

We reserve the right to summarise and edit comments received during engagement, 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 during engagement 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.

Clinical expert statement

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

NICE National Institute for Health and Care Excellence

Part 1: Treating relapsed or refractory multiple myeloma after 4 or more therapies and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Rakesh Popat
2. Name of organisation	University College London Hospitals NHS Foundation Trust, UK Myeloma Society
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory multiple myeloma after 4 or more therapies? ☒ A specialist in the clinical evidence base for relapsed or refractory multiple myeloma after 4 or more therapies or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for relapsed or refractory multiple myeloma after 4 or more therapies? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To reduce the risk of progression
9. 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)	A partial response as per IMWG criteria (i.e. a 50% reduction in paraprotein)
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma after 4 or more therapies?	Yes, this represents a large unmet need currently in the UK treatment paradigm. Current treatment options are limited and have low efficacy.
11. How is relapsed or refractory multiple myeloma after 4 or more therapies currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care? • What proportion of this population have treatment with panobinostat with bortezomib and dexamethasone in clinical practice?	Treatment guidelines: EHA-ESMO myeloma guidelines (Dimopoulos et al., Ann Oncol 2021 Mar;32(3):309-322) and IMWG recommendations (Moreau et al., Lancet Oncol 2021 Mar;22(3):e105-e118). Both guidelines recommend Belantamab Mafodotin for 2nd or higher relapse. The treatment pathway for myeloma is well defined and follows NICE and CDF recommendations. However the options available at 4 or more prior lines are limited with little evidence to support use; hence there is some variability The incorporation of this technology would standardise treatments position and provide an evidence based treatment for patients that are triple class refractory. Current treatments were evaluated historically prior to CD38 antibodies being approved and hence have a limited evidence base. Panobinostat bortezominb and dexamethasone is not clinically recommended for patients that are refractory to a proteasome inhibitor (i.e. bortezomib) as per the registration phase 3 trial eligibility (Panorama 1 trial, San Miguel et al, Lancet Oncol 2014;15: 1195–206) which was for 1-3 prior lines and bortezomib sensitive. Real world UK evidence (Bird et al., Br J Haematol 2020 Dec;191(5):927-930) demonstrates poor outcomes when used in this situation. Any use of this regimen is likely out of desperation as all other options have been exhausted.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Belantamab is administer iv every 3 weeks, but in practice less frequently due to corneal adverse events. There is therefore a reduced burden for day care resource compared to bortezomib and Panobinostat. However compared to pomalidomide there will be additional infrequent day care visits for the infusion. Ophthalmology/ optician review is mandated as per licence. This will be used in secondary or tertiary care under a haematologist. Sufficient ophthalmology/ optician support will be required for each patient treated and they will need to understand the specific requirements.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	There is no head-to-head comparison in this setting to provide the evidence to answer this. However treatment options in the UK are extremely limited and a variety of different approaches are taken. The overall survival data from DREAMM-2 is encouraging compared to that expected in the UK at this stage. For responders, the expectation is that HRQOL will improve as per DREAMM-2 trial. Of note this is a dexamethasone sparing regimen which is advantageous from a toxicity perspective and is likely to improve fatigue as shown in DREAMM-2.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, all groups may benefit from this. Specifically this treatment is also suitable for older, frailer patients due to the infrequent nature of infusions and reversible adverse events.
15. 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 affecting patient	The commonest adverse event is keratopathy which requires regular ophthalmology/ optician review and frequent administration of preservative free eye drops. This will pose an additional burden for patients. Monitoring of full blood count is required due to treatment emergent thrombocytopenia; however this is the same for current treatments.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A reduction in best corrected visual acuity, eye symptoms or grade 3 keratopathy will lead to interruption of treatment. Resolution will allow treatment to continue. Regular ophthalmology, optician monitoring is required.
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Compared to Panobinostat, bortezomib dexamethasone or any other intravenous chemotherapy, there will be a reduced burden on chemotherapy units due to the reduced frequency of administration.
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is the first BCMA directed treatment to be licensed for myeloma and no other BCMA treatments are currently approved within the NHS. Due to the high number of triple class refractory patients, treatments with new targets and mechanisms of action are urgently required. Belantamab fulfils this and is also the first antibody drug conjugate to be licensed for myeloma. Consequently it represents a "step-change" in management for such patients. As many patients at 5th line and beyond are remaining fit and physically well, this meets an unmet need for such patients who would otherwise predominantly receive limited treatment.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The ocular adverse events were not shown to significantly impact the global health scale in PRO assessments, however the blurring of vision is expected to lower QOL transiently when symptomatic. As this is a reversible condition, the symptoms are not present throughout the treatment, but is intermittent.
20. Do the clinical trials on the technology reflect current UK clinical practice?	Whilst very few UK patients were enrolled into DREAMM-2, the population was a difficult to treat group with no standard treatments available. Therefore this will be similar to that treated in the UK. The PFS, DOR and response rate is likely to be indicative of the UK population. Overall survival may be different due to more

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	restricted post-progression treatments; however at the time the trial was performed, there were no other licensed treatments available that significantly improve survival. So the effect of post-progression treatments available in the US is likely to be small. For this population overall response rate, duration of response and survival are the most important. PFS for novel treatments does not always correlate well with overall survival. No new adverse effects have been demonstrated with longer follow-up or in clinical practice to date.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real world evidence in the UK has been generated for Belantamab Mafodotin through the named patient programme. Results have been submitted to the British Society for Haematology Annual Congress in April 2023.
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA427 and TA380?	No
23. How do data on real-world experience compare with the trial data?	There is data from other countries published and from the UK (see Q22). Overall the data is consistent and in some cases better than the DREAMM-2 trial.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. 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.	No equality issues are identified with this technology

Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

NICE National Institute for Health and Care Excellence

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Appropriateness of pomalidomide plus dexamethasone as a valid comparator to belantamab mafodotin in the NHS context (section 3.5.1.3, Table 3)	Pomalidomide and dexamethasone is the most appropriate comparator within the NHS (excluding CDF approvals). Panobinostat, bortezomib and dexamethasone is rarely used and not appropriate in a setting where patients are refractory to bortezomib or another PI as per Panorama 1 trial (see question 11 above).
Key issue 2: Inappropriate source data presented as evidence for efficacy of belantamab mafodotin and pomalidomide plus dexamethasone (section 3.2.1, 3.2.2)	The only data available for patients at 4 or more prior lines and triple class exposed comes from DREAMM-2. The DREAMM-3 trial population is at an earlier stage in the treatment pathway and are les heavily pre-treated as globally pomalidomide is used from 2nd line and later.

Other issue 3: Minor changes to the economic model which include EAG preferred assumptions on: - calculated utility weights - severity modifier choice (section 5.4.3, Table 2)	No comments
Other issue 4: Inappropriate selection of proxy progression-free survival (PFS) measure (section 3.5.1.1, 3.5.1.2)	No comments
Are there any important issues that have been missed in EAR?	No

NICE National Institute for Health and Care Excellence

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Pomalidomide and dexamethasone is an appropriate comparator

The technology represents a step change for treatment of patients at 4th line and beyond

Patients that respond have a long duration of response, demonstrating clinical efficacy of the technology

There is an additional burden of ophthalmology/ optician assessments that needs to be considered

The technology is suitable for all patients, including those older and frailer

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 our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13 February 2023**. 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 received during engagement, 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 during engagement 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.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Myeloma UK – stakeholder
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Appropriateness of pomalidomide plus dexamethasone as a valid comparator to belantamab mafodotin in the NHS context (section 3.5.1.3, Table 3)	No	Due to the limited provision of approved drugs and clinical data at this advanced stage of the myeloma treatment pathway, it is not easy to define clear-cut comparators to belantamab mafodotin. From our engagement with patients we understand that some will still be naïve to pomalidomide plus dexamethasone after four or more therapies and that this treatment is currently used as standard practice in the NHS at fifth line and beyond. Other options include chemotherapy and a corticosteroid, an expanded access scheme or a clinical trial, but these are not suitable for nor readily available to all patients. At this stage, a certain proportion of patients will be refractory to pomalidomide plus dexamethasone having received the CDF approved combination of isatuximab, pomalidomide and dexamethasone (TA658) as their fourth line of treatment, yet this does not necessarily represent the majority of patient experiences. We therefore still support the inclusion of PomDex as a valid comparator to belantamab mafodotin.
Key issue 2: Inappropriate source data presented as evidence for efficacy of belantamab mafodotin and pomalidomide plus dexamethasone (section 3.2.1, 3.2.2)	No	No comment

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Other issue 3: Minor changes to the economic model which include EAG preferred assumptions on: - calculated utility weights - severity modifier choice	Section 5.4.3, Table 2	No	No comment
Other issue 4: Inappropriate selection of proxy progression-free survival (PFS) measure	Sections 3.5.1.1, 3.5.1.2	No	No comment
Other issue 5: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Other issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

External Assessment Group Technical Engagement Response

Title: *ID2701- Multiple myeloma (relapsed or refractory after 3 therapies) - Belantamab mafodotin*

Produced by	*Warwick Evidence*
Authors	*Dr Martin Connock, Honorary Senior Research Fellow, Warwick Medical School* *Dr Hesam Ghiasvand, Research Fellow, Warwick Medical School* *Iman Ghosh, Research Associate, Warwick Medical School* *Anna Brown, Information Specialist, Warwick Medical School* *Dr Mandy Maredza, Senior Research Fellow, Warwick Medical School* *Dr Alex Tsertvadze, Independent Consultant, Warwick Medical School* *Professor Amy Grove, Professor of HTA and Implementation Science, Warwick Medical School*
Correspondence to	*Amy Grove* *Warwick Evidence* *Division of Health Sciences* *Warwick Medical School* *University of Warwick* *Coventry, CV4 7AL* *A.L.Grove@warwick.ac.uk*
Date completed	*Date completed 07/03/2022*

Source of funding
This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135711.

Declared competing interests of the authors
None.

Acknowledgements
The EAG would like to acknowledge our clinical advisors and clinical quality assessor:
Emeritus Professor Steven Schey, Consultant Haematologist, Kings College Hospital
Professor Supratik Basu, Consultant Haematologist, Royal Wolverhampton NHS Trust
Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services Research. University of Warwick.

Rider on responsibility for report
The views 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.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

EAG Introduction

The company's addendum introduces two major new data sources:
a] outcomes from the NPP (Named Patient Programme) "investigative follow up" study, that now replaces those from the DREAMM-2 trial;
b] outcomes for a 5L+ TCR subgroup of the DREAMM-3 RCT.

The proxy comparator data (PomDex) remain those from the NCRAS single arm study and the belantamab mafodotin (Belamaf) vs PomDex analysis undertaken is again a naive comparison, in this case NPP vs NCRAS.

Key issues for engagement

Key issue 1: Appropriateness of pomalidomide plus dexamethasone as a valid comparator to belantamab mafodotin in the NHS context (section 3.5.1.3, Table 3)

The EAG thank the company for the new feedback from their clinical experts and new analyses of the NCRAS dataset. The EAG have critiqued this additional data. As per the EAG report, the EAG accept that PomDex was included in the NICE Final Scope as a relevant comparator. The EAG also recognise the uncertainty in clinical practice due to the "world where CDF options are available" versus the "world where CDF-options are not considered", neither option is ideal or representative of real-world practice. This is outlined by the company. The new NCRAS dataset reflect the "world where CDF-options are not considered". As per the EAG report page 35, NCRAS is a descriptive, retrospective, non-interventional study. As the NCRAS study is a real-world dataset, it has several uncertainties across methodological domains, including no specific hypothesis, loss to follow up data, absence/incomplete data on baseline characteristics or efficacy response outcomes, no safety data, and lack of representativeness of a wider UK patient population.

In summary, uncertainty remains for PomDex, which cannot be resolved with the evidence available.

Key issue 2: Inappropriate source data presented as evidence for efficacy of belantamab mafodotin and pomalidomide plus dexamethasone (section 3.2.1, 3.2.2)

1. ***New evidence provided in an addendum to the submission***

The EAG disagree with the company statement "*However, the original submission included data from the final analysis of the DREAMM-2 trial which is a key source of evidence providing a robust demonstration of the clinical effectiveness of Belamaf in a population of 5L+ TCR MM patients. The DREAMM-2 trial underpins the current GB license for Belamaf in the population under evaluation*."

The EAG suggest that this trial does not provide comparative effectiveness of Belamaf relative to another legitimate comparator. Although the trial used two different doses of Belamaf, it was not designed to compare them.

2. UK RWE study of Belamaf efficacy from the NPP

As outlined in 2.1 above, NPP is an additional RWE study. This introduces additional uncertainty in the cost-effectiveness estimates, rather than reducing uncertainty in what was originally presented in the CS (see exploratory EAG analysis below and overview on page 65 of the EAG report). It is well established that naïve indirect treatment comparison (ITC) is a methodologically flawed approach which generates biased results. Therefore, it should be avoided. The post-TE unadjusted naive comparison undertaken lacks validity and should not be used for an economic analysis. In particular, the two RWE studies included as clinical evidence both have very small samples ([redacted] subjects), lack a control, and their populations are likely to differ regarding prognostic factors. This is associated with very substantial uncertainties that are impossible to adjust for or calibrate in a meaningful way, this thereby likely invalidates the cost-effectiveness results presented by the company.

Exploratory analysis undertaken by the EAG: NPP study

The EAG note that the company have changed the intervention source to NPP from DREAMM-2. The company do not provide a valid reason for this change.

NPP suffers from the same problems as DREAMM-2 (smaller sample, shorter median follow-up [redacted], no control group, not matching characteristics in NCRAS PomDex comparator, MAIC not feasible/reliable). However, as single arm studies are used as proxy-comparator both are unsatisfactory. Moreover, the EAG consider NPP to have even less relevance than DREAMM-2: fewer patients [redacted] vs 97, less mature data (fewer outcome events with [redacted]), therefore more uncertainty.

NPP is less favourable for Belamaf than DREAMM-2, however, the perceived dominance of Belamaf in the economic modelling (as a consequence of poor NCRAS PomDex performance) mitigates the less favourable impact of NPP. See EAG Figures 1-7 below which highlight these issues.

Overall survival

KM plots for DREAMM-2 and NPP align to 9-months after which NPP is associated with great uncertainty (Figure 1) and modelling problematical.

Figure 1: Comparison of OS NPP vs DREAMM-2 (KM plots of OS)

The EAG note wide 95% confidence internals (CI) in the Weibull NPP model and more uncertainty in NPP. The company Weibull models mean [redacted] we see poor fit for NPP because of the very uncertain data beyond month 9. The EAG note that we now have another source of 5L+ TCR Belamaf survival supplied by DREAMM-3. Figure 2 compares OS in DREAMM-3 Belamaf subgroup with NPP.

[redacted].

Figure 2 Comparison of OS in NPP with that in DREAMM-2

Progression free survival and proxy-progression free survival (TTNT).

Despite supposedly similar populations the median PFS results are remarkably discordant between NPP and DREAMM-2 (Table 3 and Figure 3). Although not used in the base case cost-effectiveness analysis such results imply more time in the pre-progression health state for NPP than for DREAMM-2 and because this state carries higher utility than other health states, would generate more QALYs and would favour NPP relative to DREAMM-2. As both studies lack a control arm it is impossible to gauge precisely how much of the observed PFS is due to Belamaf intervention and how much would have occurred anyway. Relative to the DREAMM-2 population that in NPP appear remarkably resistant to progression.

Table 2 PFS and proxy-PFS reported outcomes in NPP, DREAMM-2 and DREAMM-3 subgroup

Study	DREAMM-2	NPP	DREAMM-3 5L+ TCR subgroup
Number	97	[redacted]	[redacted]
Max follow up	[redacted]	[redacted]	[redacted]
Events	[redacted]	[redacted]	[redacted]
Median PFS	[redacted]	[redacted]	[redacted]
Median PROXY-PFS (TTNT)	[redacted]	[redacted]	[redacted]

Figure 3 KM plots; PFS from NPP and DREAMM-2

The difference in PFS between NPP and DREAMM-2 is so [redacted] that one or both are unlikely to represent a population relevant to the decision problem. However, the DREAMM-3 5L+ TCR Belamaf subgroup PFS (Figure 4)
[redacted]. The nature of participant selection in the NPP appears to identify patients with remarkably slow progression and superior prognosis. In the opinion of the EAG this apparent bias means that

outcomes delivered in the NPP population are unlikely to reflect those that would occur in a UK 5L+ TCR population should Belamaf be adopted. Cost-effectiveness analysis based on NPP outcomes are unlikely to be reliable indicators for the specified decision problem.

Figure 4 KM plots; PFS from NPP, DREAMM-2, and DREAMM-3 Belamaf

This discordance carries over to KM plots for proxy-TTNT (Figure 5) that is used instead of PFS in the company's cost-effectiveness analyses. The KM for NPP TNTT is highly uncertain beyond about [redacted]. TTNT data is not available for DREAMM-3.

Figure 5 KM plots; TTNT (proxy-PFS) from NPP and DREAMM-2

Parametric models of NPP population TTNT and PFS present poor fit because of uncertainty beyond about [redacted] months. The company selected exponential models for TTNT for their economic model. Both exponential and Weibull distributions deliver similar extrapolations whether TTNT or PFS are modelled (Figure 6)

Figure 6 NPP KM plots for TTNT and PFS with Weibull and exponential models.

[redacted]

Overall Response Rates (ORR)

Response rates were approximately correspondent between NPP and DREAMM-2 (CS addendum Table 14, and submission 1, Table14). The EAG reiterate that since these studies lack a control group, the reported ORR do not demonstrate causation by Belamaf, good responses may merely act as a marker for patients with superior prognosis.

Time to treatment discontinuation BELAMAF (TTD)

Figure 7 shows the KM plots for TTD BELAMAF from the three available sources (NPP, DREAMM-2 and DREAMM-3). Although associated with considerable uncertainty it is clear that [redacted].

Figure 7 KM plots for TTD with Weibull models.

[redacted]

While extended TTD in NPP will not favour BELAMAF in cost effectiveness analysis the large discrepancy relative to other data sources brings into question the appropriateness of NPP as a source for modelling clinical outcomes (e.g. Weibull models shown in Figure 7)

International comparison

The EAG identified an article during TE which presents US registry information on Triple Class Refractory patients receiving post 4-line treatments (Lee et al 2023). In this paper 40% receive Pom at some point in time (5L or 5L+), and the majority of patients received alternative treatments (See Figure 4 e.g., carfilazommib). Note Belamaf/PomDex are not listed. This international comparison shows us that like UK patients (Company TE Fig 1 PomDex = [redacted]), most US patients receive other treatments.

Figure 4. Table 2 from Lee et al. 2023.

Table 2 Number and Timing of LOTs in the Post-TCR-Treated Subgroup

	Post-TCR-Treated Patients ($n = 155$)
Index date to start of first post-index LOT, median (range), d	9.0 (0-594)
Duration of first post-index LOT, median (range), mo	3.3 (0-31.1)
Duration of all post-index LOTs, median (range), mo	7.4 (0-52.1)
Number of LOTs on or after index date, median (range)	1.0 (1.0-8.0)
Time from first post-index LOT start date to start of next LOT, median (range), mo[a]	4.2 (0.5-35.1)
Post-index treatment, *n* (%)[b]	
Carfilzomib	73 (47)
Pomalidomide	62 (40)
Alkylating therapies[c]	50 (32)
Daratumumab	40 (26)
Bortezomib	39 (25)
Lenalidomide	36 (23)
Ixazomib	23 (15)
Newly approved therapies[d]	5 (3)
Isatuximab	0 (0.0)

Abbreviations: LOT = line of therapy; TCR = triple-class refractory.
[a] Among 77 of 155 (49.7%) post-TCR-treated patients who received a subsequent LOT.
[b] Percentages add up to >100% since patients could have >1 post-index treatment.
[c] Melphalan, cyclophosphamide, melflufen, or bendamustine.
[d] Belantamab mafodotin, selinexor, melflufen, and/or idecabtagene vicleucel.

The EAG consider OS shown in Figure 5, is quite similar to the NCRAS PomDex OS (Figure 6). Therefore, treatment choice seems potentially inconsequential (effectiveness and cost-effectiveness remain uncertainty), as prognosis remains the same.

Figure 5. Taken from Lee et al. 2023.

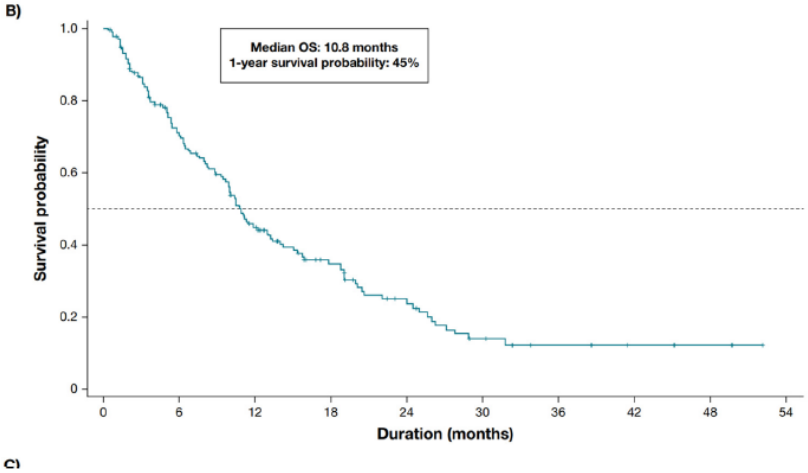


Figure 6. Green NCRAS PomDex, Brown DREAMM-2 Belamaf

[redacted]

3.Subgroup of 5L+ TCR MM patients from the DREAMM-3 trial

[redacted]

The EAG consider the very small, randomised subgroup data (from DREAMM-3; n=[redacted]) may be less biased. However, results have uninformatively wide confidence intervals, generating great uncertainty. Whilst not wanting to compare DREAMM-3 data to naïve data, the EAG note that in the naïve ITC, it is difficult to predict the direction and magnitude of bias, it could even switch the effect estimate qualitatively (from harm to benefit).

On balance, the EAG consider the randomised subgroup data from DREAMM-3 study preferable for assessment, even if it is uncertain (interpretation difficult due to wide confidence intervals). However, the TE company model and addendum only include clinical

effectiveness outcome data from NPP, NCRAS and DREAMM-2. Therefore, the EAG were unable to explore this further.

Exploratory analysis undertaken by the EAG: DREAMM-3

A MAIC exercise was undertaken by the company, but again judged uninformative due to missing or lack of balance in likely prognostic factors across NPP and NCRAS (Company TE Addendum). Based on newly presented TE data, this Section reviews and critiques data from NPP and from the 5L+ TCR DREAMM-3 subgroups in the context of other studies.

Table 1 summarises key relevant features of NPP and DREAMM-2.

STUDY	Population (N)	Outcomes
Named Patient Programme (NPP)	~24 month follow up of "compassionate" 5L+ TCR BELAMAF recipients ([redacted])	ORR PFS Proxy-PFS OS TTD
DREAMM-2	~ [redacted] month follow up of 5L+ TCR BELAMAF recipients recruited into a registered trial (97)	ORR** PFS Proxy-PFS OS TTD
** IRC assessed.		

DREAM 3 RCT

The DREAMM-3 study is an RCT with 325 participants who had received at least 2 prior lines of therapy and were dual class refractory randomised (2:1 to Belamaf or PomDex) reported no significant effect (Table 3) for any outcome including the primary outcome (PFS, HR 1.03), possibly bringing into question EMA/GB licensing and the FDA fast-track licencing of Belamaf for RRMM. PFS medians were reported as 11.28 and 7.0 months (Belamaf vs. PomDex respectively). Barely differing OR rates of 41% and 36% (Belamaf vs. PomDex respectively) were reported. OS HR 1.14 (95% CI: 0.77, 1.68) and median survival of 21.2 months (Belamaf) and 21.1 months (PomDex), results that are consistent with those for PFS and OR. As far as medians are concerned the major difference between DREAMM-3 arms and the company submission's naïve comparison of DREAMM-2.1, 2 vs. NCRAS is that the former generates a 0.1-month advantage for Belamaf but the latter generates a larger [redacted]-month advantage.

Table 3 summarises DREAMM-3 public domain results and compares these with DREAM2 and NCRAS results. Please note that this is ITT population, not the subgroup submitted with the company TE addendum.

Table 3. Median (95% CI) months reported for outcomes DREAMM-2, DREAMM-3, and NCRAS

Outcome	**DREAMM-2.[1, 2] Belamaf**	**DREAMM-3 Belamaf**	**DREAMM-3 PomDex**	**NCRAS PomDex**
OS	[redacted]	21.2	21.1	[redacted]
PFS	[redacted]	11.28	7.0	[redacted]
PROXY PFS	[redacted]	NA	NA	[redacted]
Differences between OS medians DREAMM- 3 vs. DREAMM-2/ NCRAS				
BELAMAF DREAMM-3 vs BELAMAF DREAMM-2			21.2 – [redacted] = [redacted]	
POMDEX DREAMM-3 vs. NCRAS POMDEX			21.1 – [redacted] = [redacted]	
Differences between OS medians BELAMAF vs POMDEX				
DREAMM-2 BELAMAF vs. NCRAS POMDEX			[redacted]	
DREAMM-3 BELAMAF vs DREAMM-3 POMDEX			21.2 – 21.1 = 0.1	
OS: overall survival, PSF: Progression free survival: NCRAS: National Cancer Registration and Analysis Service				

From these results there seems no a priori reason to expect superior performance of Belamaf vs. PomDex in 5L+ TCR treatment, however this question is addressed directly in the submission of new evidence Addendum doc. in which the company presents KM analyses of outcomes for the 5L+ TCR subgroup from DREAMM-3. [redacted]. The company have not explored the subgroup results beyond KM analysis on the grounds that uncertainty is sufficiently large as to render such analyses uninterpretable.

The EAG disagree because:

a) the compared subgroups come from a single study rather than two independent studies are inherently more comparable; this is supported by fact that the number of subgroup participants identified (n=[redacted], and n=[redacted], by treatment) align with the randomisation ratio of 2:1 in DREAMM-3

b) DREAMM-3 data is more mature than NPP data; [redacted] (Table 4).

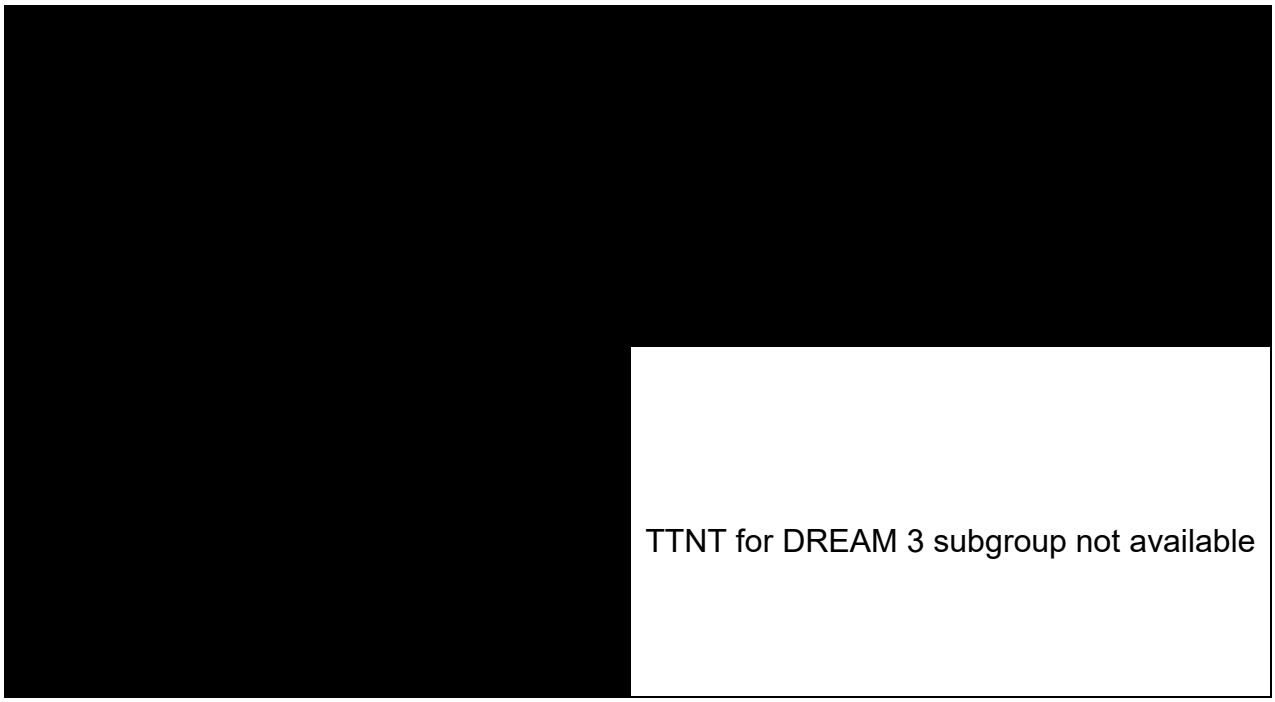
Table 4 Percentage of patients experiencing an event (DREAMM-3 vs. NPP)

	DREAMM-3 5L+ TCR Belamaf	DREAMM-3 5L+TCR PomDex	NPP Belamaf
PFS	[redacted]	[redacted]	[redacted]
Proxy PFS	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]

c) DREAMM-3 provides PFS results for both arms so there is no necessity to invoke a proxy-PFS (TTNT) measure that is subject to potentially different practices between separate studies (e.g. NPP vs. NSCAR).

d) both PFS and TTNT in the NPP population are noticeably out of alignment with the corresponding outcomes for DREAMM-2 whereas [redacted] (Figure 8).

Figure 8 Misalignment of PFS and TTNT in NPP relative to other sources.



e) although there is substantial uncertainty associated with outcomes in the DREAMM-3 5L+ TCR subgroup data this does not seem greater than that in the NPP study used in the company's economic analysis as evidenced by the 95% CI around KM estimates of PFS (Figure 8).

Therefore, consistent with the company's approach of naïve comparisons between groups that likely differ in prognosis, the EAG have undertaken further analyses using DREAMM 3 5L+ TCR subgroups and has explored these in CE estimation. DREAMM 3 KM plots were digitised and IPD reconstructed using the method of Guyot et al. 2012. The primary outcome in DREAMM 3 was specified as PFS.

Figure 9 shows the reconstructed KM plots for each subgroup arm; [redacted]. Figure 10 shows the reconstructed OS KM plots for each subgroup arm; [redacted]

Figure 9 Reconstructed KM for PFS in each subgroup arm of DREAMM 3

Figure 10 Reconstructed KM for OS in each subgroup arm of DREAMM 3

To be consistent with the company approach, Weibull models were fit for each outcome; these models were more or equally plausible relative to alternative parametric models. Weibull models for DREAMM-3 5L+TCR subgroup outcomes are summarised in Figure 11

Figure 11 Reconstructed KM and Weibull models for DREAMM-3 5L+ TCR subgroups

[redacted]

The EAG briefly explored the use of DREAMM-3 subgroup Weibull models for CE estimation. Economic model survival outputs are summarised in Figure 12. The model output is summarised in Table 5 and compared to the company base case. For the DREAMM 3 model no waning was implemented and PFS was cut off at 24 months.

Figure 12 Economic model survival output using DREAMM-3 subgroup data.

[redacted]

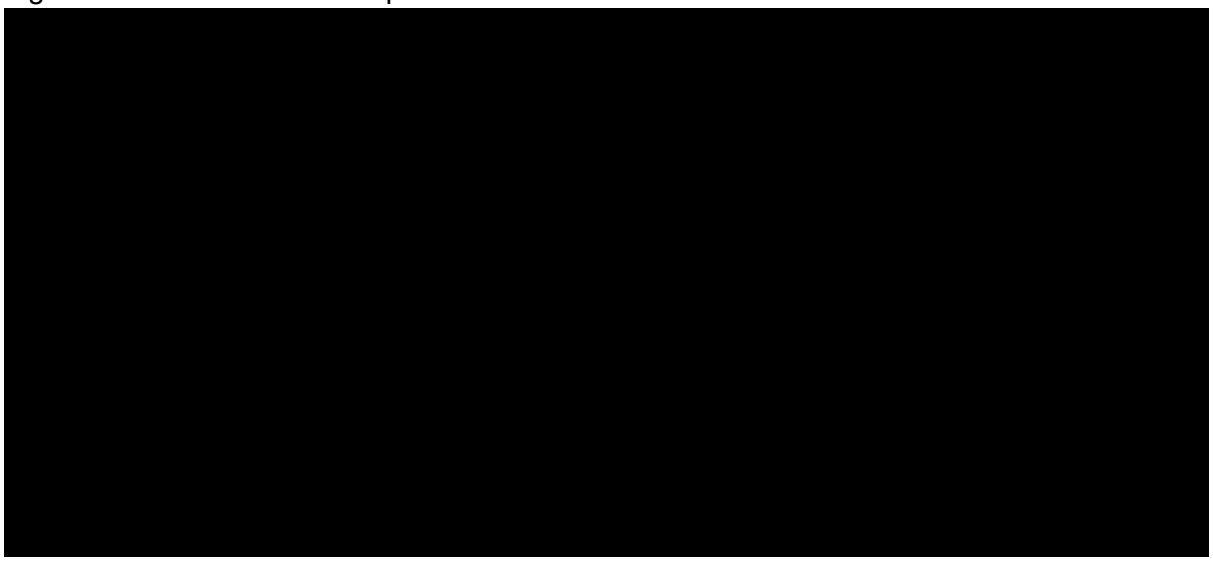
[redacted]

Table 5 Cost effectiveness using DREAMM 3 5L+ TCR data

Treatment	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus severity modified incremental (QALYs)
PomDex	[redacted]							
Belamaf	[redacted]							
[redacted]								
PomDex	[redacted]							
Belamaf	[redacted]							

Belamaf is no longer [redacted]. The ICER now falls in the [redacted] quadrant of the cost effectiveness plane (Figure 13) and indicates that for [redacted]

Figure 13 Cost-effectiveness plane with DREAMM- 3 data



EAG briefly explored requirement to move the ICER to the [redacted] quadrant [redacted]).

[redacted]. Model output is as summarised in Table 6.

Table 6 Cost effectiveness using DREAMM-3 TCR 5+L data modified by PomDex cost and PomDex OS modelling

Treatment	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus severity modified incremental (QALYs)
PomDex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Belamaf	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The resulting cost-effectiveness plane and the changed POMDEX OS model are shown in Figure 14.

Figure 14 PomDex OS and cost-effectiveness plane
([redacted]).

EAG summary

Overall assessment of the TE evidence/new evidence (NPP and DREAMM-3 subgroups)

- The evidence base is too incomplete to allow an adequate comparative effectiveness assessment of the technology of interest. Specifically, the only head-to-head comparative study that compares Belamaf to the chosen comparator treatment in 5L + TCR patients [redacted]. The EAG consider that the available outcome measure from DREAMM-3 subgroups, although associated with appreciable uncertainty, [redacted]. [redacted]. The DREAMM-3 trial evaluates safety/efficacy of Belamaf compared to PomDex is still ongoing.

- Non head-to-head alternative sources of comparative evidence from single arm studies, such as NPP and NCRAS, do not establish reliable measures of clinical outcomes because their lack of a control group means it is impossible to gauge what depends on the intervention from what would have happened anyway with no intervention.

- The representativeness and relevance of the NCRAS data as a source of the comparator is questionable due to its non-overlap with the NPP (and DREAMM-2 trial). In particular NPP outcomes PFS, TTNT and TTD [redacted]. NPP does not appear to be an appropriate study for decision question.

- The feasibility of a valid MAIC was not improved by introducing NPP as the source of BELAMAF clinical outcomes.

4. Use of single arm trial data in previous NICE technology appraisals

The EAG recognise that single arm trial data is used in NICE TA. In the context of ID2701, the EAG consider the use of a single arm trial data inappropriate and insufficient to demonstrate the comparative clinical efficacy of Belamaf given the absence of an adequate control arm and considerable uncertainty. Providing previous examples of using single arm evidence for comparative efficacy/safety does not justify the appropriateness of their use for this case.

5.Unadjusted HRs for the efficacy outcome measures

The Company did not provide unadjusted (before matching or naïve comparison-based) HRs for the efficacy outcome measures in their initial submission. This was provided at TE, EAG reproduced in Table 7. The EAG note that in the company TE model and addendum they use a naïve comparison (critiqued in Section 2 above). The company state OS is modelled as follows: "*Given the level of missing data for baseline characteristics in the NPP and NCRAS datasets, an unanchored MAIC was deemed unfeasible due to likely reduction in ESS and instead, a naïve comparison was selected as the most appropriate source of evidence in the base case cost-effectiveness analysis*."

Table 7 HR adjusted and unadjusted comparison

Outcome	HR Belamaf (DREAMM-2) vs PomDex (NCRAS)	
	Unadjusted/unmatched – naïve comparison	Unanchored MAIC matched/adjusted comparison
OS	[redacted]	[redacted]
TTNT	[redacted]	[redacted]
TTD	[redacted]	[redacted]

Additional issues

Other issue 3: Minor changes to the economic model which include EAG preferred assumptions on:

Calculated utility weights

The EAG agrees that the company have adjusted the utility values by using the latest data and analysis from DREAMM-2. The current utility values for the health states appears more realistic and the 95% CI around the utility values are also consistent.

The EAG's previous concern was based on EAG clinical opinion. Experts suggested that the age, comorbidity, and treatment toxicity affect QoL markedly. They acknowledge that the QoL varies noticeably with age, and the EAG agree that the company has applied the age decrement on QALYs.

The EAG clinical expert refer to a study by Yong K. et al. (2016) which is a real-world multi-country study (n=4,997 [n=753 from UK]). Most patients (64%) in this study were at least 65 years old; 42% were aged between 65 and 75 years and 22% were over 75 years old. The paper states that "*The proportion of patients ending treatment because of toxicity or poor performance status increased with later lines of therapy (2% in patients at first line, compared with 20% for those at fifth or later lines). At first line the most common toxicity was neuropathy and cytopenia and that toxicity and co-morbidity increased with each line of treatment. 60% of patients had at least one toxicity or comorbidity at the end of the first line, compared with 77% at the end of the fifth line or later. Similarly, the pro- portion of patients with normal renal function decreased in later lines of treatment (70% at first line versus 45% at fifth line or later.*" Renal impairment and performance status were the most important considerations in selecting patients for next line of treatment. York and colleagues showed that after first line, toxicities and co-morbidities affected planned treatment in 23% of patients, compared with 40% at completion of third-line treatment. Given the ascending pattern for toxicities and co-morbidities with line of treatment, it would be hard to assume that patients with such a pre-heavily profile can be assumed at the company's former level of QoL.

Regarding the utility associated with Progressive Disease (PD) the EAG agree it should not exceed beyond PFS and agree with the company's approach for considering the PD states.

In conclusion, the EAG agrees with the utility adjustments and new values looks more reasonable to be used in the cost-effectiveness analysis.

Severity modifier choice

The EAG maintains that its preferred approach to calculating severity weighting is in accordance with NICE guidance, is transparent and has already been used and accepted by Committee in a recently published appraisal (TA866). To re-iterate, according to the NICE guidance, "*the QALY weightings for severity are applied based on absolute and proportional shortfall, whichever implies the greater severity level. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply*" (see Table 8). In the company's analysis, the proportional QALY shortfall implied the greater severity level and was appropriately chosen. However, the proportional shortfall was [redacted] and not at the cut-off (0.95), suggesting that a QALY weighting of x1.2 should have been chosen.

Table 8 QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
X1.2	0.85 to 0.95	12 to 18
X1.7	At least 0.95	At least 18

Source: NICE technology guidance manual (2022)

The company state that they have used probabilistic results (and 95% confidence intervals around deterministic model outputs) to justify applying a severity weighting of x1.7. However, the EAG note the following:

- If a probabilistic analysis was to be chosen, the EAG argue that the mean QALYs for current treatment (used to derive absolute and proportional QALY shortfalls) should have been based on the company's main PSA analysis. That mean QALY value would incorporate uncertainty around all key parameters including age at which treatment is started. At clarification (Appendix A), the company reported mean QALY values for PomDex and PanoBorDex for the PSA analysis as [redacted] respectively. Using, the same approach as done for the deterministic outputs, the EAG recalculated the QALY shortfalls as below in Table 9.

Table 9 Summary of QALY shortfall analysis based on mean QALYs derived from PSA analysis

Factor	**Mean QALY in expectation**	**Absolute shortfall**	**Proportional shortfall**
No disease	[redacted]	[redacted]	[redacted]
PomDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
PanoBorDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
Weighted average of real-world usage of PomDex and PanoBorDex	[redacted]	[redacted]	[redacted]

*Note: values may slightly differ due to rounding off in QALY calculator (Schneider et al 2021).

The EAG acknowledge that results from a PSA will not remain constant but are of the opinion that if PSA results are to be used then this approach would be a more acceptable alternative.

- The company justifies using the highest severity weighting based on a scenario analysis which showed that the applicable severity weight varies by age **but does not specify** which comparator treatment was used to generate the data for both figures (15 and 16 below). According to the CS, Appendix P, "*The mechanism by which this heterogeneity affects the severity modifier calculations is depicted in* ***Error! Reference source not found.****. The red bell curve represents the total number of QALYs generated by one of the comparators across 1000 scenarios varying age, using the same values used in the PSA base case in the main submission*." This presents a challenge. As the company's deterministic results already illustrate, the proportional QALY shortfall for PanoBorDex vs PomDex span severity weights, with high proportional QALY shortfall for PanoBorDex. By not specifying which comparator treatment was used to produce the referenced graphs, the EAG cannot verify that the following conclusion by the company is justified "approximately [redacted]% of outputs lie above the 95% proportional shortfall modifier which represents the proportion of patients that would qualify for the 1.7x severity modifier."

In addition, in their base case analysis (for calculating severity weighting), the company has assumed a weighted average of real-world usage of PomDex and PanoBorDex to represent

background treatment to arrive at a proportional QALY shortfall of [redacted]%. However, the PSA analysis seems to deviate from this approach and presents analysis by either PanoBorDex or PomDex. There was no attempt to indicate what the severity weighting would be if a weighted average of real-world usage of both comparator treatments was applied (different ages) as was the case in the deterministic outputs. See company Figure 25 replicated as EAG Figure 15.

Figure 15 Demonstration of mechanism by which heterogeneity impacts the severity modifier calculations
Source: CS, Figure 25, Appendix P

Figure 16 Graphical demonstration of heterogeneity in the 5L+ TCR MM population, and related severity modifiers
Source: CS Figure 26, Appendix P

- Post-TE, the company updated utility values in the model. The change will impact on the estimates of mean QALY in expectation values. The company has not presented

an updated analysis to indicate what the proportional QALY shortfall would be (either deterministic or probabilistic) based on the updated values.

In conclusion, the EAG does not agree with the company that the PSA analysis they presented offers a better approach to calculating severity weighting but rather increases the uncertainty about the correct severity weighting to apply.

Other issue 4: Inappropriate selection of proxy progression-free survival (PFS) measure

The company state that EAG issue 4 is addressed because the NPP and NCRAS are both UK studies so that access to next treatment would be equitable. However, no additional evidence is provided to support this argument. The NPP TTNT and PFS are almost identical. Uncertainty remains as to whether this also applies to NCRAS as no PFS data are available from NCRAS. The Company refers to previous TAs which have used the same approach and incorporating the TTNT as a proxy for the PFS in the CEA. The EAG consider issue 4 an inherent problem that cannot be addressed without access to PFS from a real-world dataset.

Summary of changes to the company's cost-effectiveness estimate(s)

The Company's new model (post TE) has used the results from a real-world study (NPP) for Belamaf efficacy. Other changes to company's Post-TE analysis include: RDI for Belamaf was updated from [redacted]% to [redacted]% to reflect dosing in NPP; Belamaf PFS is capped at 2 years and similar assumption is applied to PomDEX PFS; a 50% waning is applied to PFS to adjust the proportion of patients in PFS after 1-year in both Belamaf and PomDex arms. In addition, the company have used the final data cut ([redacted]) from DREAMM-2 for the health state utility values in the base-case 4-health state model.

Alongside these, the company has increased the discount for Belamaf by [redacted].

These adjustments altogether have been applied on a four-state partitioned survival analysis for the cost-effectiveness analysis.

The updated model has led the changes in the base-case and probabilistic ICERs for Belamaf against PomDex as below:

Belamaf vs PomDex:

1- The total QALYs for PomDex has [redacted] from [redacted] to [redacted] ([redacted] change).
2- The total QALYs for Belamaf has [redacted] from [redacted] to [redacted] ([redacted] change).
3- The YLG for PomDex has not changed ([redacted], no change).
4- The YLG for Belamaf has [redacted] from [redacted] to [redacted] [redacted] change).

5- The base case ICER (x1.7 severity modifier) has changed from [redacted] to [redacted] ([redacted] change).
6- No change in the [redacted] situation for Belamaf against PomDex.

Belamaf vs PanoBorDex (scenario Analysis):

Note: The results for Belamaf against PanoBorDex are based on the NCRAS Naïve (Belamaf DREAMM-2) as the source of the comparative effectiveness. This source is in line with the chosen source of the analysis by the Company in their clarification response model. The EAG selected this source because it seems that the Company has not run the analysis for Belamaf versus PanoBorDex by using their NCRAS Naïve (Belamaf NPP) in their updated model (post TE) therefore the LYGs and QALYs for PanoBorDex are [redacted]. The EAG note this inconsistency in the analysis, so undertook scenario analysis by changing the source of comparative effectiveness to the NCRAS Naïve (Belamaf DREAMM-2).

The EAG retains all the other assumptions in the company's previous model (after clarification) for presenting the scenario analysis results for Belamaf vs PanoBorDex and only uses the updated utility values based on the DREAMM-2 final analysis.

1- Total costs for PanoBordex are [redacted], No Change.
2- Total QALYs for PanoBorDex are [redacted] change.
3- Total costs for Belamaf are [redacted], No Change.
4- Total QALYs for Belamaf are [redacted] Change.
5- The incremental costs are [redacted], No Change.
6- The incremental QALYs are [redacted] Change.
7- The ICER shows [redacted] state for Belamaf

References

Lee, H.C., Ramasamy, K., Weisel, K., Abonour, R., Hardin, J.W., Rifkin, R.M., Ailawadhi, S., Terebelo, H.R., Durie, B.G., Tang, D. and Joshi, P., (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 and Leukemia*,*23*(2), pp.112-122.

Schneider, McNamara, Love-Koh, Doran, Gutacker. (2021) QALY Shortfall Calculator.

Yong K. et al. (2016) . Multiple myeloma: patient outcomes in real-world practice; British Journal of Haematology, 2016, 175, 252–264

The EAG's critique on the Severity modifier choice after the TE meeting

Deterministic Calculations

After the TE meeting, the company has updated its utility weights and used the final cut of the DREAMM-2 (at [redacted] months of follow-up) for calculating the Quality of Life. The company also use the NPP data as a real-world dataset instead of DREAMM-2 as the source of input data for patient characteristics (i.e., age distribution, and sex distribution) as required for the QALY shortfall calculation. The EAG has raised some concerns about the NPP as an appropriate dataset for cost-effectiveness analysis which can be found in Part-2 of the EAG's technical engagement response. In general, using the NPP introduces more uncertainty around the data and inputs for the cost-effectiveness analysis.

Using the NPP for the source of data has caused differences in the mean of age and male-to-female ratio (%) as two underlying factors for calculating the severity modifier.

In the CS table 7, the mean of age in DREAMM-2 study (patients in 5L+ only) was reported [redacted], and [redacted] of participants were male.

In the company's updated severity modifier document, the mean of age the NPP participants is [redacted] with an interquartile range of [redacted]. It also reports that [redacted] of participants were male in line with the NPP study cohort. However, the EAG note two inconsistencies between the company's document for the updated severity modifier and the company's post-TE submission:

1- In the company's addendum (table 8) shows [redacted] of the participants in NPP were male. Changing the proportions does not significantly impact the proportional shortfall calculation.
2- In the company's submitted model, the mean QALYs for PomDex ([redacted]) are different from the company's updated severity modifier document ([redacted]). This changes the shortfall calculations.

Considering the issues raised by the EAG about the suitability of the NPP as a data source for this appraisal (EAG post -TE response), the EAG prefers NCRAS as a more suitable data source for deriving patient characteristics for the comparators as this was the dataset the company used to derive evidence on real-world use of PomDex and PanoBordex. Table 11 of the main CS shows the mean age for patients on PomDex is [redacted], and [redacted] of participants are male in the NCRAS study. The company's calculated severity modifiers are presented in table (1) below. The EAG have re-calculated the proportional shortfalls based on NCRAS data as the preferred data source for patient characteristics (table 2). Please note that the EAG has calculated the severity modifier only for PomDex since the model with updated information for PanoBorDex was not provided by the company.

Table 1. The Company's Summary of model outputs for proportional shortfall (deterministic calculations)

Factor	Mean QALY in expectation	Absolute shortfall	Proportional shortfall
No disease	[redacted]	[redacted]	[redacted]
PomDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
PanoBorDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]
Weighted average of real-world usage of PomDex and PanoBorDex	[redacted]	[redacted]	[redacted]

Table 2. The EAG's calculated Severity modifiers for PomDex by using patient characteristics from NCRAS databases (deterministic calculations)

Database	Factor	Mean QALY in expectation	Absolute shortfall	Proportional shortfall
NCRAS	No disease	[redacted]	[redacted]	[redacted]
	PomDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]

The company has maintained its approach for weighting the PomDex and PanoBorDex usage in its deterministic calculations. However, the model that the EAG had access to (post-TE) did not allow an NPP naïve analysis to allow cross-checking with the results currently presented by the company for the PanoBorDex comparison. Post-TE, the EAG requested that the company provide the updated analysis also showing 95% CI in the spreadsheet model, but the EAG did not receive this.

It is worth noting that the company considers PomDex the most relevant comparator for this appraisal. Thus, the most applicable proportional shortfall calculations would be for PomDex.

The EAG maintains its initial position that the most applicable severity weight is x1.2. (Please see table 2).

Probabilistic Calculations

The company has not changed the approach it used in its probabilistic calculations therefore the EAG's Post-TE critique remains relevant here. It is worth noting that the company state that the improved case for a x1.7 severity modifier is due to the patient

population in the UK real-world NPP study being slightly younger than the population of the DREAMM-2 trial ([redacted] years old at baseline) and from the age distribution being more heterogenous in the UK than in the DREAMM-2 study. However, the EAG does not agree that NPP should be the source of data for patient characteristics and NCRAS data source indicates that the patient population for PomDex is much older ([redacted]) years than that reported in both DREAMM-2 and NPP. Thus, using the same rationale as the company's would suggest that changing to this data source would reduce the proportion of patients that would benefit from a x1.7 severity modifier.

Specifically, the EAG maintains:

- If a probabilistic analysis was to be chosen, that mean QALY value should have been derived from the main PSA analysis and would incorporate uncertainty around all key parameters including age at which treatment is started. The EAG has recalculated the QALY shortfall based on company's PSA main analysis) and using the EAG's preferred data source (NCRAS) for age and sex distribution (table 3). In both tables, only PomDex could be calculated based on reasons given above.

Table 3. The EAG's calculated Severity modifiers for PomDex by using company's post-TE model and patient characteristics from NCRAS databases (probabilistic calculations)

Database	**Factor**	**Mean QALY in expectation**	**Absolute shortfall**	**Proportional shortfall**
NCRAS	No disease	[redacted]	[redacted]	[redacted]
	PomDex 5L+ TCR MM	[redacted]	[redacted]	[redacted]

The EAG calculations by using NCRAS database for age and sex distributions yields a QALY shortfall that equal to [redacted] proportional shortfall. This justifies a QALY weighting of x1.2.