Single Technology Appraisal

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Myeloma UK
   b. UK Myeloma Society & Royal College Physicians

4. **Expert personal perspectives from:**
   a. Karthik Ramasamy - clinical expert, nominated by GSK

5. **External Assessment Report prepared by York – response to Factual accuracy check**

6. **External Assessment Report – EAG report post factual accuracy check**

7. **Additional information post committee meeting**
   a. Company further information
   b. Company technical appendix
   c. EAG critique

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 with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Document B

Company evidence submission

May 2024

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

B.1.1 Decision problem

Multiple myeloma (MM) is an incurable haematological cancer which causes multiple painful and debilitating symptoms. A characteristic feature of MM is the evolution of the cancer and the build-up of resistance to different classes of therapies as the disease progresses. This therefore creates a constant unmet need for new therapies with novel mechanisms of action, to prolong life when the disease enters a relapse stage. The requirement to frequently reassess treatment pathways as new treatments enter and the standard of care (SoC) improves can also create 'gaps' in those pathways, for example where a SoC in a later line is combined into a triplet in an earlier line, leaving patients with fewer options in that later line.

Belantamab mafodotin ('belamaf', Blenrep®) is a first-in-class B-cell maturation antigen-targeted (BCMA) antibody-drug conjugate. In this submission, GlaxoSmithKline (GSK) considers the clinical and cost-effectiveness of belamaf in combination with bortezomib and dexamethasone (BVd) for the treatment of adults with relapsed refractory multiple myeloma (RRMM) who have had one prior line of therapy (LoT).

The decision problem addressed within this submission is broadly consistent with the National Institute for Health and Care Excellence (NICE) final scope for this appraisal as outlined in Table 1. The principal difference relates to the positioning of BVd in the treatment pathway (GSK propose it should be considered in the second line [2L] only) and thus the relevant comparators considered for the appraisal. The reason for focussing the submission on this subgroup is that clinical feedback has informed us that 2L is one of the areas of highest unmet need in the pathway currently, the comparator within DREAMM-7 is NICE approved at 2L (and 2L only) and the evidentiary case for BVd being a cost-effective use of National Health Service (NHS) resources is strongest in this subpopulation.

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	People with RRMM who have had at least 1 prior LoT	Adults (≥18 years) with RRMM who have had 1 LoT (2L patients)	There is a considerable unmet need in current NHS practice at 2L for a new, more efficacious triplet regimen for patients who are at first relapse. This subpopulation is an area of high unmet need and is supported by head-to-head clinical data. See Sections B.1.3.2 and B.3.9.1 for more details.
Intervention	Belantamab mafodotin ('belamaf', Blenrep®) in combination with bortezomib and dexamethasone	As per scope	N/A
Comparator(s)	For people who have had 1 prior therapy, NICE recommends: • Bortezomib monotherapy • Lenalidomide plus dexamethasone • Carfilzomib plus lenalidomide and dexamethasone • Carfilzomib plus dexamethasone • Daratumumab plus bortezomib and dexamethasone • Selinexor plus bortezomib and low-dose dexamethasone For people who have had more than one prior therapy, NICE recommend a number of options; these are cut from this table for brevity, since they	For people who have had 1 prior therapy: • Carfilzomib plus dexamethasone • Daratumumab plus bortezomib and dexamethasone • Selinexor plus bortezomib and low-dose dexamethasone (for a subgroup of patients who are refractory to daratumumab and lenalidomide	The comparators in the final scope are not aligned with UK clinical practice for people who have had 1 prior therapy because most patients at first relapse are refractory to lenalidomide or it is unsuitable for them (see Section B.1.3.2.2 and B.1.3.2.3 for additional details). Therefore, the decision problem addresses only those comparators with the potential to affect prescribing decisions in England and Wales.

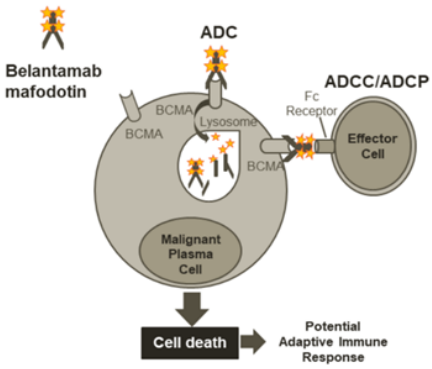
	are not relevant to the 2L decision problem.		
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope	N/A
Economic analysis	As per NICE reference case	As per scope	N/A

Abbreviations: 2L, second line; LoT, line of therapy; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RRMM, relapsed refractory multiple myeloma; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

Table 2 presents a brief description of technology being appraised: BVd.

Table 2. Technology being evaluated

UK approved name **Brand name**	• Belantamab mafodotin ('belamaf') • Blenrep®
Mechanism of action	Belamaf is a first-in-class BCMA targeted ADC. Belamaf is a humanised, afucoslyated, anti-BCMA monoclonal antibody conjugated to the microtubule inhibitor auristatin-F by a protease-resistant cysteine linker. BCMA is an established therapeutic target for MM due to its highly selective expression on malignant plasma cells (1-3). Belamaf provides patients with a unique mechanism of action (MoA) without impacting BCMA expression, leaving this open for future targeting by BCMA-directed agents (3). 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) (4). **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.

	Initial data demonstrates that belamaf does not impact BCMA expression. Therefore, as belamaf has minimal interference with normal immune surveillance, it can be partnered with other therapies with different MoAs and does not interfere with the subsequent use of other anti-BCMA therapies (3).
Marketing authorisation/CE mark status	The Great Britain marketing authorisation came into effect on 01 January 2021. The Annual Renewal procedure for belamaf is ongoing and is currently under the Medicines, and Healthcare Regulatory Agency (MHRA) assessment. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted]
Method of administration and dosage	[redacted] For further details see Appendix C.
Additional tests or investigations	[redacted] For further details see Appendix C.
List price and average cost of a course of treatment	• The list price of belamaf is £[redacted] for 1 vial of 100 mg powder for concentrate for solution for infusion (pending confirmation with the Department of Health and Social Care). • The list price of the 70mg dose will be priced proportionally per mg.
Patient access scheme (if applicable)	• A confidential simple Patient Access Scheme (PAS) has been proposed to NHS England/Patient Access Schemes Liaison Unit (PASLU) whereby 1 vial of 100 mg powder for concentrate for solution is made available to the NHS at a discounted price of [redacted]. This equates to an indicative discount of approximately [redacted]% • The net price of the 70mg dose will be priced proportionally per mg.

Abbreviations: ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BVd, belamaf in combination with bortezomib, and dexamethasone; CE, cost-effectiveness; DREAMM-7, DRiving Excellence in Approaches to Multiple Myeloma; GB, Great Britain; MHRA, Medicines and Healthcare Regulatory Agency; mg, milligram; MM, multiple myeloma; MoA, mechanism of action; PAS, Patient Access Scheme; PASLU, Patient Access Schemes Liaison Unit; RRMM, relapsed refractory multiple myeloma; SmPC, Summary of Product Characteristic.

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

Unmet need in MM

- MM is a rare cancer, characterised by the abnormal proliferation of clonal B cells in the bone marrow (6). Patients with MM typically experience multiple painful and debilitating symptoms, including fatigue, bone pain and peripheral neuropathy.
- There is no cure for MM, and the main goal of treatment is to avoid or delay progression, through a deep response to treatment that is also durable (7-15).
- One of the major challenges in MM is the evolution of the cancer and the build-up of resistance to different classes of therapies as the disease progresses (16-18). This creates a tension in the treatment landscape; in principle combining effective treatments in earlier lines may provide a deeper and more durable remission, but it can also lead to 'gaps' in the treatment pathway if new classes of treatment are not introduced to replace older treatments which have been combined in this way.
- SoC treatment options at first relapse (2L) are associated with poor outcomes, demonstrating the need for an efficacious backbone of choice, with a unique mode of action within the NICE treatment pathway. (19)
- Due to the widespread use of lenalidomide in first line (1L) in the UK, there is an emergent and acute unmet need for new treatment options to maintain patients at first relapse.

Treatment pathway in MM

- Although it might appear that patients with 2L MM are well served with six NICE approved treatment options, in fact the complexity of MM as a disease hides the acute unmet need in this population. The efficacy of a given MM therapy largely depends on prior exposure to MM drugs, particularly those from the same class, meaning that treatments which may have been a good choice when initially recommended by NICE may now be unsuitable for most patients.
- In general, clinicians consider two main treatment pathways at frontline; treatment for those who are eligible for a stem cell transplant (SCT) and treatment for those who are not eligible for a SCT.
    - Regardless of classification, almost all patients for whom lenalidomide is suitable will receive it until progression. Consequently, almost all patients enter their first relapse either refractory or ineligible for lenalidomide (20, 21).
    - In addition, patients who are ineligible for SCT are likely to enter 2L refractory to daratumumab too (22).
    - There are limited treatment options at 2L for patients who are lenalidomide-refractory or are patients for whom lenalidomide is unsuitable, and only 1 triplet is approved for a subgroup also refractory to daratumumab. Data suggests corresponding outcomes for all of these treatment options are suboptimal in these subgroups. (19, 23-27)

Belamaf in MM

- Belamaf has demonstrated superior efficacy to all existing 2L treatment options (Section B.2.6 and Section B.2.9), meaning it can serve the unmet need described above very effectively.
- If approved, belamaf would be the first BCMA targeted therapy available to NHS patients, serving the acute unmet need for treatments with different mechanisms of action.

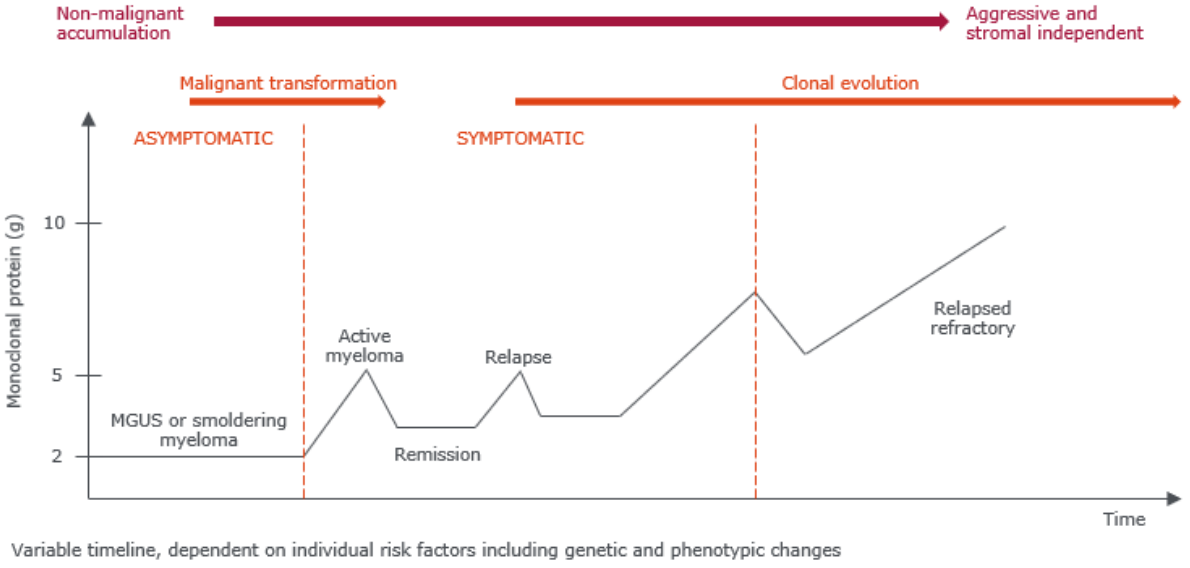
- Belamaf has demonstrated a remission nearly three times more durable than any existing MM treatment available to NHS patients (28, 29), serving the treatment goal of deep and durable remissions as early in the course of treatment as possible.

B.1.3.1 Disease overview

B.1.3.1.1 Overview of 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. (6) 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 (30). The clinical course of the disease, although variable, typically includes periods of treatment and remission separated by inevitable relapses, with the duration of response (DoR) to treatment decreasing with subsequent treatments as shown in Figure 2 (31, 32).

Figure 2. Clinical course of multiple myeloma



Adapted from Kurtin et al. 2013 (32).
Abbreviations: MGUS, monoclonal gammopathy of undetermined insignificance.

One of the major challenges in MM is the evolution of the cancer and the build-up of resistance to different classes of therapies as the disease progresses, i.e., RRMM (16-18). RRMM is defined as MM that is non-responsive to therapy or has progressed within 60 days of the last line of treatment in patients who previously achieved a minimal response (MR) or better (33, 34). The pathophysiology of RRMM is poorly understood but generally accepted to be due to the increasing genomic complexity and shifting of the dominant and subdominant plasma cell clones, acquisition of

mutations and epigenetic alterations, and subsequent immune system dysfunction (35).

Patients with RRMM typically achieve shorter remission duration with each subsequent treatment regimen. In a retrospective study evaluating the clinical course of patients with MM, event-free survival decreased from approximately 10 months with the initial regimen to 7.3 months with 2L therapy, respectively demonstrating the progressive and aggressive nature of RRMM, as well as the need for effective treatments with a diverse range of mechanisms of action as early as possible in the treatment pathway (31, 36).

B.1.3.1.2 Epidemiology

MM is a rare disease accounting for approximately 2% of all new cancer cases and 10.1% of haematological malignancies in the UK (37, 38). 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 (39). Five-year prevalence of MM in the UK is estimated to be 26 per 100,000 (40). The incidence rates (IRs) are reported to be lower in the Asian ethnic group, higher in the Black ethnic group, and similar in people of mixed or multiple ethnicity, compared with the White ethnic group, in England (2013-2017 data) (37).There is a greater incidence in males, accounting for 58% of cases in the UK (39).

MM contributes to an estimated 3,098 deaths every year in the UK, which equates to more than eight deaths each day (41).

Each year, more than 43% of all new UK MM cases are diagnosed in patients aged 75 and over (39, 42-44). 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 (45).

In Europe, 95% of the patients diagnosed with MM receive 1L treatment (46). Subsequently, 61% of those patients receive 2L treatment (46), rising to 64% in the UK. (47) This results in approximately 3,360 patients in the UK who are eligible for 2L treatment (22, 46, 48). Furthermore, a chart review study describing real-world MM treatment patterns in Europe showed an increasing use of second-generation agents and monoclonal antibodies, especially following relapse after SCT. (47).

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 (49). At diagnosis, the clinical manifestations of symptomatic MM are present in approximately 70% of patients and are commonly defined using the term “CRAB”: hypercalcaemia, renal insufficiency, anaemia, and bone lesions (36, 50).

Vascular, metabolism & nutrition, and musculoskeletal & connective tissue comorbidities are common among patients with RRMM (7). Approximately 1% to 2%

of patients have extramedullary disease (EMD) (myeloma cells forming tumours outside of the bone marrow) at the time of diagnosis, and 8% develop EMD 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%) (51). Furthermore, patients with RRMM were also found to have a higher Charlson Comorbidity Index compared to those with newly diagnosed MM (45, 52-55).

As the disease progresses, symptoms and complications from previous treatments may persist. In 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) (51, 56).

Although new targeted treatment options for MM have extended survival for patients, i.e., help maintain HRQoL by delaying disease progression, there remains a significant adverse event (AE) burden. An interview study with patients with RRMM from across Europe (n=30), reported that the most common AEs were peripheral neuropathy and swelling of hands and feet (92%), diarrhoea/constipation (83%) and cognitive impairment (67%) (57). Moreover, pain and fatigue have been reported to be the most debilitating symptoms for patients, and an international HRQoL and economic questionnaire found that 30.4% of patients with RRMM had moderate to severe pain and 70.6% reported fatigue (13, 58).

B.1.3.1.4 Life expectancy

Although there is currently no cure for myeloma, it is highly treatable in most patients. The prognosis and life expectancy of myeloma patients has greatly improved over recent years, with an increasing number of new and effective treatment options. According to the most recent statistics available, just over half of myeloma patients in England will live for at least five years and a third with live for at least 10 years. (37) With the improvements in treatments and life expectancy, myeloma has the potential to become a cancer that is treatable over a very long period.

The SoC for 2L patients in the UK for whom lenalidomide is an unsuitable treatment is daratumumab in combination with bortezomib and dexamethasone (DVd).

UK real world evidence (RWE) for this triplet in this setting is emerging from the National Cancer Registration and Analysis Service (NCRAS), which collates retrospective England-based patient-level health data. A GSK-commissioned study (poster abstract accepted for publication at European Hematology Association (EHA) 2024 (25); manuscript in preparation (26)) identified 2L+ MM patients from NCRAS, to reflect the inclusion and exclusion criteria of the DREAMM-7 trial. The DREAMM-7-like cohort included 10,720 patients. Among these, 361 (3.4%) were lenalidomide-refractory. Among lenalidomide-refractory patients, 143 (39.6%) patients in the DREAMM-7-like cohort were treated with DVd at 2L. The median overall survival (OS)

for this group was 23.0 months (12.9-not reached (NR)), which is markedly lower than the overall 2L only cohort ([redacted]).

B.1.3.1.5 Humanistic burden

The high symptom burden experienced by MM patients often results in a detrimental impact on HRQoL, with the impairment found to be greater with a higher degree of symptoms severity, which can be either disease or treatment-related (8).

As patients transition from a treatment free interval (TFI) at 1L, to 2L treatment and subsequent treatment phases, it has been observed that the HRQoL deteriorates (59). A UK based study, conducted in 370 patients with MM, demonstrated that the HRQoL profile for most parameters (European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Questionnaire Module 20 [EORTC QLQ-MY20]: disease symptoms, side effects, future perspectives, body image; European Quality of life-5 Dimensions [EQ-5D]: mobility, self-care, pain/discomfort and anxiety/depression; European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire [EORTC QLQ-C30]: physical, emotional) of patients in later phases of treatment was worse than in their first TFI. This deterioration in HRQoL is an indicator of the increasing symptom burden and cumulative toxicities as patients progress through treatment lines. Thus, remission in earlier lines of treatment (i.e., 2L) is essential for improving the quality of life (QoL) of patients (59).

A RW study conducted in Europe across ten countries, aimed at characterising the psychological burden of relapse on patients with RRMM (60). The study charted the evolution of negative emotional outcomes in patients during relapse of the disease, especially during the first relapse (60). Additionally, patients reported worsened energy levels, increased tiredness, impaired concentration ability to perform daily activities, decreased participation in social activities and overall quality of life, upon progression from stable disease to disease relapse (60). Furthermore, multiple relapses lead to a lack of optimism regarding a sustained period of remission and a growing sense of despair due to the depletion of viable treatment choices (60).

Another study reported the decline in the EORTC QLQ-C30 Global Health Status scores as treatment line progressed, beginning at a mean score of 63.0 at 1L to 59.7 at 2L for patients receiving supporting care ($p<0.0001$; $p=0.0005$ excluding supportive care, analysis of variance), highlighting the need for treatments that maintain or improve HRQoL (10). Scores for all five of the functional scales were lower in later treatment lines; a significant effect was observed when including ($p<0.05$ for all functional scales) or excluding ($p<0.0001$ for all functional scales) supportive care (10). The same pattern was reported with the EORTC QLQ-MY20 scores, demonstrating a worse HRQoL with more relapse cycles (10).

The symptoms of MM also affect patients' ability to work and conduct normal activities of living. For instance, 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 (61). 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 (61, 62).

B.1.3.1.6 Economic burden

Developments in the treatment of MM have resulted in patients living longer. However, this has placed additional burden on the NHS, since healthcare resource utilisation (HCRU) and costs have increased as patients survive to experience multiple lines of therapy. Evidence suggests that HCRU increases in patients whose disease has repeatedly progressed on multiple LoTs (11, 64).

For example, 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 2L to 22% for fifth-line and onwards (5L+) (11). The main reasons for hospitalisations among patients on active treatment were drug administration and management of AEs (11). UK hospitalisation rates in patients with three prior lines of therapy (at fourth line [4L] treatment) were also higher during active treatment (67%) than during off treatment periods of remission/stable disease (29%) or post-progression periods (21%) (11).

Effective treatment that induces a long remission can therefore save the NHS significant costs, particularly if it can be administered in earlier lines of therapy, for example, at first relapse.

B.1.3.2 Clinical management of relapsed/refractory multiple myeloma and place of belamaf in the treatment pathway

B.1.3.2.1 Anticipated positioning of belamaf in combination with bortezomib, and dexamethasone in the treatment pathway

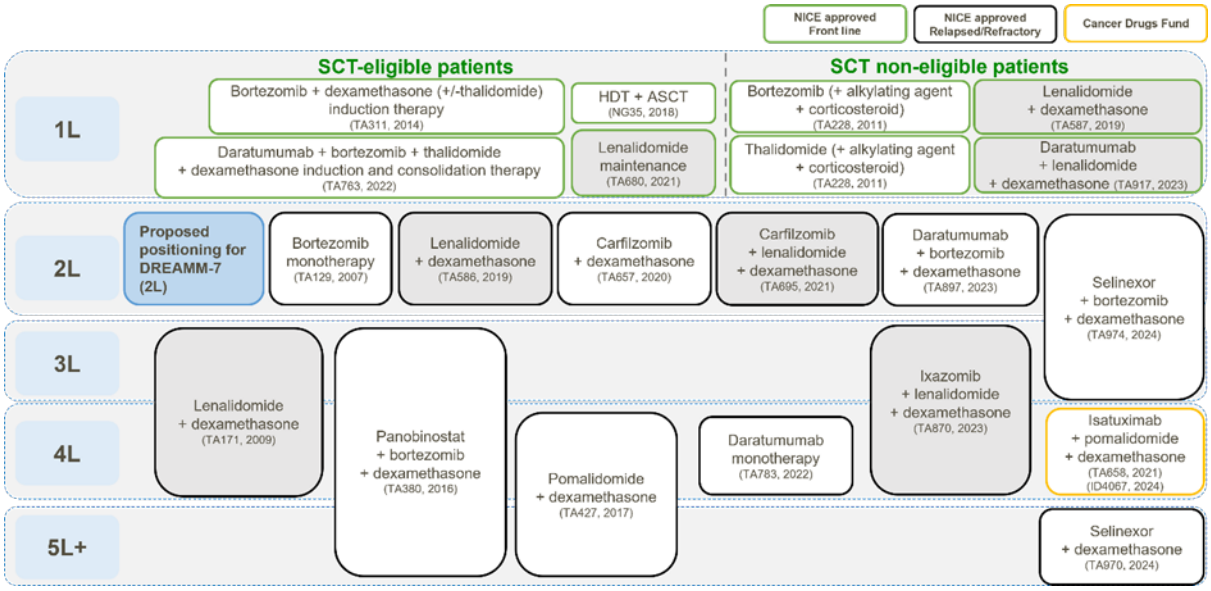
The clinical care pathway for MM patients in the UK is presented in Figure 3, including the proposed positioning of BVd as a 2L treatment option.

Although it might appear that patients with 2L MM are well served with six NICE approved treatment options, in fact the complexity of MM as a disease hides the acute burden of unmet need in this population. The efficacy of a given MM therapy largely depends on prior exposure to MM drugs, particularly those from within the same class, meaning that treatments which may have been a good choice when initially recommended by NICE are now unsuitable as 1L treatment has evolved. In particular, patients are notably underserved if a lenalidomide-containing regimen is unsuitable for them (highlighted in grey in Figure 3) (20, 21).

Section B.1.3.2.2 describes why GSK believes most patients in England and Wales will be lenalidomide-refractory when they enter 2L, and Section B.1.3.2.3 describes the impact this has on the treatment options of the clinician treating that patient.

Given the approval of SVd at both 2L and third line (3L) and the relative clinical strength of BVd over SVd, GSK and clinicians believe that the one of the highest areas of unmet need is at 2L, especially for patients for whom a lenalidomide-containing regimen is unsuitable. GSK notes that initial exploratory work with UK clinicians has indicated that the clinical case is strongest in 2L (since the DREAMM-7 trial is a head-to-head with the current 2L SoC DVd) and that positioning BVd at 2L results in the most cost-effective use of NHS resources compared to other possible positionings and restrictions. For these reasons GSK proposes the positioning outlined in Figure 3.

Figure 3. Anticipated positioning of belamaf in combination with bortezomib, and dexamethasone in the NICE treatment pathway



Notes: The subpopulation of patients for whom lenalidomide is unsuitable shows the greatest unmet need (65). Selinexor in combination with bortezomib, and dexamethasone(SVd) is recommended only for patients with RRMM that are refractory to both lenalidomide and daratumumab (NICE (TA974)), at 2L and for patients who are refractory to lenalidomide at 3L (29). Isatuximab in combination with pomalidomide, and dexamethasone (IsaPomdex) is currently available via the Cancer Drugs Fund and has received preliminary NICE rejection and is subject to final NICE guidance (66).
The proposed positioning for DREAMM-7 has been shaded in blue. Treatment regimens in the pathway containing lenalidomide have been shaded in grey.
Abbreviations: 1L–5L+, first- to fifth-line and onwards; ASCT, autologous stem cell transplant; BVd, belamaf in combination with bortezomib, and dexamethasone; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; HDT, high dose therapy; NICE, National Institute for Health and Care Excellence; RRMM, relapsing/refractory multiple myeloma; SCT, stem cell transplant; TA, technology appraisal

This positioning proposes BVd as the new SoC for all eligible 2L patients, but we note that this submission concerns itself with the cost-effectiveness of BVd in patients for whom lenalidomide is an unsuitable treatment. The number of lenalidomide-suitable 2L patients is small (and it might in fact be zero based on clinical feedback (67)) and therefore at the margin the bulk of the impact on the NHS of approving BVd will be due to the lenalidomide-unsuitable patients this submission focusses on. We note also that lenalidomide-suitable patients have access to two additional 2L treatments (carfilzomib in combination with lenalidomide and dexamethasone [KRd] and

lenalidomide plus dexamethasone [Rd]) which reduces the urgency of the unmet need in this population (20, 21).

The most common reason for a lenalidomide regimen to be unsuitable for a patient is that the patient is refractory to lenalidomide. According to the International Myeloma Working Group (IMWG) criteria, patients are defined as refractory to lenalidomide when presenting a non-responsive disease while on a lenalidomide-containing therapy or have progressed within 60 days of the last date of lenalidomide (68). However, lenalidomide refractoriness is not the only reason a lenalidomide-containing therapy might be considered unsuitable for a patient; this may be the case if they are contraindicated to lenalidomide (including because they are pregnant / are a woman of childbearing age) (69), or because they have been treated with lenalidomide at 1L, and found they could not tolerate it due to AEs such as gastrointestinal disturbances, fatigue, blood clots, peripheral neuropathy, low blood counts, or skin rashes (70).There is also an area of clinical judgement where a clinician might be unwilling to re-challenge a patient with lenalidomide if a non-lenalidomide alternative was available. The focus on lenalidomide-unsuitability rather than lenalidomide refractoriness is a nuance which GSK believes will make eventual recommendations more consistent and equitable with the complexity of the MM clinical pathway.

[redacted]

B.1.3.2.2 Treatment pathway for 1L relapsed/refractory multiple myeloma

The efficacy of a given MM therapy largely depends on prior exposure to MM drugs, particularly those from within the same class. Although the pathophysiology of RRMM is poorly understood, it is well known that retreatment with the same class of therapy following relapse promotes substandard outcomes for the patient (31, 36, 71). Consequently, the treatment of choice at 2L will be strongly influenced by the SoC at 1L.

Due to the complex and rapidly shifting nature of SoC in MM it is difficult to outline a single treatment strategy which will be followed for all patients in the frontline setting. However, in general, clinicians consider two main treatment pathways at frontline:

1. Treatment for those who are **eligible** for a SCT.
2. Treatment for those who are **ineligible** for a SCT.

The principal difference between the two groups of relevance to this submission is that each are likely to have a different mix of treatments that they are eligible for at 2L, due to physicians' unwillingness to rechallenge with a therapy which ceased to provide remission in 1L.

<u>Treatment for those who are eligible for a stem cell transplant</u>

The first-choice treatment for patients with MM is autologous stem cell transplantation (ASCT), where eligible (72). To stabilise the disease prior to ASCT, and deepen and

prolong the response after ASCT, systemic anti-cancer therapies (SACTs) are administered prior to and post-ASCT. For a patient beginning treatment in 2024, this is likely to be daratumumab plus bortezomib, thalidomide and dexamethasone as both induction and consolidation (DVTd) (72, 73). However, time to progression (TTP) is relatively long in 1L and so there may be some patients still experiencing remission from earlier SoC treatments such as high dose chemotherapy (usually melphalan) who have not received daratumumab.

Induction and consolidation are usually followed by lenalidomide maintenance therapy until progression, regardless of which treatment was used to induce the remission.

Therefore, almost all patients eligible for a SCT will be refractory to lenalidomide, and patients who are not refractory to lenalidomide because lenalidomide was unsuitable for them in 1L are likely to also find that lenalidomide is unsuitable for them in 2L.

Since NICE has approved a fixed number of cycles of DVTd (4 x induction, 2 x consolidation), few ASCT-eligible patients will also be refractory to daratumumab in 2L.

Treatment for those who are ineligible for a stem cell transplant

For ASCT-ineligible patients, SoC for a patient beginning treatment in 2024 is daratumumab in combination with lenalidomide and dexamethasone (DRd) (74). As this is a very recent addition to the MM treatment pathway in the NHS, many patients will still be taking a more established 1L treatment, which is likely to be lenalidomide and dexamethasone (Rd) (75). Patients who cannot tolerate Rd may be offered a thalidomide- or bortezomib-based regimen (76).

Therefore, almost all new starters in 1L who do not receive an ASCT will eventually become refractory to both lenalidomide and daratumumab. In addition, almost all patients who started treatment prior to 2024 and are currently still on 1L treatment will eventually become refractory to lenalidomide (but not daratumumab). As with the ASCT-eligible group, the small number of patients who do not receive lenalidomide in this line because lenalidomide is an unsuitable therapy for them are likely to find lenalidomide remains an unsuitable choice of therapy in 2L.

It is also relevant for assessing the cost-effectiveness of BVd that the proportion of patients who are daratumumab-refractory in this group will grow over time; therefore, the cost-effectiveness estimates presented in this dossier are an extreme lower bound of how cost-effective BVd will eventually become for the NHS as the proportion of daratumumab-treated 1L patients entering 2L each year increases.

B.1.3.2.3 Treatment pathway for 2L relapsed/refractory multiple myeloma

As described in Section B.1.3.2.2, treatment at 2L depends significantly on the treatment regimen at 1L, which itself mostly depends on characteristics of the patient.

Since lenalidomide is likely to be unsuitable for almost all patients at 2L, lenalidomide-sparing regimens form the backbone of 2L treatment in England and Wales. Typical lenalidomide-sparing regimens available for clinical use in RRMM in the UK include carfilzomib and dexamethasone (Kd) (77), or DVd (77). Unfortunately, both have limited efficacy in a lenalidomide-refractory population (78). DVd is typically preferred to carfilzomib and dexamethasone (Kd), as European Society for Medical Oncology (ESMO) guidelines generally recommend the use of triplet regimens, although doublet therapies may be prescribed for patients who are too frail to receive triplets (72).

Selinexor in combination with bortezomib, and dexamethasone (SVd) is a promising third option which has recently gained approval at both 2L and 3L, although outcomes are also poor for this triplet in a lenalidomide-refractory cohort and the use of SVd in 2L precludes its use in 3L, creating a problematic gap in the MM treatment pathway.

The unmet need in the current 2L treatment armamentarium is summarised in Table 3.

Table 3. Limitations of existing 2L lenalidomide-sparing options

Option	Limitations
DVd	• Over time, it is likely most patients will enter 2L refractory to daratumumab, owing to the widespread use of DRd at 1L. This will make DVd an entirely inappropriate option for those patients. • Notably, median PFS for the lenalidomide-refractory subgroup in CASTOR was substantially lower than that for the 2L subgroup (7.8 months versus 27 months) (19). The value of 7.8 months is consistent with the corresponding value for lenalidomide-refractory patients in the DVd arm of DREAMM-7 ([redacted]) (Section B.2.7.1). • The poor outcomes for DVd in the lenalidomide-refractory subgroup from CASTOR are also aligned with a recent UK real-world study where median TTNTD (used as proxy for PFS) was 10.3 months for lenalidomide-refractory patients at 2L (95% CI: 7.4, 13.9) (25).
Kd	• Notably, median PFS for the lenalidomide exposed subgroup in ENDEAVOR was substantially lower than that in the 2L subgroup (8.6 months versus 22.2 months (79)). • ESMO guidelines recommend against the use of doublet regimens when triplets are available (72). • Undesirable cardiac side effect profile (23).
SVd	• Overall poor clinical outcomes in lenalidomide-refractory patients (median PFS of 10.2 months reported in the BOSTON trial) (28). • Not available to patients unless they are also refractory to daratumumab (29). • Usage of SVd in 2L would preclude usage of SVd in 3L and create a situation where there are no NICE approved 3L treatments for lenalidomide-refractory patients.

Abbreviations: 1L, first line, 2L second line; 3L, third line; BVd, Belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DRd, daratumumab in combination with lenalidomide and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; DREAMM-7, DRiving

Excellence in Approaches to Multiple Myeloma; ESMO, European Society of Medical Oncology; Kd, carfilzomib and dexamethasone; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; SVd, Selinexor in combination with bortezomib, and dexamethasone; TTNTD, time to next treatment or death.

Therefore, there is a pressing need for effective lenalidomide-free regimens to address the limitations of current combinations for patients in England and Wales, who are either refractory to lenalidomide or are patients for whom lenalidomide is unsuitable, particularly after their first relapse. This need is expected to increase significantly following the positive NICE recommendation for DRd in 1L (74). Based on expert advice from English clinicians, the DRd triplet is the 1L SoC for transplant-ineligible patients (representing approximately two thirds of all newly diagnosed patients) (67).

For the avoidance of doubt, bortezomib monotherapy is not considered to be a relevant treatment in the 2L space, as it is rarely used in the treatment of MM in clinical practice in the UK (80). Clinical experts have highlighted that bortezomib treatment is rarely considered as a monotherapy treatment alone, and a bortezomib and dexamethasone doublet (Vd) would instead be used in the NHS (although use of this doublet is also very limited in clinical practice) (29). Much like Kd, in general clinicians would prefer not to use a doublet when a triplet is available, especially if that triplet has notably superior clinical performance.

Thus, there is a considerable unmet need in current NHS practice at 2L for a new, more efficacious triplet regimen for 2L MM patients, especially for those whom a lenalidomide-containing regimen would be unsuitable (which GSK expects to be effectively all patients at this line). A treatment with a novel MoA, such as belamaf, can offer an alternative and clinically important treatment option for this patient population.

B.1.4 Equality considerations

There are several risk factors associated with MM, including age, gender, and ethnicity (81-83). Therefore, there is the potential for NICE to inadvertently discriminate against any of these groups if they reject promising MM treatments, especially those such as belamaf which fill a clear unmet need. For example, MM disproportionately burdens Black people, and therefore improving the SoC in 2L MM would improve overall equity of healthcare outcomes (84, 85). The DREAMM-7 study, the source of efficacy evidence in the model presented in this submission, included adult (≥18) years), male and female patients of different ethnic backgrounds and included UK centres (86-88).

B.2 Clinical effectiveness

Summary of clinical effectiveness

- DREAMM-7, a multicentre phase III trial, compared the technology being evaluated (BVd) to the current UK 2L SoC within the NICE pathway (DVd). The trial included 243 patients (BVd arm) / 251 patients (DVd arm) in the intention-to-treat (ITT) population and 242 patients (BVd arm) / 246 patients (DVd arm) in the safety population. At the point of the primary analysis (data cut-off: 02 October 2023), the median study follow-up was 28.24 months.
- The primary endpoint of this trial was PFS based on independent review committee (IRC) assessment of response, and the secondary endpoints were DoR, OS, minimum residual disease (MRD), complete response rate (CRR), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), TTP, PFS-2, sustained MRD, very good partial response (VGPR), time to best response (TTBR) and HRQoL.
- There is a high unmet need at 2L for patients for whom lenalidomide is unsuitable, as options are limited and outcomes are poor even if lenalidomide-sparing regimes can be found (as outlined in Section B.1.3.2). The DREAMM-7 study results demonstrate that BVd can potentially be the new SoC for patients for whom lenalidomide is unsuitable at first relapse in the UK owing to the robust efficacy, manageable safety, and ease of administration.
    - BVd demonstrated a statistically significant and clinically meaningful IRC-assessed PFS benefit in the ITT population (95% confidence interval (CI): 0.31, 0.53; hazard ratio (HR), 0.41; p<0.00001; showing a 59% reduction in risk of disease progression or death) with a median PFS that was 23 months longer than that with DVd (36.6 vs 13.4 months).
        - PFS benefit consistently favoured BVd vs DVd across prespecified subgroups, including patients with lenalidomide-refractory or high-risk cytogenetic MM. In the lenalidomide-refractory subgroup, median PFS (95% CI) was [redacted] months ([redacted]) with BVd versus [redacted] months ([redacted]) with DVd (HR, [redacted]; 95% CI, [redacted]). In the high-risk cytogenetic subgroup, the median PFS (95% CI) was [redacted] months ([redacted]-NR) with BVd versus [redacted] months ([redacted]) with DVd (HR, [redacted]; 95% CI, [redacted]).
    - OS showed an early, strong, and clinically meaningful trend favouring the BVd arm in the ITT population (95% CI: 0.40, 0.80; HR, 0.57; p=0.00049)
        - Median OS was NR in both groups. Landmark analysis of OS at 18 months showed a higher survival rate in the BVd group compared with the DVd group (84% vs.73%).
    - BVd was associated with greater depth of response in the ITT population with a ≥ CRR that was double that with DVd (34.6% vs 17.1%). MRD negativity rate (10^{-5}) in patients treated with BVd was more than double that in patients treated with DVd (24.7% vs 9.6%; p<0.00001, nominal; ≥ complete response [CR])
        - 65.8% and 46.2% of responders in the BVd and DVd group achieved deep responses of VGPR or better with a median TTR of [redacted] and [redacted] months in the ITT population, respectively.
    - The median time to treatment discontinuation (TTD) was [redacted] months for the BVd group vs. [redacted] months for the DVd group.

- The safety and tolerability of BVd was consistent with those previously described for belamaf, despite the longer time on treatment compared to previous monotherapy studies. (89, 90)
  - Eye-related side effects, a known risk with belamaf, were manageable and resolved with dose modifications including delays and reductions and led to a low rate of discontinuations.
  - Despite the higher incidence of eye-related side effects in the BVd arm, overall health-related QoL did not differ between arms over time.
  - The rates of infections, including opportunistic infections, a known risk with chimeric antigen receptor T-cell and bispecific T-cell engager BCMA-targeting agents (91-94) was similar between treatment arms in the DREAMM-7 trial.
- Network meta-analysis (NMA) results suggest that BVd is more efficacious compared to all lenalidomide-sparing comparators (DVd, SVd, Kd), for all populations in terms of PFS, OS, and ORR.
  - In terms of PFS, BVd demonstrated statistically significant improvements over all comparator treatments in the ITT population including over SVd (HR, [redacted]; 95% CI: [redacted]), hKd (HR, [redacted]; 95% CI: [redacted]) and DVd (HR, [redacted]; 95% CI: [redacted]), with consistency across populations of interest: ITT and lenalidomide-refractory patients.
  - All the HR results indicated an OS benefit for BVd over SVd (HR, [redacted]; 95% CI: [redacted]), hKd (HR, [redacted]; 95% CI: [redacted]) and DVd (HR, [redacted]; 95% CI: [redacted]) in the ITT population.
  - BVd demonstrated a higher probability of achieving ORR over DVd, hKd, and SVd in the ITT population.

B.2.1 Identification and selection of relevant studies

In line with NICE reference case requirements to identify all relevant sources of clinical evidence, a clinical systematic literature review (SLR) was undertaken. The main aim of this SLR was to summarise the efficacy and safety of treatments for RRMM in clinical trials enrolling adult patients (≥18 years) with at least one prior LoT (95).

The cut-off date for inclusion in the SLR was 04 February 2024. This was achieved by conducting a major review of the literature in December 2021 (covering studies from January 2008 to December 2021) and then incrementally updating the SLR with three additional review passes (26 March 2023, 18 October 2023 and finally 04 February 2024).

This SLR was conducted following the recommendations of the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) Protocols checklist (95-97) and is considered suitable to inform single technology appraisals that are submitted to NICE (95, 98).

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Belamaf in combination with bortezomib and dexamethasone

DREAMM-7 is a multicentre phase III, randomised, open-label trial evaluating the clinical efficacy and safety of BVd compared with the current SoC: DVd for the treatment of adult RRMM patients with at least one prior LoT (86-88, 99). This is the only trial directly comparing BVd vs DVd, and therefore the clinical data and cost-effectiveness analyses presented in this submission are based on this trial.

The DREAMM-7 trial evaluated the efficacy and safety of belamaf at a dose of 2.5 mg/kg (intravenous [IV]) once every 3 weeks (Q3W) in combination with bortezomib, and dexamethasone in adult RRMM patients who have had at least 1 prior LoT.

The clinical effectiveness evidence summary for DREAMM-7 is presented in Table 4. (86-88, 99).

Table 4. Clinical effectiveness evidence

Trial name	DREAMM-7 trial (87, 88, 99)
Trial design	Phase III, multicentre, randomised, open-label trial comparing BVd with DVd
Population	Adults (≥18 years) with RRMM who have had at least 1 prior LoT
Intervention(s)	BVd: Belamaf was administered IV at the dose of 2.5 mg/kg on Day 1 of every 21-day cycle. Dose delays and reductions were permitted throughout the study as described in Section 6.6.1 of the DREAMM-7 protocol. Bortezomib 1.3 mg/m^2 was administered SC on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles. On days where bortezomib and belamaf administrations coincided, bortezomib was to be administered approximately 1 hour after the belamaf infusion was complete. Dexamethasone 20 mg (PO or IV) was administered on the day of and the day after bortezomib treatment. Starting dose of dexamethasone was reduced to 10 mg for participants older than 75 years of age, who had a body-mass index of <18.5 kg/m^2, who had previous unacceptable side effects associated with glucocorticoid therapy, or who were unable to tolerate the starting dose. On days where bortezomib and dexamethasone administration coincided with administration of belamaf, dexamethasone was to be administered PO or IV prior to the infusion of belamaf.
Comparator(s)	DVd:

	Daratumumab 16 mg/kg IV was administered according to the approved label schedule in combination with bortezomib/dexamethasone weekly for Cycles 1 through 3 (Weeks 1 to 9) (21-day cycles, total of 9 doses), on Day 1 of Cycles 4 through 8 (Weeks 10 to 24) (21-day cycles, total of 5 doses), and then every 4 weeks from Cycle 9 (Week 25) onwards (28-day cycles). For the first dose of daratumumab dosing at Week 1 only, the single infusion of daratumumab could be split over 2 days. Bortezomib and dexamethasone dosing schedule in DVd arm was same as that of BVd arm.		
Indicate if study supports application for marketing authorisation	Yes	**Indicate if study used in the economic model**	Yes
Rationale if study not used in model	Not applicable.		
Reported outcomes specified in the decision problem	• OS • PFS • Response rates • AEs of treatment • HRQoL as measured by EQ-5D-3L, EORTC QLQ-C30 and EORTC IL52 (disease symptoms domain from the EORTC QLQ-MY20)		
All other reported outcomes	• DoR • TTP • TTR • TTBR • TTD • TTNT • Sustained MRD* • PFS-2		

Abbreviations: AE, adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; DoR, duration of response; DVd, daratumumab in combination with bortezomib, and dexamethasone; DREAMM-7, DRiving Excellence in Approaches to Multiple Myeloma; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire; EORTC IL52, European Organisation for Research and Treatment of Cancer IL52; EQ-5D-3L, European Quality of life-5 Dimensions 3 levels; HRQoL, health-related quality of life; IV, Intravenous; LoT, line of therapy; kg, kilogram; mg, milligram; MRD, minimum residual disease; OS, overall survival; PFS, progression-free survival; PFS-2, progression-free survival-2; PO, periorbital; RRMM, relapsed refractory multiple myeloma; SC, subcutaneous; TTBR, time to best response; TTD, time to discontinuation; TTNT, time to next treatment; TTP, time to progression; TTR, time to response.

* Sustained MRD negativity rate was defined as the percentage of participants with MRD negativity confirmed by NGS (next generation sequencing) minimum of 1 year apart per IMWG criteria. Please refer to Section 5.1.4.3 of DREAMM-7 primary analysis report for additional details on sustained MRD (99).

B.2.2.2 Comparators

Three potential comparators approved by NICE for the current submission for patients for whom lenalidomide is unsuitable at 2L were identified in Section B.1.3.2. These are: DVd, SVd and Kd. The clinical SLR report retrieved the following findings for these comparators:

For DVd:

- Efficacy and safety in patients with RRMM who had received at least one prior LoT was assessed in two randomised, multicentre, phase III clinical trials, CASTOR and LEPUS (19, 22, 100, 101). In both of these trials, DVd was compared to Vd.
- In addition to these clinical trials, a UK retrospective multicentre analysis also assessed the ORR and PFS in routine clinical practice for patients at first relapse treated with DVd incorporating weekly bortezomib with secondary aims assessing time to next treatment (TTNT), OS and efficacy in subgroups (102).

For SVd:

- The efficacy and safety of SVd in patients with RRMM who had received at least one prior LoT was also assessed in a phase III multicentre trial, BOSTON (103, 104). SVd was compared to Vd.

For Kd:

- The efficacy and safety of Kd in patients with RRMM who had received at least one prior LoT was also assessed in a phase III multicentre trial, ENDEAVOR (103, 104). Kd was compared to Vd.

Additional details of these trials can be found in Appendix D.

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

- In the DREAMM-7 trial (~13-month from first patient in (FPI) [FPI- 07 May 2020] to last patient in (LPI) [LPI- 28 June 2021], the efficacy and safety of the intervention BVd was compared to SoC DVd in the population of interest (2L RRMM).
- Participants were stratified based on the number of prior LoTs (1 vs. 2/3 vs. ≥4), prior bortezomib (yes vs. no), and the Revised International Staging System (R-ISS) stage (I vs. II/III), and centrally randomised in a 1:1 ratio to either arm. No cross-over was allowed and no more than 50% of participants with ≥2 prior lines of treatment were enrolled.
- Participants were eligible to be included in this trial if they were 18 years or older with a confirmed diagnosis of MM as defined by the IMWG criteria.
- Key inclusion criteria included previous treatment with at least 1 prior line of MM therapy with documented disease progression during or after their most recent therapy, and at least 1 aspect of measurable disease. Key exclusion criteria included intolerance to daratumumab and bortezomib; refractoriness to either daratumumab or any anti-CD38

therapy or bortezomib (on a twice-weekly regimen), and prior treatment with anti-BCMA therapy.

- In the current submission, GSK reports results for efficacy outcomes (PFS, OS, ORR, DoR, and other efficacy outcomes) & HRQoL for the intention-to-treat (ITT) Population (N=243 for BVd and N=251 for DVd). Safety results are presented for the Safety analysis population (N=[redacted] for BVd and N=[redacted] for DVd).
- Results presented are based on the primary Analysis for DREAMM-7 (Data cut-off: 02 October 2023) with the median study follow-up was 28.24 months.

B.2.3.1 Belamaf in combination with bortezomib and dexamethasone (DREAMM-7)

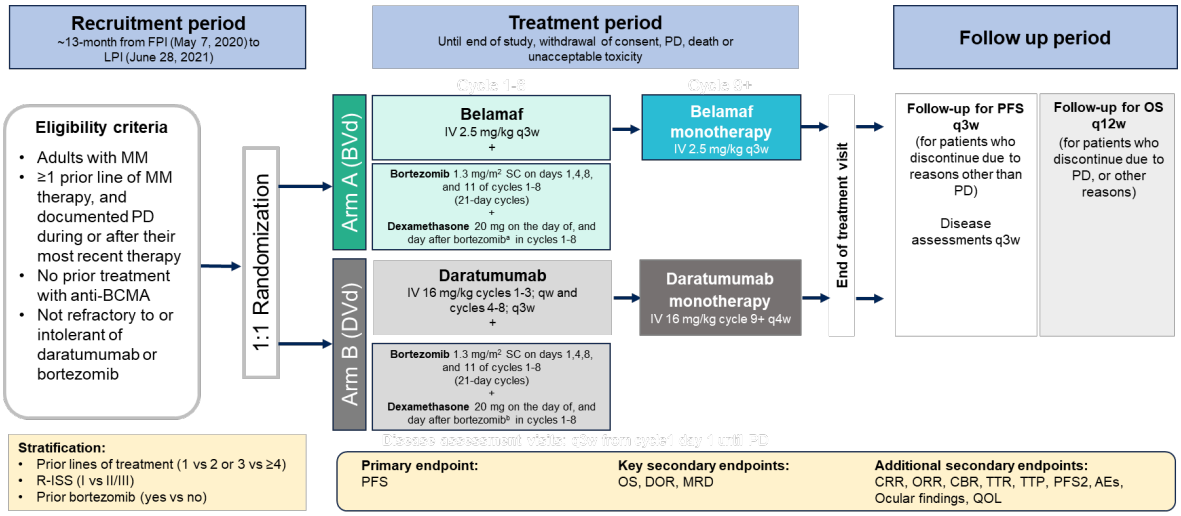
Summary of trial methodology

DREAMM-7 is a phase III, open-label, randomised trial to investigate the efficacy and safety of BVd compared with the SoC: DVd, in adults (≥18 years) with RRMM who have had at least 1 prior LoT. It was conducted in 142 MM specialty centres in 20 countries (Australia, Canada, France, Germany, Italy, Spain, the UK, and the US, Russian Federation, Poland, New Zealand, Netherlands, Republic of Korea, Japan, China, Israel, Greece, Czech Republic, Brazil, Belgium), including 7 centres in the UK (86).

The trial included a Screening Period, a Treatment Period, and a Follow-up Period (Figure 4). Patients were randomly assigned in a 1:1 ratio to belamaf 2.5 mg/kg IV Q3W in combination with bortezomib and dexamethasone, through central assignment of a randomisation number, generated by the Company's Clinical Statistics Department. Stratification factors included the number of prior LoTs (1 vs. 2/3 vs. ≥4), prior bortezomib (yes vs. no), and the R-ISS stage (I vs. II/III). No cross-over was allowed and no more than 50% of participants with ≥2 prior LoTs were enrolled (87, 88, 99).

Treatment was continued in both arms until progressed disease (PD) per IMWG criteria, death, unacceptable toxicity, investigator's discretion, withdrawal of consent, or end of study, whichever occurred first. For participants who discontinued study treatment for reasons other than PD or death, disease evaluations were performed Q3W (±3 days) until confirmed PD (documented), death, start of a new anti-myeloma treatment, withdrawal of consent, loss to follow-up, or end of the study, whichever occurred first. In case of PD, participants were followed to ascertain subsequent anti-myeloma therapy, PFS-2, and survival status every 12 weeks (Q12W) (±14 days) until withdrawal of consent, loss to follow-up, death, or the end of the study (87, 88, 99).

Figure 4. Overview of the DREAMM-7 trial design



Abbreviations: AE, adverse event; BCMA, B-cell maturation antigen; BVd, belamaf in combination with bortezomib, and dexamethasone; CBR, clinical benefit rate; CRR, complete response rate; DREAMM-7, DRiving Excellence in Approaches to Multiple Myeloma; DoR, duration of response; DVd, daratumumab in combination with bortezomib, and dexamethasone; FPI, first patient in; IV, intravenous; LPI, last patient in; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; q4w, every 4 weeks; q12w, every 12 weeks; qw, every week; QoL, quality of life; R-ISS, Revised International Staging System; SC, subcutaneous; TTP, time to progression; TTR, time to response.

[a,b]Reduce starting dose of dexamethasone to 10 mg for patients >75 years of age, who have a body-mass index <18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting.

Source: DREAMM-7 trial protocol (87); DREAMM-7 trial protocol amendment (88); DREAMM-7 primary analysis clinical study report (99).

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

The primary endpoint of the DREAMM-7 trial was PFS, defined as the time from randomisation until the earliest date of PD, determined by an IRC, according to IMWG criteria or death due to any cause (99).

Other outcomes included:

- Key secondary outcomes: DoR, OS, MRD (99).
- Other secondary outcomes: CRR, ORR, CBR, TTR, TTP, PFS-2, AEs, eye-related findings, HRQoL (99).
- Exploratory outcomes: TTBR, VGPR rate, sustained MRD (99).
- Additional outcomes: TTD, TTNT (105)

B.2.3.2 Comparative summary of the methodology of the DREAMM-7 trial

A summary of the trial design and methodology is reported in Table 5, and efficacy outcome measures in Table 5 and Table 6.

Table 5. DREAMM-7 trial methodology

Trial name	DREAMM-7 trial (87, 88, 99).
Location	Global, multicentre study, including the UK
Trial design	Multicentre, phase III, randomised, open-label trial comparing BVd with DVd.
Key dates	First patient dosed: [redacted] Data cut-off dates: 02 October 2023 (primary analysis)
Patient disposition & follow-up	A total of 494 participants with RRMM were randomised to either BVd or DVd. There were 2 participants who were randomised to the DVd group, but were not treated, and were re-screened and re-randomised each to the BVd and the DVd group within a short timeframe. Given these participants were randomised multiple times, with multiple sets of baseline data, the recommended approach to preserve the balance in prognostic factors achieved by randomisation was to retain both sets of baseline data along with the randomisations; they were counted as 4 unique participants (106). [redacted] participants ([redacted] withdrew from the study ([redacted] in the BVd group and [redacted] in the DVd group). The primary reasons for study discontinuation included withdrawal by participant and physician decision. There were more deaths in the DVd group ([redacted]) compared with the BVd group ([redacted]). More participants were ongoing in study in the BVd group ([redacted]) compared with the DVd group ([redacted] at the data cut-off. At the data cut-off, 33% participants in the BVd vs. 20% participants in the DVd group were on study treatment.

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 (107).
	• Previously treated with at least 1 prior line of MM therapy and must have documented disease progression during or after their most recent therapy according to the IMWG criteria (108).
	• Has measurable disease with at least one of the following:
	  ○ Serum M-protein ≥0.5 g/dL (≥5 g/L)
	  ○ Urine M-protein ≥200 mg/24h
	  ○ Serum 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 SCT were eligible for study participation provided the following eligibility criteria were met:
	  ○ Transplant was >100 days prior to study enrolment
	  ○ No active infection(s)
	  ○ 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 haematologic, hepatic, and renal functions) • All prior treatment-related toxicities, defined by NCI-CTCAE, version 5.0, must be ≤Grade 1 at the time of enrolment except for alopecia **Exclusion criteria:** The main exclusion criteria were: • Intolerance to daratumumab and bortezomib • Refractoriness to either daratumumab or any anti-CD38 therapy or bortezomib (on a twice-weekly regimen) • 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 • Has received radiotherapy to a large pelvic area (check with sponsor). Bridging radiotherapy otherwise is allowed • Symptomatic amyloidosis, active POEMS syndrome or 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. Patients with curatively treated non-melanoma skin cancer may be enrolled • Detailed exclusion criteria is provided in DREAMM-7 trial protocol Section 5.2 (87, 88).

Settings and where data were collected	151 MM specialty centres in 20 countries, including 7 centres in the UK (86).
Trial drugs and concomitant medications	The only trial drug included was belamaf, at 2.5 mg/kg Q3W in combination with bortezomib and dexamethasone 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:
	  ○ PFS
	• Key secondary efficacy endpoints:
	  ○ DoR
	  ○ OS
	  ○ MRD
	• Other secondary efficacy endpoints:
	  ○ CRR
	  ○ ORR
	  ○ CBR
	  ○ TTR
	  ○ TTP
	  ○ PFS-2
	• Exploratory efficacy endpoints:
	  ○ TTBR
	  ○ VGPR
	  ○ Sustained MRD
	• Additional efficacy endpoints:
	  ○ TTD
	  ○ TTNT
	
	All efficacy endpoints are defined in Table 6.
	
	Safety outcomes
	• AEs overview, by SOC, by severity
	• SAEs
	• Death
	• Treatment-related AE
	• AEs leading to discontinuation, dose delay and dose reduction of study treatment
	• AESI; corneal events, thrombocytopenic events, infusion-related reactions

	Health outcomes • Patient reported symptoms, functioning, and HRQoL
Disease response assessment	Response evaluation was performed according to the IMWG Uniform Response Criteria for MM (108), as determined by a blinded IRC. Per the IMWG, quantitative Ig levels by nephelometry could be used in place of SPEP for routine M-protein measurement for patients with IgA or IgD myeloma. Also, per the IMWG, response could be confirmed if the patient failed to provide a 24-hour urine sample after screening activities occurred. Two consecutive assessments were needed to confirm response. For patients who achieved CR or sCR, confirmatory samples for SPEP with serum protein immunofixation, quantitative Ig, and serum FLC were collected in duplicate at the time of the response and the duplicate samples were provided to the central laboratory. A confirmatory 24-hour urine sample was also collected, and an aliquot was provided to the central laboratory for UPEP with urine protein immunofixation.
Assessment schedule	All efficacy assessments were performed on a calendar schedule and must not be affected by dose interruptions/delays. For post-baseline assessments, a window of ± 3 days was permitted to allow for flexible scheduling. For participants who were discontinuing study intervention due to PD, the confirmation of laboratory parameters must be performed from a different blood collection either on the same day, or within 14 days of the original date of suspected disease progression, preferably before initiation of any new anti-myeloma therapy. The assessments to be performed during the End of Treatment Visit are described in the schedule of activities (SoA) (87, 88) If the last imaging assessment was greater than or equal to 8 weeks prior to the participant's discontinuation from study treatment and progressive disease has not been documented, a new disease assessment must be obtained at the time of discontinuation from study treatment. For participants with PD due to EMD, confirmatory scans were not required. The laboratory parameters do not need to be repeated if the EMD is the only site of progression.
Pre-planned subgroups	Age group; sex; race; ethnicity; region; prior bortezomib therapy, prior lenalidomide therapy; refractory to lenalidomide therapy, number of prior anti-MM LoTs; revised ISS stage at screening; baseline cytogenetic abnormalities; EMD at baseline; time to relapse after completion of first LoT.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; BCMA, B-cell maturation antigen; BVd, belamaf in combination with bortezomib, and dexamethasone; CBR, clinical benefit rate; CR, complete response; CRR, complete response rate, DREAMM-7, DRiving Excellence in Approaches to Multiple Myeloma; DoR, duration of response; DVd, daratumumab in combination with bortezomib, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; ISS, International Staging System; FLC, free light chains; HRQoL, health-related quality of life; Ig, Immunoglobulin; IMWG, International Myeloma Working Group; IRC, Independent Review Committee; LoT, line of therapy, MM, multiple myeloma; MRD, sustained minimal residual disease; NCI-CTCAE, National Cancer Institute- Common Toxicity Criteria for Adverse Event; ORR, overall response rate; OS, overall survival; PD, progressed disease; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder; PFS, progression-free survival; PFS-2, progression-free survival-2; Q3W, once every 3 weeks; RRMM, relapsed refractory multiple myeloma; SAE, serious adverse event; sCR, stringent complete response; SCT, stem cell transplant; SoA, schedule of activities; SOC, system organ class; SPEP, serum protein electrophoresis; TTBR, time to best response; TTD, time to discontinuation, TTNT, time to

next treatment; TTP, time to progression; TTR, time to response; UK, United Kingdom; UPEP, urine protein electrophoresis; VGPR, very good partial response.

Table 6. DREAMM-7 efficacy outcome measures definitions

Endpoint type	Measure	Description
Primary	Progression-free survival (PFS)	Defined as the time from the date of randomisation until the earliest date of documented disease progression according to IMWG criteria (108) or death due to any cause
Secondary	Overall response rate (ORR)	Defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, sCR) as determined by an IRC, according to IMWG criteria (108)
	Complete response rate (CRR)	Defined as the percentage of participants with a confirmed CR or better (i.e., CR, sCR) as determined by an IRC, according to IMWG criteria (108)
	Clinical benefit rate (CBR)	Defined as the percentage of participants with a confirmed MR or better as determined by an IRC, according to IMWG criteria (108)
	Duration of response (DoR)	Defined as the time from first documented evidence of PR or better until PD or death due to PD among participants who achieve confirmed PR or better
	Time to response (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 as determined by an IRC, according to IMWG criteria (108)
	Time to progression (TTP)	Defined as the time from the date of randomisation until the earliest date of documented PD as determined by an IRC, according to IMWG criteria (108) or death due to PD
	Overall survival (OS)	Defined as the interval of time from randomisation to the date of death due to any cause. Participants who are alive will be censored at the date of last contact or last known alive.
	Minimal residual disease (MRD)	Defined as the percentage of participants who achieve MRD negative status (as assessed by NGS at 10-5 threshold) at least once during the time of confirmed CR or better response as determined by an IRC, according to IMWG criteria (108)

Endpoint type	Measure	Description
	Progression-free survival-2 (PFS-2)	Defined as time from randomisation to disease progression after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy could not be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier
Exploratory	Sustained Minimal residual disease (sMRD)	Defined as the percentage of participants with MRD negativity confirmed by NGS minimum of 1 year apart, per IMWG criteria (108)
	Time to best response (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 determined by an IRC, according to IMWG criteria (108)
	Very good partial response (VGPR)	Defined as the percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, sCR) as determined by an IRC, according to IMWG criteria (108)
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 prespecified outcome. It was reconstructed by combining TTD to TSNT from discontinuation

Abbreviations: CBR, clinical benefit rate; CR, complete response; CRR, complete response rate; DoR, duration of response; IMWG, International Myeloma Working Group; IRC, independent review committee; MR, minimal response; 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; sCR, stringent complete response; TSNT, time to start of next therapy; TTBR, time to best response; TTD, time to discontinuation, TTNT, time to next treatment; TTP, Time to progression; TTR, Time to response; VGPR, very good partial response.
Source: DREAMM-7 trial protocol (87); DREAMM-7 trial protocol amendment (88); DREAMM-7 primary analysis clinical study report (99).

B.2.3.2.1 Patient disposition

A total of 494 participants with RRMM were randomised to either BVd or DVd. [redacted] participants ([redacted]) withdrew from the study ([redacted] in the BVd group and [redacted] in the DVd group. The primary reasons for study discontinuation included withdrawal by participant and physician decision. There were more deaths in the DVd group ([redacted]) compared with the BVd group ([redacted]). More participants were ongoing in the study in the BVd group ([redacted]) compared with the DVd group ([redacted]) at the data cut-off. At the data cut-off, 33% participants in the BVd vs. 20% participants in the DVd group were on study treatment.

The flow of participants through the DREAMM-7 trial is summarised in a CONSORT diagram in Appendix D.

In the BVd vs. DVd groups, the median duration of follow-up was similar ([redacted] [range: [redacted]] vs. [redacted] [range: [redacted]]) (Table 7).

Table 7. Duration of follow-up (intention to treat [ITT] population)

	BVd (N=243)	DVd (N=251)	Total (N=494)
Duration of follow-up (months)[a]			
Min	[redacted]	[redacted]	[redacted]
1st quartile	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]
Duration of follow-up (months) for participants with ongoing follow-up[a]			
n	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]
1st quartile	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
3rd quartile	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]

a. Duration of follow-up was defined as the time from randomisation to last contact or death.
Note 1: There was 1 participant who had a study conclusion record with no date provided. This participant was considered to have ongoing follow-up for duration of follow-up.
Note 2: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this table.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; ITT, intention-to-treat.
Source: DREAMM-7 primary analysis clinical study report (99)
At the data cut-off, the percentage of participants who discontinued belantamab mafodotin (66%) was lower compared with the percentage of participants who discontinued daratumumab (78%) (99). The primary reasons for discontinuation of belamaf or daratumumab were disease progression (24% vs. 59%), AEs (19% vs. 9%), and physician's decision (14% vs. 4%). At the data cut-off, all participants on treatment were in the monotherapy phase of the study (99). In the BVd group, 62% (n=150) and 70% (n=169) completed 8 full or truncated cycles of bortezomib and dexamethasone, respectively, and in the DVd group, 62% (n=155) and 70% (n=175) completed 8 full or truncated cycles of bortezomib and dexamethasone, respectively. TTD related to study treatment was reported as [redacted] and [redacted] in the BVd and DVd groups, respectively (99).

B.2.3.2.2 Patient demographics and baseline characteristics

Baseline characteristics and prior treatments were well balanced between arms (Table 8). 51% of patients had received 1 prior line of treatment, 52% (257/494) had prior lenalidomide exposure, 34% (166/494) had disease refractory to lenalidomide, and 28% (136/494) had high-risk cytogenetics.

Table 8. Baseline demographics, clinical characteristics, and prior therapies (ITT population)

Characteristics	BVd (N=243)	DVd (N=251)
Age, median (range), years	65.0 (34-86)	64.0 (32-89)
Age category, n (%)		
18 to <65 years	121 (50)	126 (50)
65 to <75 years	85 (35)	95 (38)
≥75 years	37 (15)	30 (12)
Sex, n (%)		
Male	128 (53)	144 (57)
Female	115 (47)	107 (43)
Race, n (%)		
White	206 (85)	203 (81)
Black	8 (3)	12 (5)
Asian	28 (12)	33 (13)
East Asian	[redacted]	[redacted]
Japanese	[redacted]	[redacted]
Southeast Asian	[redacted]	[redacted]
Central/South Asian	[redacted]	[redacted]
Mixed race*	[redacted]	[redacted]
ECOG PS ≤1, n/N (%)	232/242 (96)	235/246 (96)
R-ISS stage at screening, n (%)		
I	102 (42)	103 (41)
II	130 (53)	132 (53)
III	9 (4)	14 (6)
Unknown	2 (<1)	2 (<1)
Time since diagnosis, median (range), years	4.28 (0.2-26.0)	3.94 (0.1-23.4)
Cytogenetic risk, n (%)		
Standard†	175 (72)	175 (70)
High‡	67 (28)	69 (27)
t(4;14)	[redacted]	[redacted]
t(14;16)	[redacted]	[redacted]
del(17p13)	[redacted]	[redacted]
Missing or nonevaluable	1 (<1)	7 (3)

Characteristics	BVd (N=243)	DVd (N=251)
Other cytogenetic abnormalities, n (%)		
del 13	[redacted]	[redacted]
del 1p	[redacted]	[redacted]
Hyperdiploidy	[redacted]	[redacted]
t(11;14)	[redacted]	[redacted]
t(14;20)	[redacted]	[redacted]
1q21+	[redacted]	[redacted]
Other	[redacted]	[redacted]
Extramedullary disease, n (%)		
Yes	13 (5)	25 (10)
No	230 (95)	226 (90)
Myeloma immunoglobulin, n (%)		
IgG	[redacted]	[redacted]
Prior lines of therapy, n (%)		
1	125 (51)	125 (50)
2 or 3	88 (36)	99 (39)
4+	30 (12)	27 (11)
Time to relapse on latest prior line of therapy, n (%)[§]		
≤12 months	[redacted]	[redacted]
>12 months	[redacted]	[redacted]
Prior proteasome inhibitor, n (%)		
Any	218 (90)	216 (86)
Bortezomib	210 (86)	211 (84)
Carfilzomib	[redacted]	[redacted]
Ixazomib	[redacted]	[redacted]
Prior immunomodulatory drugs, n (%)		
Any	198 (81)	216 (86)
Lenalidomide	127 (52)	130 (52)
Thalidomide	121 (50)	144 (57)
Pomalidomide	[redacted]	[redacted]
Prior daratumumab, n (%)	3 (1)	4 (2)
Prior ASCT, n (%)	164 (67)	173 (69)

Characteristics	BVd (N=243)	DVd (N=251)
Chemotherapy, n (%)	[redacted]	[redacted]
Steroids, n (%)	[redacted]	[redacted]
Positive refractory status by agent, n (%)		
Proteasome inhibitor	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]
Ixazomib	[redacted]	[redacted]
Immunomodulatory drugs	[redacted]	[redacted]
Lenalidomide	79 (33)	87 (35)
Thalidomide	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Steroids	[redacted]	[redacted]

* Mixed race included a patient who was Native Hawaiian or other Pacific Islander and White.

† Standard risk cytogenetics was defined as having negative results for all high-risk abnormalities: t(4;14), t(14;16), or del(17p13).

‡ High-risk cytogenetics was defined as the presence of ≥1 of the following: t(4;14), t(14;16), or del(17p13).

§ Patients could be included in more than 1 category.

¶Time to relapse was defined as the time between start date of 1L of therapy to PD date on 1L treatment. If no PD date was available, start date of second line of treatment was used. If no PD date on start date of second line treatment was available, date of randomisation in the trial was used.

Abbreviations: ASCT, autologous stem cell transplant; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; IgG, immunoglobulin; PD, progressive disease; R-ISS, Revised International Staging System.

B.2.3.2.3 Follow-up anti-myeloma therapy

At the data cut-off, 66% of participants in the BVd group and 78% in the DVd group had discontinued study treatment (Section 4.5.3 of Clinical study report [CSR]) (99). Follow-up anti-myeloma therapy was initiated in [redacted] and [redacted] of participants in the BVd and DVd groups, respectively (Table 9).

The median time from study treatment discontinuation to start of subsequent anti-myeloma therapy was longer in the BVd group compared with the DVd group ([redacted] vs. [redacted]) (Section 4.5.3 of CSR) (99).

For any line of subsequent therapy, a higher percentage of participants in the DVd group, calculated as the percentage of all participants in the treatment group, initiated immunomodulators ([redacted] proteosome inhibitors ([redacted] and steroids ([redacted] as follow-up therapy compared with the BVd group (Table 9 and Section 4.5.3 of CSR) (99). More participants in the BVd group initiated monoclonal antibody therapy ([redacted]

Post BVd treatment, [redacted] of participants received monoclonal antibodies [redacted] participants received bi-specific antibody, [redacted] of participants received antibody-drug conjugate (ADC), and [redacted] participants received Chimeric antigen receptor (CAR) T-cell therapy. Post DVd treatment, [redacted] of participants received mAbs, [redacted] participants received bi-specific antibody, [redacted] of participants received ADC, and [redacted] of participants received CAR-T cell therapy (Section 4.5.3 of CSR (99)). Not all of these treatments are NHS approved treatments, thus, inverse-probability of censoring weighting (IPCW) analysis has been performed to understand the true OS benefits of the BVd and DVd arm.

For the first subsequent anti-myeloma therapy post study treatment, more participants in the BVd group received mAbs ([redacted] whereas more participants in the DVd group were treated with ADCs ([redacted] (Table 9).

Table 9. Follow-up anti-myeloma therapy (ITT population)

Drug Class, n (%)	Any Anti-Myeloma Subsequent Therapy		First Anti-Myeloma Subsequent Therapy	
	BVd (N=243)	DVd (N=251)	BVd (N=243)	DVd (N=251)
Any anti-myeloma therapy	[redacted]	[redacted]	[redacted]	[redacted]
Steroids	[redacted]	[redacted]	[redacted]	[redacted]
Immunomodulator	[redacted]	[redacted]	[redacted]	[redacted]
Proteasome inhibitor	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Monoclonal antibody	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Antibody-drug conjugate	[redacted]	[redacted]	[redacted]	[redacted]
Bi-specific antibody	[redacted]	[redacted]	[redacted]	[redacted]
Engineered T/NK cell therapy	[redacted]	[redacted]	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]	[redacted]	[redacted]

Note 1: Drug class contains all medications taken for the specific follow-up anti-cancer line of therapy.
Note 2: Drug class percentages are based off the number of participants who received the subsequent line of therapy number.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; ITT, intention-to-treat, T/NK, T-cell lymphoma/ Natural killer.
Source: DREAMM-7 primary analysis clinical study report. (99)

B.2.3.3 Methods used for expert elicitation or expert opinion

Three consultant haematologists practicing in England and Wales were engaged to validate the following components of the NICE submission: DREAMM-7 data and its Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

reflection of RW practice in England/Wales, treatment pathway and unmet need in earlier LoTs for RRMM, positioning of BVd in the treatment pathway, OS adjustment for therapies not used in the UK, administration and wastage, HCRU, survival curve extrapolations, OS adjustments for subsequent treatments and budget impact estimates (67, 109, 110). A 1:1 advisory format was chosen for the expert elicitation meetings, with individual 2-hour meetings held for each of the three experts. Six 1:1 advisory meetings were held in total.

Clinical experts were selected based on:

- Their experience of belamaf via the DREAMM clinical trial programme and/or GSK's [redacted],
- Their experience of NICE Technology Assessments in myeloma
- Their extensive experience in managing myeloma patients in the UK expertise in MM.

The biographies of the clinical experts and meeting notes for clinical validation meetings are presented in Appendix M.

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

Two patient analysis populations relevant to this submission were evaluated during the study (87, 88, 99).

1) ITT Population included all randomised patients: 243 patients (BVd arm) / 251 patients (DVd arm), whether or not randomised treatment was administered.
2) The Safety Population included all randomised patients: [redacted] patients (BVd arm) / [redacted] patients (DVd arm) who received at least one dose of study treatment.

The primary analysis based on the data cut-off date of 02 October 2023 was conducted per Committee for Medicinal Products for Human Use request (99). Three interim analyses (IA) were planned for the study (88):

- IA1 was planned at the time of approximately 250 PFS events (89% information fraction) (~32 months under H1 to observe ~250 PFS events) (88).
- IA2 was planned at the time of approximately 280 PFS events (~100% information fraction) if PFS does not demonstrate statistical significance at IA1 OR alternatively when: ~178 OS events (~50% OS information fraction), if PFS demonstrates statistical significance at IA1.
- IA3 was planned at the time of approximately 266 OS events (~75% OS information fraction) (88)

The statistical analysis undertaken in the DREAMM-7 trial is presented in Table 10.

Table 10. DREAMM-7 statistical analysis

Trial number (acronym)	DREAMM-7 trial, NCT04246047 (86-88, 99)
Hypothesis objective	The overall study objective was to evaluate the clinical efficacy and safety of BVd in patients with RRMM who had received at least 1 prior LoT. The primary efficacy analysis was the comparison of the distribution of PFS between the 2 treatment groups. $H_0: \theta \geq 1$ VS. $H_1: \theta < 1$ where, θ is the PFS HR (belamaf/ bortezomib/ dexamethasone vs. daratumumab/ bortezomib/ dexamethasone arm).
Sample size, power calculation	The primary PFS analysis was conducted after observing approximately 280 PFS events. With ~280 events, the study had a power of 92% to detect a HR of 0.67 at 1-sided alpha of 0.025 (corresponding to a critical value of 0.783 for the HR). This calculation assumed participants are randomised to the two treatment arms in a 1:1 randomisation ratio. Assuming that a total of 478 participants were randomised in a 1:1 ratio to Arm A or Arm B and a uniform enrolment rate of 30 participants per month, enrolment continued for approximately 16 months. It was estimated that the targeted 280 PFS events were observed approximately 37 months from the time when the first participant was randomised under H1, assuming an annual dropout rate of 5%. These calculations were conducted using East 6.4 There was a 15% global enrolment cap on Northeast Asia countries. If the number of participants required by local regulatory agencies were not recruited within the planned recruitment target, enrolment might continue in separate cohorts until the country enrolment requirements, as required by local regulatory bodies, had been reached. Additional participants that were enrolled in separate cohorts were not included in the analysis portion of the study planned for the marketing application, which was based on approximately 280 events. However, these additional participants were included in country-specific supplemental analyses, requested by the applicable regulatory authorities concerned, as detailed in the country-specific SAP

Trial number (acronym)	DREAMM-7 trial, NCT04246047 (86-88, 99)
Statistical analysis	The primary analysis for all efficacy endpoints was based on assessments determined by an IRC with the ITT population unless otherwise specified and is reported in Section B.2.6.1.1 - B.2.6.1.6 and Appendix N. Sensitivity analysis was conducted using investigator-assessed responses. Stratification factors used for the stratified analyses included number of prior lines of therapy (1 vs 2/3 vs ≥4), prior bortezomib (yes vs no) and the R-ISS at screening (R-ISS I vs II/III). Appropriate subgroup analyses might be performed if data permits, e.g., the primary endpoint PFS may be analysed by age (<65 years, ≥65 years), gender (Female, Male), ethnicity (Hispanic, non-Hispanic) and race groups (American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race), region (North America, Europe, Northeast Asia, etc.), prior anti-cancer therapy and other baseline characteristics. **Primary endpoint** **PFS** was the primary endpoint of this study. Final PFS (primary efficacy) analysis was conducted at the time of observing approximately 280 PFS events. The distribution of PFS for each treatment arm was estimated using the KM method. The median, 25th and 75th percentiles of PFS were estimated and corresponding 95% CIs were estimated using the Brookmeyer Crowley method (111). The PH assumption was checked through the KM plot, log(-log(survival) against log (survival time) plot, Schoenfeld residuals, and evaluation of time dependency of HR by adding an interaction term of time by treatment in the Cox PH model. The distribution of PFS was compared between the 2 treatment arms using log-rank test stratified by randomisation factors used for randomisation. A one-sided p-value was produced. HR and corresponding two-sided 95% CI was estimated from Cox proportional hazard model stratified by randomisation factors with treatment arm as the sole explanatory variable. If the PH assumption did not hold, RMST might be conducted in addition as appropriate. **Secondary endpoints** ORR, CRR, CBR, DoR, MRD, TTP, PFS-2, OS and TTR were assessed using the ITT Population (Section B.2.6) Analyses conducted are as follows: • **ORR**– The number and percentage of participants with best overall response (BoR) in the following categories was summarised by treatment arm: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease, progressive disease (PD), and NE.

	The corresponding exact 95% CI for ORR was also be 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. ORR was also compared between treatment arms using the Cochran Mantel Haenszel test stratified by randomisation factors. The exact 95% CI for the difference was calculated. • **CRR**– summaries of CRR (sCR, CR) by treatment arms were provided in the same way as ORR • **CBR**– summaries of CBR (MR or better) by treatment arms were provided in the same way as ORR • **DoR**– For the primary analysis of DoR, all participants were included in the analysis regardless of response status, to enable a valid statistical comparison between the two arms. Response were based on IRC assessment per IMWG criteria [Kumar, 2016] (108). • **MRD**– Participants with a confirmed CR or better response who do not achieve MRD negative status (including missing/inconclusive assessment(s)) and participants without a confirmed CR or better response were considered as having non-negative MRD. MRD negativity rate was summarised by treatment arm. Corresponding two-sided 95% exact CIs were also be provided. MRD negativity rate was also compared between treatment arms using the Cochran Mantel Haenszel test stratified by the three randomisation factors: number of prior lines of therapy, prior bortezomib use, and R-ISS stage. A one-sided p-value was produced. • **TTP**– TTP analysis was conducted using similar approach as for the PFS analysis. • **PFS-2**– Distribution of PFS2 for each treatment arm was estimated using the KM method. PFS2 was compared using similar approach for PFS. Analysis for PFS2 used investigator-assessed responses. • **OS**– OS was conducted at planned analyses using similar approach as for the PFS analysis (i.e., KM estimates, stratified log-rank test, Cox Proportional Hazards (PH) model stratified by randomisation factors, and examination of non-PH effect). • **TTR**– TTR was summarised descriptively by treatment arm using median and quartiles in the subset of participants with a confirmed response of PR or better as the BoR. **Exploratory endpoint:** • **Sustained MRD**– The number and percentage of participants who have sustained MRD negativity (CR or better for 12 months or longer), were summarised descriptively by treatment arm, and the difference between the treatment arms was provided along with the corresponding 95% exact CIs • **VGPR**–summaries of VPPR+ (i.e., VGPR or better including sCR, CR, VGPR) by treatment arms were provided in the same way as ORR.

	• **TTBR**– was summarised descriptively by treatment arm using median and quartiles in the subset of participants with a confirmed response of PR or better as the BoR. **Additional endpoint:** • **TTD**– The time from treatment initiation until the date of all TTD or death due to any cause. The analyses were performed if the total sample size was ≥15 in the population and a minimum of 10 events per variable in the statistical model in the population. • **TTNT**– 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 are lost to follow-up were censored at the time of study discontinuation, withdrawal or lost to follow-up. The analyses were performed if the total sample size was ≥15 in the population and a minimum of 10 events per variable in the statistical model in the population. **Safety** All safety analyses were performed on the safety population. All 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 occurred first. AEs were recorded using standard medical terminology and graded according to the NCI-CTCAE, Version 5.0. For AE reporting, the verbatim term used in the eCRF by investigators to identify AEs will be coded using the latest version of MedDRA coding dictionary (112) AEs were summarised by frequency and proportion of total patients by SOC (Section B.2.10.2). Separate summaries were given for all AEs, common (>5%) AEs, treatment-related AEs, SAEs, and AEs leading to dose delays and discontinuation of study treatment and AEs of special interest. To ensure a comprehensive understanding of corneal events, data were collected in the following way during DREAMM-7: • Eye-related AEs were collected and coded using MedDRA coding dictionary and events were graded for intensity/severity using Common Terminology Criteria for Adverse Events (CTCAE) 5.0 (112). **Health outcomes** *EQ-5D-3L:* • The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some

Trial number (acronym)	DREAMM-7 trial, NCT04246047 (86-88, 99)
	problems and extreme problems. The participant was asked to indicate their health state by selecting the most appropriate statement in each of the 5 dimensions. The preference-based value sets were used for the analyses (113).
Data management and patient withdrawals	• As of the data cut-off (02 October 2023), [redacted] withdrew from the study ([redacted] in the BVd group and [redacted] in the DVd group). The primary reasons for study discontinuation included withdrawal by participant and physician decision. There were more deaths in the DVd group ([redacted] compared with the BVd group ([redacted]. More participants were ongoing in study in the BVd group ([redacted]) compared with the DVd group ([redacted]) at the data cut-off. At the data cut-off, 33% participants in the BVd vs. 20% participants in the DVd group were on study treatment.

Abbreviations: AE, adverse event; BoR, best overall response; BVd, belamaf in combination with bortezomib, and dexamethasone; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CRR, complete response rate; CTCAE, Common Terminology Criteria for Adverse Events; DREAMM-7, DRiving Excellence in Approaches to Multiple Myeloma; DoR, duration of response; DVd, daratumumab in combination with bortezomib, and dexamethasone; eCRF, electronic case report form; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Questionnaire Module 20; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire; EQ-5D-3L, European Quality of life-5 Dimensions 3 levels; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; KM, Kaplan Meier; LoT, line of therapy; MedDRA, Medical Dictionary for Regulatory Activities; MR, minimal response; MRD, minimal residual disease; NCI-CTCAE, National Cancer Institute- Common Toxicity Criteria for Adverse Event; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PFS-2, progression-free survival-2; PH, proportional hazard; PR, partial response; QoL, Quality of life; R-ISS, Revised International Staging System; RRMM, relapsed refractory multiple myeloma; RMST, Restricted Mean Survival Time; SAP, statistical analysis plan; SAE, serious adverse events; sCR, stringent complete response; SOC, system organ class; TTP, time to progression; TTD, time to treatment discontinuation; TTNT, time to next treatment or death; TTBR, time to best response; TTR, time to response; VGPR, very good partial response; VPPR, very poor partial response VS, versus.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Table 11 presents a summary of quality assessment for the DREAMM-7 trial. Further details for complete quality assessment can be found in Appendix D.

Table 11. Quality assessment for DREAMM-7 trial

Was randomisation carried out appropriately?	**Yes** - All participants were centrally randomised using an IRT system, RAMOS NG, by the investigator or authorised site staff. RAMOS NG allows study sites to register and randomise participants, and also records stratification information. Randomisation list was done centrally using a randomisation schedule generated by the GSK Clinical Statistics Department in RandALL NG, which assigned participants in a 1:1 ratio to Treatment Arm A (BVd) and Treatment Arm B (DVd). Separate randomisation lists were generated for any extension cohorts required.
Was the concealment of treatment allocation adequate?	**Yes** - DREAMM-7 is an open-label study; therefore, no blinding of treatment identity was needed for either treatment Arm A (BVd) or treatment Arm B (DVd). However, to ensure trial integrity steps were taken to restrict access to key information while the study is ongoing and prevent data aggregation except for where specified in the protocol
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes** - Demographic and baseline characteristics were well balanced between the two treatment groups with no categories having a difference of ≥10% (Table 8)
Were the care providers, patients and outcome assessors blind to treatment allocation?	**No** - as DREAMM-7 is an open-label trial, so care providers and patients were not blinded to treatment allocation. However, a blinded IRC was used to determine disease response for the assessment of the primary endpoint. Therefore, this is low risk for primary endpoint and for OS, and medium risk for endpoints that were not blinded or objectively defined
Were there any unexpected imbalances in drop-outs between groups?	**No** - Of the 494 patients randomised (243 in BVd and 251 in the DVd group), [redacted] received study treatment: [redacted] patients received BVd and [redacted] patients received DVd (see Section 4.6.1 of CSR) (99).

Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes** - The ITT Population was used for analysis of the primary endpoint and other time-to-event efficacy endpoints, which included all randomised patients

Abbreviation: BVd, belamaf in combination with bortezomib, and dexamethasone; CSR, clinical study report; DREAMM-7, DRiving Excellence in Approaches to Multiple Myeloma; DVd, daratumumab in combination with bortezomib, and dexamethasone; GSK, GlaxoSmithKline; IRC, Independent Review Committee; IRT, Interactive Response Technology; ITT intention-to-treat; OS, overall survival
Source**:** DREAMM-7 trial protocol (87); DREAMM-7 trial protocol amendment (88); DREAMM-7 primary analysis clinical study report (99).

B.2.6 Clinical effectiveness results of the relevant studies

As described above, DREAMM-7 is the pivotal trial providing evidence of the efficacy of BVd in the relevant population. DREAMM-7 was designed as a head-to-head study versus the UK SoC (DVd), and in Section B.2.9 GSK shows via indirect treatment comparison (ITC) that the results described in this section broadly hold against all other 2L comparators. In general, these results demonstrate that belamaf offers a 'step change' in outcomes for MM patients, in some cases demonstrating a nearly three times improvement over SoC.

DREAMM-7 was powered to detect differences in multiple outcomes of relevant clinical interest, of which six are presented below in Table 12 and the remainder are presented in Appendix N. The results presented in this document are for all primary and key secondary results, plus secondary and exploratory endpoints of high relevance to cost-effectiveness modelling.

All results in this section are presented for the ITT Population (n = 494). At the time of primary analysis (data cut-off: 02 October 2023), the median study follow-up was 28.24 months, the data for which is presented in this document.

Table 12 outlines the summary of clinical effectiveness for the endpoints described in Sections B.2.6.1.1.

Table 12. Summary of clinical effectiveness

Endpoint	**BVd (N=243)**	**DVd (N=251)**	**Reference**
Progression free survival, median months (95% CI)	36.6 (28.4, -)	13.4 (11.1, 17.5)	B.2.6.1.1
Overall survival, median months (95% CI)	33.9 (21.9, -)	15.2 (12.3, 21.1)	B.2.6.1.2

Endpoint	BVd (N=243)	DVd (N=251)	Reference
Duration of response, median months (95% CI)	35.6 (30.5, -)	17.8 (13.8, 23.6)	B.2.6.1.3
Minimal residual disease, sCR/CR % (95% CI)	24.7 (19.4, 30.6)	9.6 (6.2, 13.9)	B.2.6.1.4
Overall response rate sCR+CR+VGPR+PR % (95% CI)	82.7 (77.4, 87.3)	71.3 (65.3, 76.8)	B.2.6.1.5
Time to treatment discontinuation, median months (95% CI)	[redacted]	[redacted]	B.2.6.1.6

Note: Median overall survival not reached in either arm, so 1st quartile median months displayed in this table
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI; confidence interval; CR, Complete Response; DVd, daratumumab in combination with bortezomib, and dexamethasone; PR, Partial Response; VGPR, sCR, Stringent Complete Response; Very Good Partial Response.
Source: DREAMM-7 primary analysis clinical study report (99); GSK data on file(105).

B.2.6.1 Primary and key secondary results of the DREAMM-7 trial

B.2.6.1.1 Primary outcome - Progression-free survival

The DREAMM-7 trial met its primary endpoint for PFS assessed by IRC. It showed a statistically significant and clinically meaningful PFS benefit with BVd compared with current 2L SoC, DVd. The median PFS in the BVd group was almost three times longer than DVd (36.6 months [95% CI: 28.4, NR] vs. 13.4 months [95% CI: 11.1, 17.5] in the DVd group. GSK notes that this is supportive of the case that BVd offers a 'step change' in treatment outcomes for 2L MM patients.

The Kaplan Meier (KM) curves for PFS showed a clear and early separation between the treatment groups in favour of the BVd group (Figure 5)This is supported by a HR of 0.41 (95% CI: 0.31, 0.53; p <0.00001) showing a 59% reduction in the risk of disease progression or death (Table 13).

Follow-up is ongoing for the majority of censored participants/events ([redacted] in the BVd and DVd groups, respectively) (Table 13). Landmark analysis of PFS at 18 months showed a higher PFS rate in the BVd group compared with the DVd group (69% vs. 43%) (Table 13).

PFS analysis based on investigator-assessed responses was consistent with IRC results (Section 5.1.1.1 of the DREAMM-7 CSR (99)).

Table 13. Progression-free survival based on independent reviewer-assessed response (ITT population)

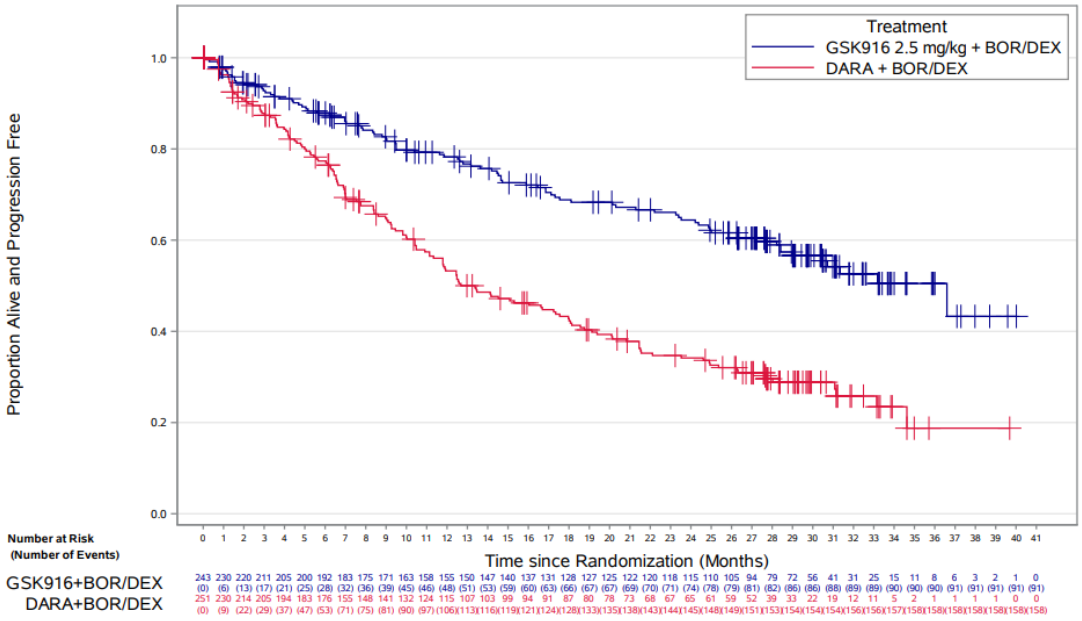
	BVd (N=243)	DVd (N=251)
Number of participants, n (%)		
Progressed or died (event)	91 (37%)	158 (63%)
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%)		
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for time variable (months)[a]		
1st Quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	36.6	13.4
95% CI	(28.4, -)	(11.1, 17.5)
3rd Quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Hazard ratio[b]		
Number of participants in the model	[redacted]	[redacted]
Estimate	0.41	
95% CI	(0.31, 0.53)	
Stratified log-rank[c]		
p-value	<0.00001	
Progression-free survival rate		
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]
Time-to-event endpoint at 18 months	0.69	0.43
95% CI	[redacted]	[redacted]

a. CIs were estimated using the Brookmeyer Crowley method (111).
b. Hazard ratios were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III), with a covariate of treatment.
c. p-value from 1-sided stratified log-rank test.

Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this table.

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; ITT, intention-to-treat; R-ISS, Revised International Staging System.
Source: DREAMM-7 primary analysis clinical study report (99).

Figure 5. Kaplan Meier curves of progression-free survival based on independent reviewer-assessed response (ITT population)



Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this figure.
Abbreviations: BOR/DEX, bortezomib/dexamethasone; DARA; Daratumumab; GSK, GlaxoSmithKline; ITT, intention-to-treat
Source: DREAMM-7 primary analysis clinical study report (99).

Additional clinical efficacy results, relevant to PFS, i.e., TTP and PFS-2 are shown in Appendix N.

B.2.6.1.2 Secondary outcome - Overall survival

At the PFS data cut-off, an early, strong and clinically meaningful OS benefit favoured the BVd group vs. the DVd group with a nominal p-value of 0.00049 (HR=0.57; 95% CI: 0.40, 0.80) (Table 14).

The KM curves for OS showed a clear and early separation between the treatment groups in favour of BVd (Figure 6). Most censoring occurred after approximately [redacted], which is in alignment with the median follow-up. At the data cut-off, there were 33 more deaths in the DVd group (87 [35%]) compared with the BVd group (54 [22%]) (Table 14).

Median OS was not reached in either treatment group; OS data have reached [redacted]) overall maturity, with an Information fraction (IF) equal to [redacted], where [redacted] were the planned deaths for OS analysis according to the statistical analysis plan (SAP) (see SAP Section 4.7.2) (114). Landmark analysis of OS at 18 months showed a

higher survival rate in the BVd group compared with the DVd group (84% vs.73%) (Table 14). Follow-up for OS is ongoing.

The median time from study TTD to start of subsequent anti-myeloma therapy was longer in the BVd group compared with the DVd group (69.0 days vs. 44.0 days) (Section 4.5.3 of CSR) (99).

Table 14. Summary of overall survival (ITT population)

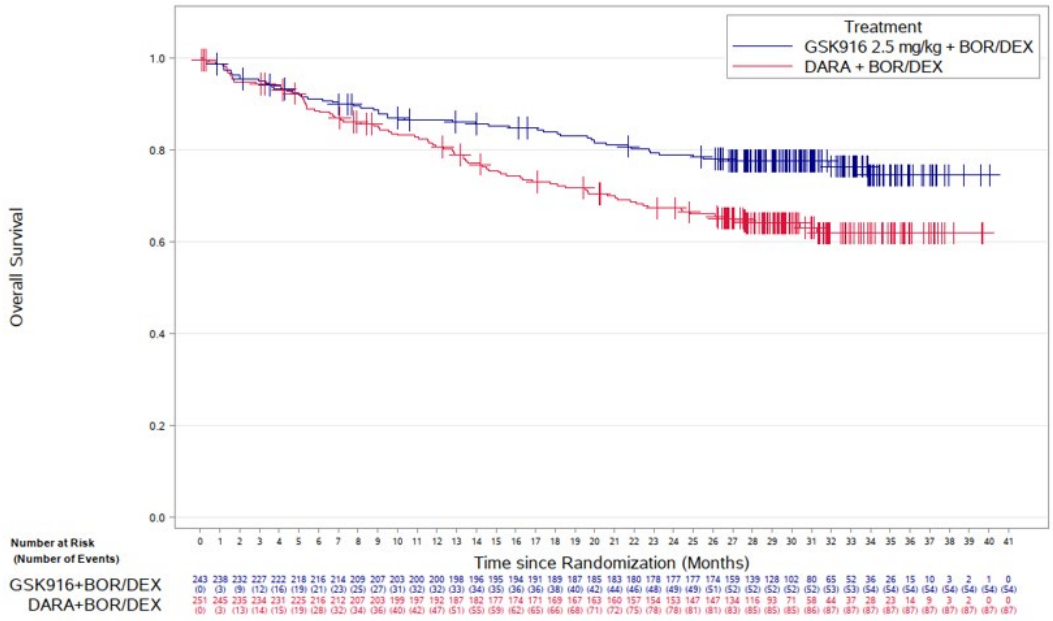
	BVd (N=243)	**DVd (N=251)**
Number of participants, n (%)		
Died (event)	54 (22%)	87 (35%)
Censored, follow-up ended	[redacted]	[redacted]
Alive date obtained	[redacted]	[redacted]
No alive date obtained	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%)		
Death	54 (22%)	87 (35%)
Estimates for time variable (months)[a]		
1st quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	-	-
95% CI	(-, -)	(-, -)
3rd quartile	-	-
95% CI	(-, -)	(-, -)
Hazard ratio[b]		
Number of participants in the model	243	251
Estimate	0.57	
95% CI	(0.40, 0.80)	
Stratified log-rank[c]		
p-value	0.00049	
Overall survival rate		
Time-to-event endpoint at 6 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 12 months	0.87	0.81
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 18 months	0.84	0.73

	BVd (N=243)	DVd (N=251)
95% CI	[redacted]	[redacted]

a. CIs were estimated using the Brookmeyer Crowley method (111).
b. Hazard ratios were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes), and R-ISS at screening (I vs. II/III), with a covariate of treatment.
c. p-value from 1-sided stratified log-rank test.

Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They are counted as 4 unique participants in this table.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; ITT, intention-to-treat; R-ISS, Revised International Staging System.
Source: DREAMM-7 primary analysis clinical study report (99).

Figure 6. Kaplan Meier curves of overall survival (ITT population)



Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They are counted as 4 unique participants in this figure.
Abbreviations: BOR/DEX, bortezomib/dexamethasone; DARA; Daratumumab; GSK, GlaxoSmithKline; ITT, intention-to-treat
Source: DREAMM-7 primary analysis clinical study report (99).

B.2.6.1.3 Secondary outcome - Duration of response

At the PFS data cut-off, BVd showed greater response durability than DVd (35.6 vs 17.8 months median DoR). DoR was defined as the time from first documented evidence of partial Response (PR) or better (based on IRC assessment per IMWG criteria) until PD or death due to any cause. (Table 15). The KM curves for DoR showed a clear and early separation between the treatment groups in favour of BVd (Figure 7).

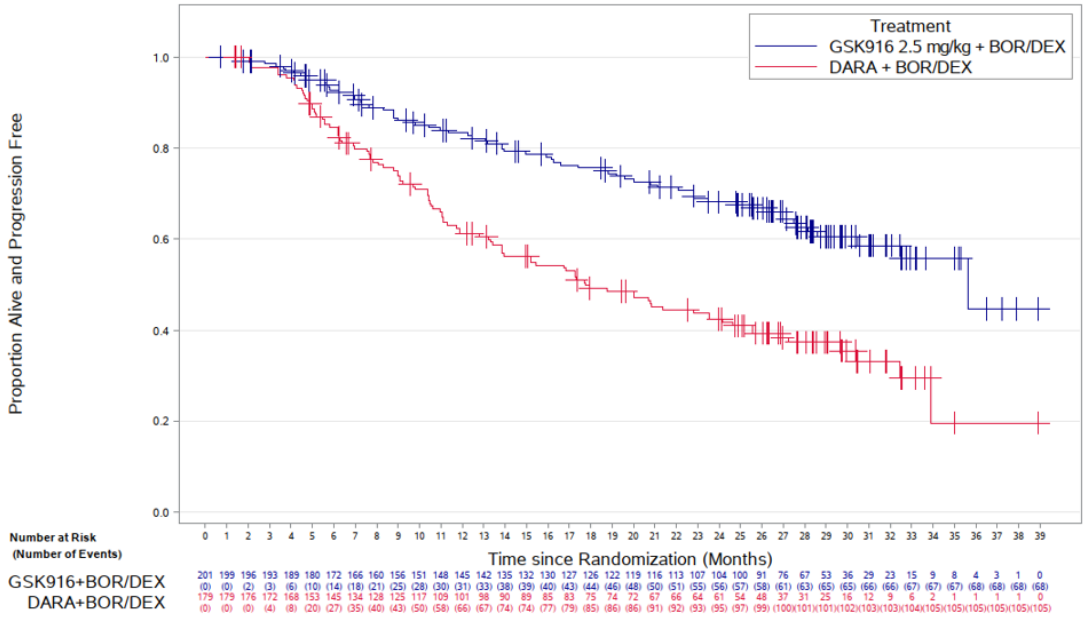
In the BVd group, 53% of participants with response had not progressed or died at the data cut-off compared with 29% of participants with response in the DVd group (Table 15), hence DoR, PFS, and OS are likely to improve with longer follow-up.

Table 15. Duration of response based on independent reviewer-assessed response (ITT population)

	BVd (N=243)	DVd (N=251)
Number of participants, n (%)		
n	201	179
Progressed or died (event)	68 (34%)	105 (59%)
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)[a]		
1st Quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Median	35.6	17.8
95% CI	(30.5, -)	(13.8, 23.6)
3rd Quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Probability of maintaining response		
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]
Time-to-event endpoint at 18 months	0.76	0.49
95% CI	[redacted]	[redacted]

a. Estimated using the Brookmeyer Crowley method (111).
Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this table.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; ITT, intention-to-treat
Source: DREAMM-7 primary analysis clinical study report (99).

Figure 7. Kaplan Meier curves of duration of response based on independent reviewer-assessed response (ITT population)



Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this figure.
Abbreviations: BOR/DEX, bortezomib/dexamethasone; DARA; Daratumumab; GSK, GlaxoSmithKline; ITT, intention-to-treat.
Source: DREAMM-7 primary analysis clinical study report (99).

B.2.6.1.4 Secondary outcome - Minimal residual disease

At the PFS data cut-off, a statistically and clinically meaningful increase of MRD negativity rate was observed in favour of the BVd group vs the DVd group (24.7% vs. 9.6%) (Table 16). MRD negativity was defined as CR or sCR, and results of MRD negativity analysis using alternative definitions (e.g., VGPR or better, MRD negativity sustained for >12m) were consistent with the primary MRD analysis. Detail on these alternative definitions is given in Appendix N.

Table 16. Summary of minimal residual disease negativity based on independent reviewer-assessed responses (ITT population)

Best Response		BVd (N=243)	DVd (N=251)
sCR/CR	MRD negativity rate	60 (24.7%)	24 (9.6%)
	95% CI	(19.4%, 30.6%)	(6.2%, 13.9%)
	p-value[a]	<0.00001	
	p-value[b]	[redacted]	

a. MRD negativity rate compared between treatment groups using CMH test, adjusting for stratification factors: number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III).

b. MRD negativity rate compared between treatment groups using unadjusted Fisher's exact test. CIs are based on the exact method. p-values presented are 2-sided 5% and as such significance only declared if MRD negativity rate is in favour of belantamab mafodotin 2.5 mg/kg (which is equivalent to 1-sided 2.5%).

Note 1: Participants without MRD assessment were assumed to be non-negative.
Note 2: All percentages were calculated out of N per treatment group.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; CMH, Cochran Mantel Haenszel; CR, complete response; DVd, daratumumab in combination with bortezomib, and dexamethasone; ITT, intention-to-treat; MRD, minimal residual disease; R-ISS, Revised International Staging System; sCR, stringent complete response.
Source: DREAMM-7 primary analysis clinical study report (99).

B.2.6.1.5 Secondary outcome - Overall response rate

At the PFS data cut-off, ORR was higher in the BVd group compared with the DVd group (82.7% vs. 71.3%) (Table 17). Alternative definitions of response such as VGPR+ Rate, CRR and CBR show a similar trend (Appendix N)

Table 17. Summary of independent reviewer-assessed best response with confirmation (IMWG Criteria) (ITT population)

	BVd (N=243)	**DVd (N=251)**
Best response, n (%)		
Stringent complete response (sCR)	34 (14.0%)	13 (5.2%)
Complete response (CR)	50 (20.6%)	30 (12.0%)
Very good partial response (VGPR)	76 (31.3%)	73 (29.1%)
Partial response (PR)	41 (16.9%)	63 (25.1%)
Overall response rate, n (%)		
sCR+CR+VGPR+PR	201 (82.7%)	179 (71.3%)
95% CI	(77.4%, 87.3%)	(65.3%, 76.8%)
Difference in overall response rate		
Difference	[redacted]	
95% CI for difference	[redacted]	

Note 1: CIs are based on the exact method.
Note 2: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this table.
Note 3: The concordance rate of investigator and IRC assessments in their assessment of best response was 99% in the BVd group and 98% in the DVd group.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; CR, complete response; DVd, daratumumab in combination with bortezomib, and dexamethasone; IMWG, International Myeloma Working Group; IRC, independent review committee; ITT, intention-to-treat; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Source: DREAMM-7 primary analysis clinical study report (99).

B.2.6.1.6 Secondary outcome -Time to treatment discontinuation

The median TTD in the BVd group was slightly longer than DVd ([redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]] in the DVd group (Table 18).

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Landmark analysis of TTD at 18 months showed a higher TTD rate in the BVd group compared with the DVd group ([redacted]) (Table 18).

Table 18. Summary of time to treatment discontinuation (Safety population)

	BVd (N=242)	DVd (N=246)
Number of Subjects	[redacted]	[redacted]
Treatment Discontinued or Death (event)	[redacted]	[redacted]
Censored, Treatment not Discontinued		
Event Summary		
Treatment Discontinued	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for Time Variable (Months)[a]		
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 Rate		
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]
Time-to-Event Endpoint at 18 Months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

a. intervals for time variables are estimated using the Brookmeyer Crowley method (111).
Note: There are two subjects within the Safety Analysis Population that were randomised, re-screened, and randomised again, reflecting 4 unique subject IDs (608, 619, 4411 and 4412).
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; TTD, time to treatment discontinuation.
Source: GSK data on file (105).

The KM curves for TTD showed a clear and early separation between the treatment groups in favour of the BVd group (Figure 8).

Figure 8. Kaplan Meier curves of time to treatment discontinuation (safety population)
[redacted]

B.2.6.1.7 Modelling outcome – Health related quality of life

The NICE reference case specifies that European Quality of life-5 Dimensions 3 levels (EQ-5D-3L) is the preferred measure of HRQoL in a NICE submission. The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The participant is asked to indicate his/her health state by selecting the most appropriate statement in each of the 5 dimensions (115).

The mean utility scores, based on EQ-5D-3L, were broadly similar between the two treatment arms across the study visits (Figure 9). This is consistent with the mean utility scores based on non-Reference alternative HRQoL instruments (EORTC QL Q-C30, EORTC QLQ -MY20 and EORTC QLQ-IL52, see Appendix N for details).

Figure 9. Plot of mean and 95% confidence interval of European Quality of life-5 Dimensions 3 levels utility scores by visits: UK value set

However, pre-progression, there was a gradual increase in the utility scores (change from baseline) from Week 31 which became very noticeable from around 43 weeks onwards (Figure 10). For the time period where most of the recorded EQ-5D-3L data lies, the BVd arm shows consistently higher mean utility scores than the DVd arm.

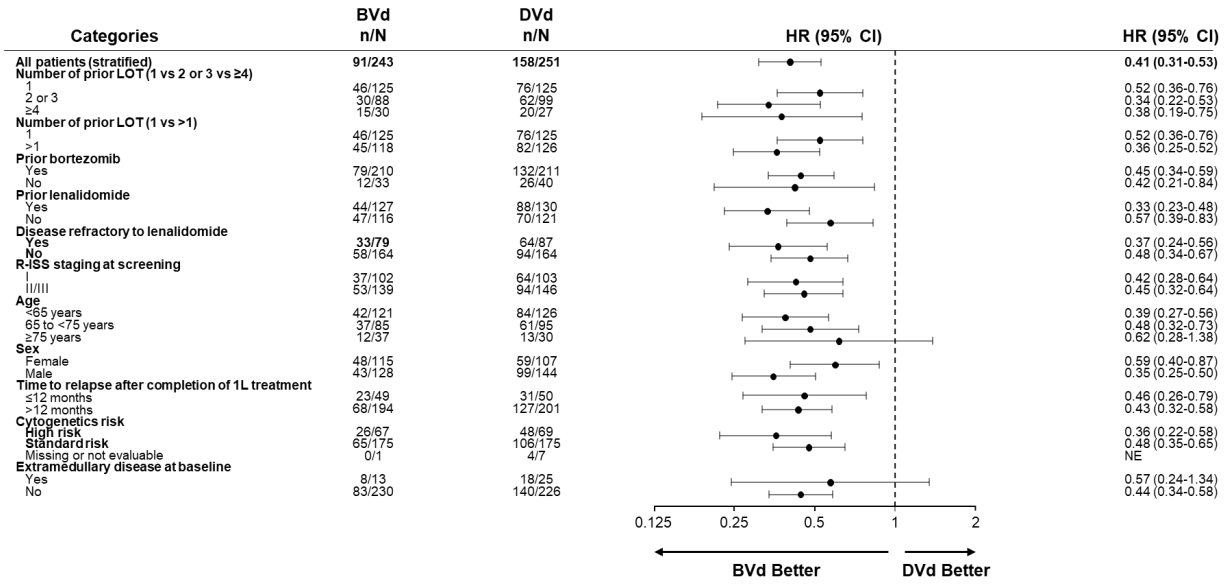
Figure 10. Plot of Mean and 95% confidence interval of change in European Quality of life-5 Dimensions 3 levels Utility scores from baseline by visits recorded before progression UK value set.

In Section B.3.4.2, statistical analysis suggests that for patients on-treatment as well as progression-free, there is a statistically significant EQ-5D-3L utility benefit for patients treated with BVd over DVd.

B.2.7 Subgroup analysis

The PFS benefit favouring BVd was consistent across all prespecified subgroups, regardless of age, prior lines of treatment, prior lenalidomide exposure or refractory status, or high-risk features (e.g., R-ISS stage II/III or high-risk cytogenetic profile (Figure 11). Of particular relevance to this submission, post-hoc analysis of the lenalidomide-refractory and high-risk cytogenetic unstratified subgroups also favoured BVd.

Figure 11. Forest plot – Progression-free survival based on independent reviewer-assessed response (ITT population, unstratified)



This forest plot is derived from a model where the hazard rations for subgroups are estimated using Cox Proportional Hazards models, without adjustment for stratification variable. Consequently there may be some slight variance from numbers presented in the text, which are stratified by the number of lines of prior therapy (1 vs. 2/3 vs. >=4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III), with a covariate of treatment.
Abbreviations: 1L, first line; BVd, belamaf in combination with bortezomib, and dexamethasone; CI, Confidence Interval; daratumumab in combination with bortezomib, and dexamethasone; HR, hazard ratio; ITT, intention-to-treat; LoT, line of therapy; R-ISS, Revised International Staging System.
Source: DREAMM-7 primary analysis clinical study report (99).

B.2.7.1 Key subgroup - Lenalidomide-refractory

In the lenalidomide-refractory subgroup (BVd, n=79; DVd, n=87), median PFS (95% CI) was [redacted] ([redacted]) with BVd versus [redacted] ([redacted]) with DVd ([redacted]). KM curves for this subgroup are reproduced in Figure 12. For details on non-Primary endpoints in this subpopulation, please see Appendix E.

Figure 12. Kaplan Meier curves of progression-free survival based on independent reviewer - assessed response by refractory status (lenalidomide-refractory)

[redacted]

B.2.7.2 Key subgroup - High-risk cytogenetics

In the high-risk cytogenetic subgroup (BVd, n=67; DVd, n=69), the median PFS (95% CI) was [redacted]) with BVd versus [redacted] with DVd [redacted] KM curves for this subgroup are reproduced in Figure 13. For details on non-Primary endpoints in this subpopulation, please see Appendix E.

Figure 13. Kaplan Meier Curves of Progression-Free Survival Based on Independent Reviewer - Assessed Response by Cytogenetic Risk (High-risk)

[redacted]

B.2.7.3 Real World Evidence National Cancer Registration and Analysis Service study

In accordance with DREAMM-7 study subgroup findings, the results from the NCRAS study are also provided (please see Section B.1.3.1.4 for background information on the NCRAS study). Initial time to next treatment or death (TTNTD) (used a proxy for PFS) and OS results from the NCRAS study are available for DVd in the NCRAS 2L DREAMM-7-like lenalidomide-refractory cohort. These results are outlined in Figure 14 which demonstrate that median OS was reached in a lenalidomide-refractory cohort (23.0 months; 95% CI: 12.9, n/a). Additionally, the median TTNTD (10.3 months; 95% CI: 7.4, 13.9) was markedly lower than the overall PFS reported by the multicentre analysis, suggesting poorer outcomes in lenalidomide-refractory patients (25)).

Figure 14. (A) Time to next treatment or death for patients treated with daratumumab in combination with bortezomib, and dexamethasone from the National Cancer Registration and Analysis Service DREAMM-7-like 2L lenalidomide-refractory cohort; (B) Overall survival for patients treated with daratumumab in combination with bortezomib from the National Cancer Registration and Analysis Service DREAMM-7-like 2L lenalidomide-refractory cohort

B.2.8 Meta-analysis

A pairwise meta-analysis was not conducted as the only identified clinical trial of BVd in RRMM was the DREAMM-7 trial (86).

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Overview

An SLR was conducted in December 2021, and has been subsequently updated, most recently in February 2024, to identify clinical evidence for therapies used in the management of patients with 2L+ RRMM (Appendix D). No direct evidence comparing BVd with the regimens defined in the final scope was identified; therefore, a network meta-analysis (NMA) was conducted to assess the relative efficacy of BVd and its comparators. This NMA was performed with a global perspective, therefore the comparators included are not limited to comparators available in England and Wales.

The primary objective was to evaluate the efficacy of BVd compared to other treatments in achieving PFS, OS, and ORR, in patients similar to the DREAMM-7 ITT population. There were secondary objectives to compare the efficacy of BVd in patients who are lenalidomide-refractory, focussing on the same outcomes: PFS, OS, and ORR. The endpoints of interest were selected based on their importance for clinical practice, and they are also expected to be used in economic modelling. Both fixed- and random- effects NMA analyses were conducted, and heterogeneity was explored through subgroup analyses, where feasible. Meta-regressions were not

feasible due to the low number of studies informing each treatment comparison in the networks of evidence.

B.2.9.2 Feasibility assessment

A feasibility assessment was conducted to evaluate the similarity of studies for pooling in an NMA in terms of homogeneity between-study and disease characteristics of included studies. The feasibility assessment details are described in Appendix D.

B.2.9.2.1 Included studies

The SLR identified 70 trials, of which 48 (including DREAMM-7) were considered in the NMA feasibility assessment. 17 out of 48 studies were found to form a connected network, anchored through three common treatments: Vd, hKd (56mg/m^2) and DVd. Clinical experts have highlighted that bortezomib monotherapy is rarely used in the NHS and Vd would instead be used in clinical practice, although use of this doublet has limited usage in clinical practice (29). The global NMA conducted was further restricted to include regimens approved by the USFDA or EMA and any treatments likely to be a future health technology assessment (HTA) comparator to the DREAMM-7 regimen, BVd (99). Hence, the network was broader than the scope of the decision problem and the network diagrams and forest plots include non-relevant comparators for the NICE appraisal. The final network of evidence comprised 12 studies, summarised in Table 19 along with the assessed intervention and comparator treatments. The network of evidence presenting all available, non-outcome specific, evidence is shown in Figure 15. Results relevant to the decision problem will be discussed. Finally, in the NMA hKd was used to specify high dose carfilzomib in combination with dexamethasone instead of Kd, to distinguish between the different trials used to connect the network. hKd was the used in the B.2.9 Section to align the terminology to the terms used in the different studies.

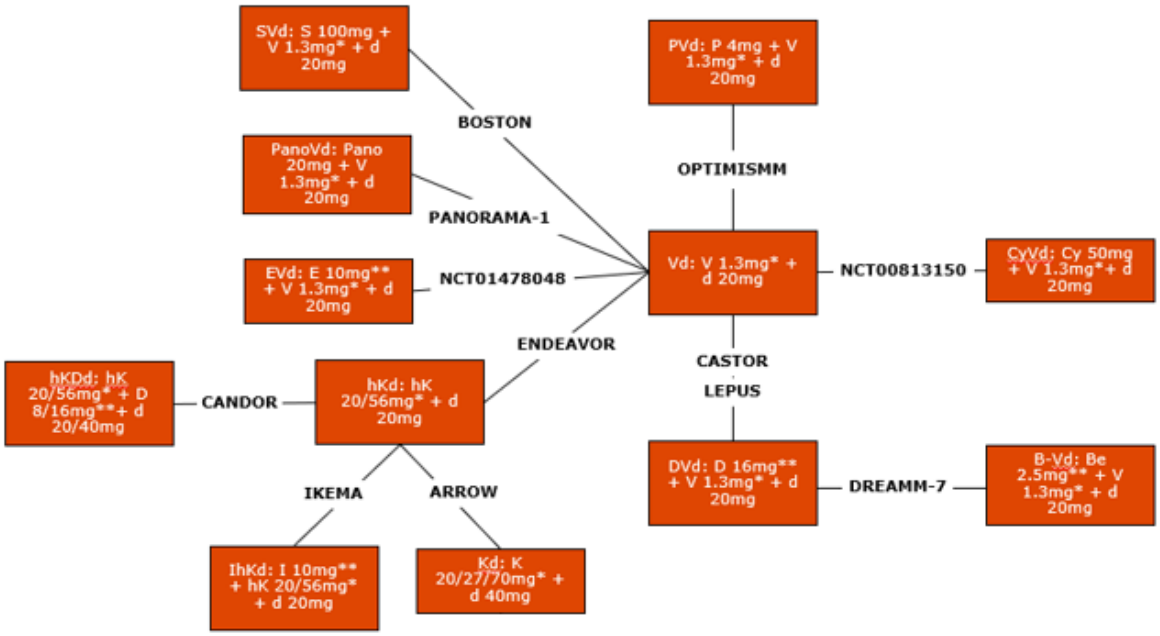
Table 19. Summary of studies considered eligible for the network meta analyses

Study, author, year	Intervention	Comparator
DREAMM-7 (86, 87)	BVd	DVd
ARROW Mateos, 2019 (117)	Kd	hKd
BOSTON Grosicki, 2020 (103)	SVd	Vd
CANDOR Dimopoulos, 2020 (118); Usmani, 2022 (119); Usmani, 2023 (120)	hKDd	hKd
CASTOR Spencer, 2018 (121) Sonneveld, 2023 (122)	DVd	Vd
ENDEAVOR Dimopoulos, 2016 (104)	hKd	Vd
IKEMA Moreau, 2021 (123) Joseph, 2022 (124); Martin, 2023 (125)	IhKd	hKd
OPTIMISMM Richardson, 2019 (126)	PVd	Vd
LEPUS Lu, 2021 (100); Fu, 2023 (101)	DVd	Vd
PANORAMA-1 San Miguel, 2014 (127)	PanoVd	Vd
NCT01478048 Palumbo, 2015 (128)	EVd	Vd
NCT00813150 Kropff, 2017 (129)	CyVd	Vd

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CyhKd, Cyclophosphamide in combination with high dose carfilzomib and dexamethasone; CyVd, Cyclophosphamide in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; Evd, Elotuzumab in combination with bortezomib, and dexamethasone; hK, high dose carfilzomib; hKd, high dose carfilzomib and dexamethasone ; hKDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; len, lenalidomide; Kd, carfilzomib and dexamethasone ; LoT, line of treatment; PanoVd, panobinostat in combination with bortezomib, and dexamethasone; PVd, pomalidomide in combination with bortezomib, and

dexamethasone; SVd, selinexor in combination with bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone.
Note: hKd was used to specify high dose carfilzomib in combination with dexamethasone within the different trials used to connect in the network.

Figure 15. Overall (non-outcome specific) network of evidence



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CyhKd, Cyclophosphamide high dose carfilzomib and dexamethasone+ high dose carfilzomib and dexamethasone; CyVd, Cyclophosphamide in combination with bortezomib, and dexamethasone+ bortezomib + dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; EVd, Elotuzumab in combination with bortezomib, and dexamethasone; hK, high dose carfilzomib; hKd, high dose carfilzomib and dexamethasone ; hKDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; len, lenalidomide; Kd, carfilzomib and dexamethasone ; LOT, line of treatment; PanoVd, Panobinostat in combination with bortezomib, and dexamethasone; PVd, pomalidomide in combination with bortezomib, and dexamethasone; SVd, selinexor in combination with bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone

B.2.9.2.2 Treatment effect modifiers

Identification of the covariates that can modify or predict the treatment effect on outcomes of interest, namely treatment effect modifiers (TEMs), is essential for the assessment of transitivity in the evidence base. To identify TEMs in RRMM, clinical expert opinion was sought, and published literature was critically appraised. In addition, subgroup analyses that were performed were reviewed to examine whether efficacy for PFS varied between subgroups for each study included in the NMA (Appendix D).

In terms of published literature, TEMs in MM have been examined in a Bayesian NMA by Dimopoulos et al., (130) as well as an NMA and simulation study by Rose et al. 2022 (131). Dimopoulos et al. identified ≥ 1 previous LoT to be a significant TEM, whilst weak evidence of an interaction for within trial effect modifiers in HR for PFS by LoT and prior immunomodulatory drugs/lenalidomide-refractory status was found by

Rose et al. 2022. In terms of clinical expert opinion, the TEMs and prognostic factors indicated were prior LoT, refractory status to the specific agent in the trial, ISS stage, cytogenetic risk profile, extramedullary disease, creatine clearance, time from diagnosis, age, gender, ethnicity, comorbidities, and Eastern Cooperative Oncology Group (ECOG) stage. While age, gender and ethnicity are important, it was stated that they are not as critical as the aforementioned variables. To explore which variables are TEMs, efficacy results by subgroup for the most important potential TEMs were explored for PFS results from each study included in the NMA. PFS results by subgroup were used to evaluate whether a variable was a TEM or not, because PFS is the primary endpoint of DREAMM-7. Potential variables were considered TEMs when they showed imbalances between studies in the ITT populations. The disease characteristics explored were:

- Prior LoT
- Prior immunomodulatory drugs exposure
- ISS stage
- ECOG performance status (PS)
- Prior lenalidomide exposure
- Prior daratumumab use
- Cytogenic risk profile

Upon assessing data availability of PFS results by subgroup across the studies included in the NMA, subgroup results indicated that prior LoT, ECOG PS and ISS stage may be TEMs in this population. It is anticipated that PFS treatment effect will reduce (i.e., HRs will increase) with more prior lines of therapy and higher ISS stages.

B.2.9.2.3 Heterogeneity and inconsistency

The networks of evidence met the assumption of transitivity since no major differences in the distribution of potential TEMs were observed. However, imbalances were identified in the distribution of patients with one prior LoT across the included studies and meta-regression and subgroup analysis were considered to account for the observed variability, where feasible. Meta-regressions to explore differences by study in key characteristics, identified as TEMs, were deemed unfeasible due to the limited number of studies informing each comparison in the networks. Moreover, upon assessing data availability, subgroup analyses were conducted to address potential heterogeneity. Analysis of inconsistency was not possible due to the absence of any closed treatment loop in the networks of evidence.

B.2.9.3 Methodology

NMA is a valuable evidence synthesis tool that generalises the two-study Bucher indirect comparison to larger networks, connecting multiple treatments from several different studies. NMAs account for both direct evidence (i.e., treatments compared head-to-head) and indirect evidence (i.e., treatment comparisons that can only be performed via one or more "common" treatment nodes across the study network). NMAs can be applied using either classical (frequentist) or Bayesian statistical models. The Bayesian approach was adopted for the purposes of this analysis, since it naturally lends itself to the decision making context by providing probabilistic interpretations and treatments rankings and is explicitly proposed in the NICE Technical Support Documents (132). Details of the Bayesian NMA methodology are described in Appendix D. An overview of the conducted NMAs is provided in Table 20.

Table 20. Overview of conducted analyses

Analysis	Population	Endpoint	Treatment effect type
Primary	ITT	PFS	Fixed-effects Random-effects
	ITT	OS	Fixed-effects Random-effects
	ITT	ORR	Fixed-effects Random-effects
	Lenalidomide-refractory patients	PFS	Fixed-effects Random-effects
	Lenalidomide-refractory patients	ORR	Fixed-effects Random-effects

Abbreviations: ITT, intention-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

B.2.9.4 Results

B.2.9.4.1 Interpretation

Both time-to-event (i.e., OS, PFS) and binary (i.e., ORR) endpoints were assessed in the NMA. For OS and PFS, HRs were estimated for the relative efficacy of BVd versus comparators. Median HR<1 suggest a lower probability of the outcome occurring with BVd compared to other treatments; values above 1 indicate a lower reduction in the outcome occurring with BVd versus comparator treatments. Where 95% CrIs cross the line of "no difference" or HR=1, this indicates a lack of statistically important difference in HR between treatments.

For ORR, odds ratios (ORs) were estimated in each analysis. The OR represents the increase or decrease in the odds of an event occurring in one treatment group compared to another. An OR>1 suggests greater odds of the outcome occurring with BVd over comparator treatments; values below 1 indicate lower odds in the outcome

with BVd versus comparator treatments. Where 95% CrIs cross the line of “no difference” or OR=1, this indicates a lack of statistically important difference in odds ratio between treatments.

B.2.9.4.2 Goodness of fit

Goodness of fit summary statistics for the primary analyses are provided in Table 21. The Deviance Information Criterion (DIC) and the total residual deviance were observed to be lower or similar for the fixed effect (FE) and random-effects (RE) models for all endpoints. Goodness of fit summary statistics for the secondary and subgroup analyses are provided in Appendix D.

Table 21. Goodness of fit summary statistics for all endpoints (primary analysis – ITT population)

Endpoint	DIC		Residual deviance	
	Fixed-effects	Random-effects	Fixed-effects	Random-effects
PFS	[redacted]	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]	[redacted]
ORR	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; ITT, intention-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

B.2.9.4.3 Primary analysis results

The primary analysis focused on the ITT population from the included studies. The FE model was preferred for the base-case. This was justified for three main reasons:

- Fixed-effects models are more parsimonious than RE models, and therefore more suitable for inference.
- RE model findings can be difficult to interpret due to the low number of studies informing each treatment comparison, which might not be sufficient to reliably estimate between-study heterogeneity.
- Regardless of the above, Table 21 indicates that there is almost no difference between the fit of the two models, so the choice does not drive decision making.

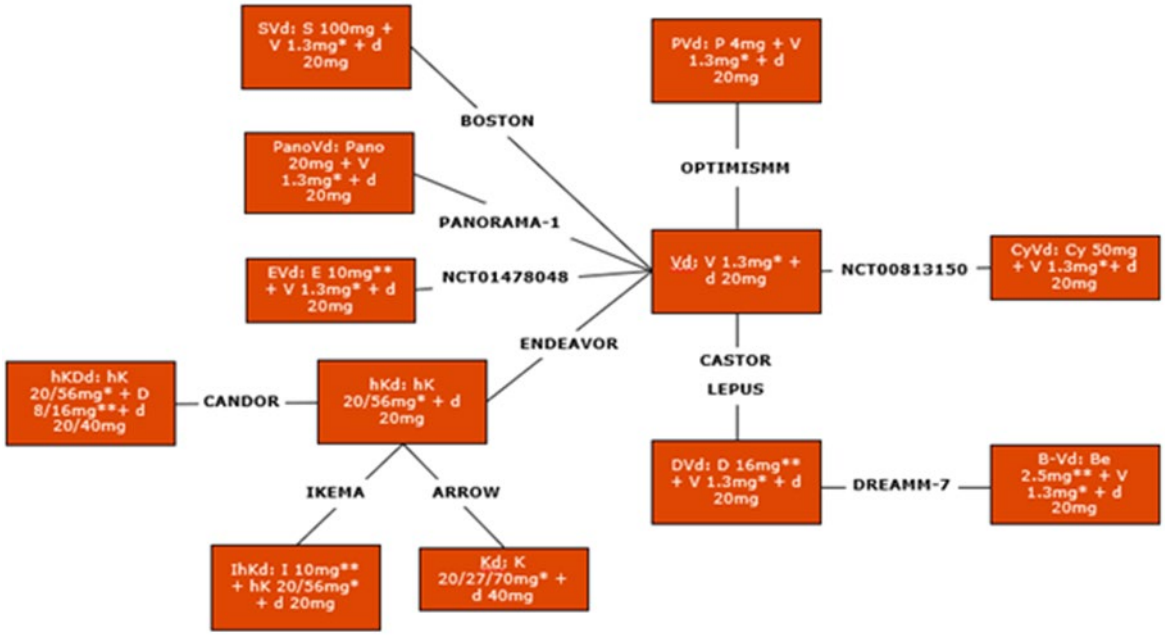
NMA results are interpreted using forest plots for FE models in the following sections, whereas additional NMA outputs such as rankograms, along with the RE model results are presented in Appendix D.

<u>Primary outcome - Progression-free survival (PFS):</u>

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

The network for PFS, shown in Figure 16 comprised 12 studies [BOSTON (103), PANORAMA-1 (127), NCT01478048 (128), OPTIMISMM (126), NCT00813150 (129), DREAMM-7 (86, 87), CASTOR (121), LEPUS (100, 101), ENDEAVOR (104), ARROW (117), IKEMA (123-125) and CANDOR (118-120)] and 12 treatment nodes.

Figure 16. Primary analysis progression free survival network of evidence



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CyhKd, Cyclophosphamide high dose carfilzomib and dexamethasone; CyVd, Cyclophosphamide in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; EVd, Elotuzumab in combination with bortezomib, and dexamethasone; hK, high dose carfilzomib; hKD, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; len, lenalidomide; Kd, carfilzomib and dexamethasone; LOT, line of treatment; PanoVd, Panobinostat in combination with bortezomib, and dexamethasone; PVd, pomalidomide in combination with bortezomib, and dexamethasone; SVd, selinexor in combination with bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone

The posterior estimates of the FE model are graphically illustrated in Figure 17. As discussed previously in Section B.2.9.2.1, the global NMA network was broader than the scope of the decision problem and included non-relevant comparators for the NICE appraisal in order to improve accuracy of the estimates made for relevant comparators. Results for the comparators relevant for the appraisal suggested superior PFS outcomes for BVd over DVd [redacted], hKd [redacted] and SVd [redacted]. All results were statistically significant to a 95% CrI. NMA results for the comparison of BVd over DVd are aligned with the DREAMM-7 efficacy results in terms of PFS, see Section B.2.6.1.1. Insofar as it is relevant as indirect evidence, BVd was superior even to comparators not approved for use in the NHS.

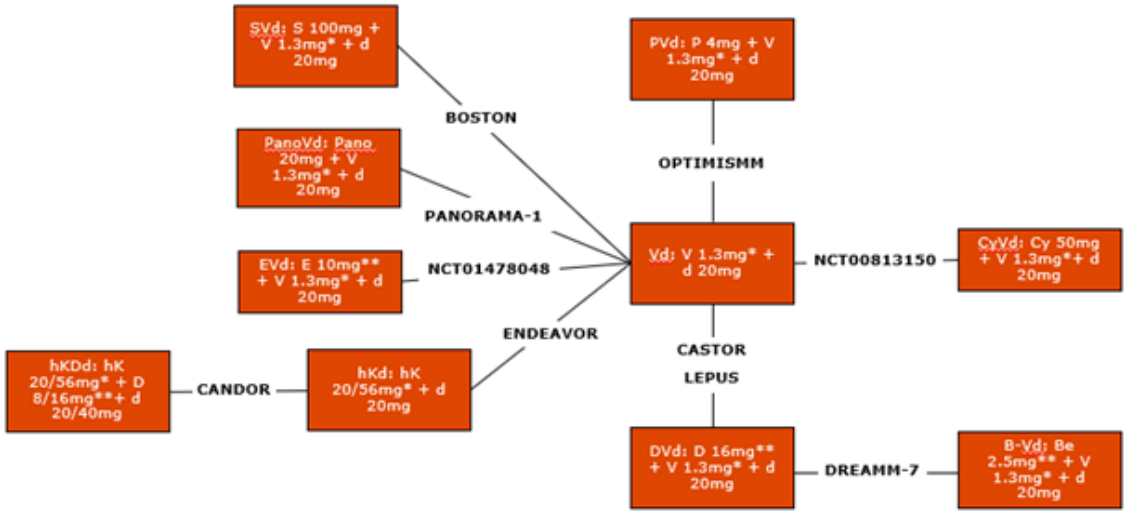
Figure 17. Relative effects for fitted fixed effect network meta-analysis model in progression free survival main analysis. Results summarised as posterior median hazard ratios and 95% credible intervals

[redacted]

Secondary outcome - Overall survival:

The network for OS, shown in Figure 18, consisted of 10 studies [BOSTON (103), PANORAMA-1 (127), OPTIMISMM (126), NCT00813150 (129), CASTOR (121, 122), LEPUS (100, 101), NCT01478048 (128), ENDEAVOR (104), CANDOR (118-120) and DREAMM-7 (86, 87)] and 10 treatment nodes.

Figure 18. Primary analysis overall survival network of evidence



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CyhKd, Cyclophosphamide high dose carfilzomib and dexamethasone; CyVd, Cyclophosphamide in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; EVd, Elotuzumab in combination with bortezomib, and dexamethasone; hK, high dose carfilzomib; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; len, lenalidomide; Kd, carfilzomib and dexamethasone ; LOT, line of treatment; PanoVd, Panobinostat in combination with bortezomib, and dexamethasone; PVd, pomalidomide in combination with bortezomib, and dexamethasone; SVd, selinexor in combination with bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone

The posterior estimates of the FE model are graphically illustrated in Figure 19. Results suggest an OS benefit for BVd compared to DVd ([redacted], hKd ([redacted]) and SVd [redacted]. Results for all relevant comparators were statistically significant to a 95% CrI, and results for all comparators (including those of no relevance to the NHS) were directionally in favour of BVd. NMA results for the comparison of BVd over DVd are aligned with the DREAMM-7 efficacy results for OS (99).

Figure 19. Relative effects for fitted fixed effect network meta-analysis in overall survival main analysis. Results summarised as posterior median hazard ratios and 95% credible intervals

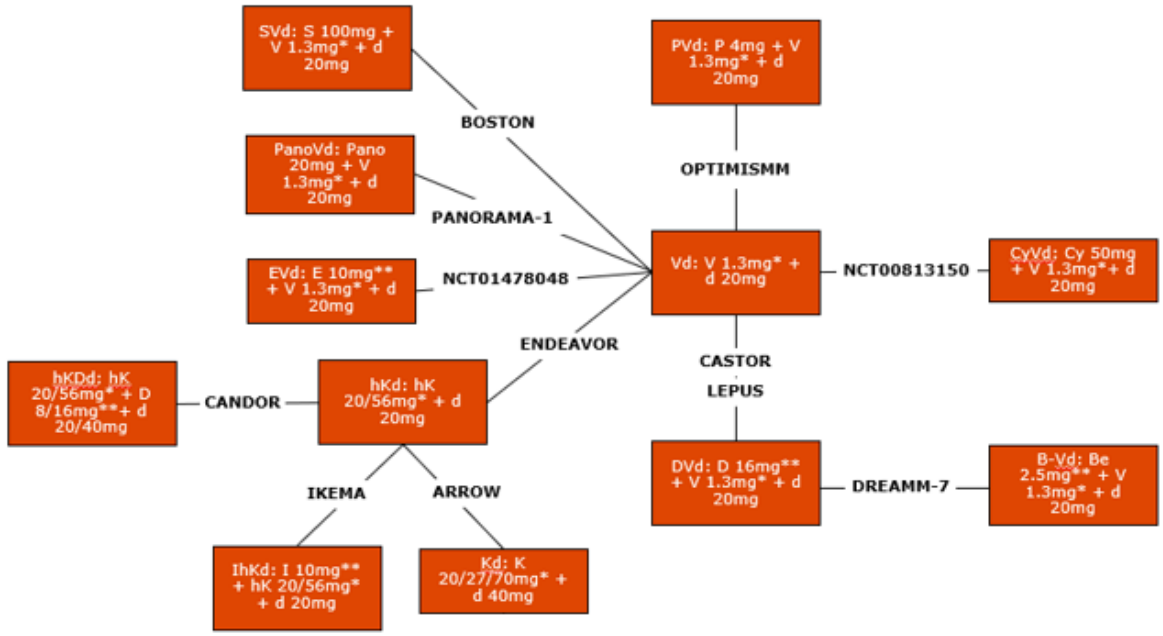
[redacted]

Secondary outcome - Overall response rate:

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

The network for ORR, shown in Figure 20, consisted of 12 studies [BOSTON (103), PANORAMA-1 (127), OPTIMISMM (126), NCT00813150 (129), CASTOR (121, 122), LEPUS (100, 101), NCT01478048 (128), ENDEAVOR (104), CANDOR (118-120), DREAMM-7 (86, 87) ARROW (117) and IKEMA (123-125)] and 13 treatment nodes.

Figure 20. Primary analysis overall response rate network of evidence



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CyhKd, Cyclophosphamide high dose carfilzomib and dexamethasone; CyVd, Cyclophosphamide in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; EVd, Elotuzumab in combination with bortezomib, and dexamethasone; hK, high dose carfilzomib; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; len, lenalidomide; Kd, carfilzomib and dexamethasone; LOT, line of treatment; PanoVd, Panobinostat in combination with bortezomib, and dexamethasone; PVd, pomalidomide in combination with bortezomib, and dexamethasone; SVd, selinexor in combination with bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone

The posterior estimates of the FE model are graphically illustrated in Figure 21. Results suggested that patients treated with BVd have a higher probability of achieving ORR compared to those treated with DVd [redacted]), hKd ([redacted]) and SVd ([redacted]). Results for all relevant comparators were statistically significant to a 95% CrI, and results for all comparators (including those of no relevance to the NHS) were directionally in favour of BVd. NMA results for the comparison of BVd over DVd are aligned with the DREAMM-7 efficacy results in terms of ORR.

Figure 21. Relative effects for fitted fixed effect network meta-analysis model in overall response rate main analysis. Results summarised as posterior median odds ratios and 95% credible intervals

[redacted]

B.2.9.4.4 Secondary analysis results

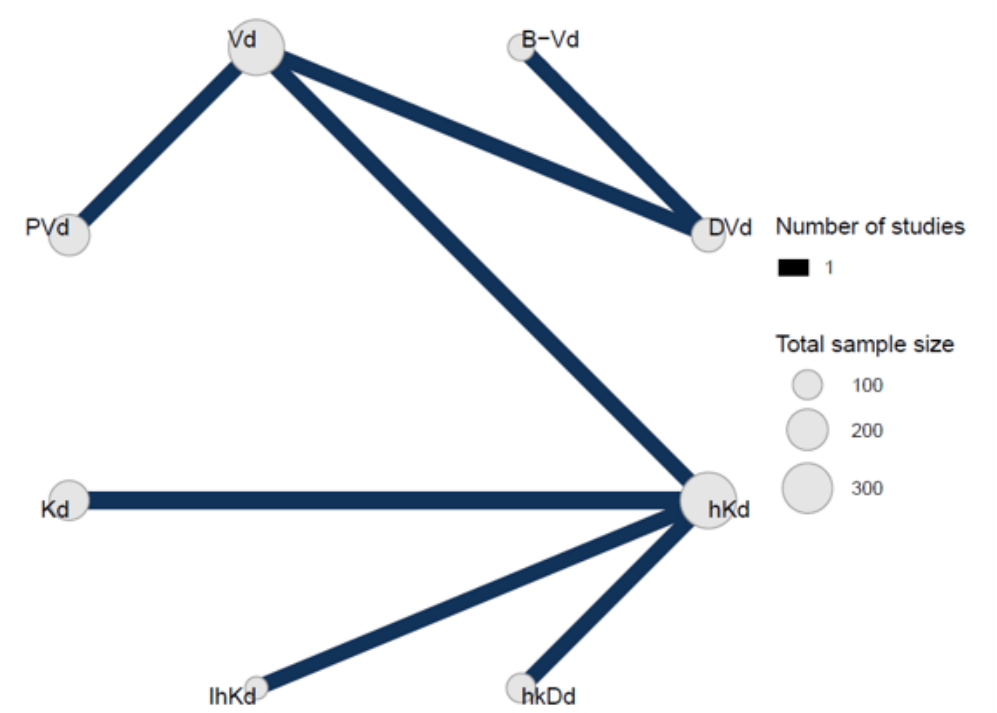
The secondary analyses considered lenalidomide-refractory patients, restricting the networks to studies reporting efficacy data for these populations. Secondary analyses were conducted for PFS and ORR only, since no subgroup data were available for OS across the comparator studies.

Lenalidomide-refractory patients

Primary outcome – Progression-free survival

The network of evidence for PFS, shown in Figure 22, consisted of 7 studies (DREAMM-7 (86, 87), CASTOR (121, 122), OPTIMISMM (126), ARROW (117), IKEMA (123-125) and CANDOR (118-120) and ENDEAVOR (104)), which reported subgroup-specific data.

Figure 22. Secondary analysis progression-free survival network of evidence – Lenalidomide-refractory population



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CyVd, Cyclophosphamide in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high dose carfilzomib and dexamethasone ; hKDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; Kd, carfilzomib and dexamethasone ; NMA, network meta-analysis; PanoVd, Panobinostat in combination with bortezomib, and dexamethasone; PFS, progression-free survival; PVd, pomalidomide in combination with bortezomib, and dexamethasone; SVd, selinexor in combination with bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone

The posterior estimates of the FE model are graphically illustrated in Figure 23. Results indicated superiority of BVd over DVd [redacted] and hKd [redacted] and all other non-relevant comparator treatments for the appraisal in terms of PFS, aligned with the primary analysis results for the ITT population. Results for all relevant comparators were statistically significant to a 95% CrI.

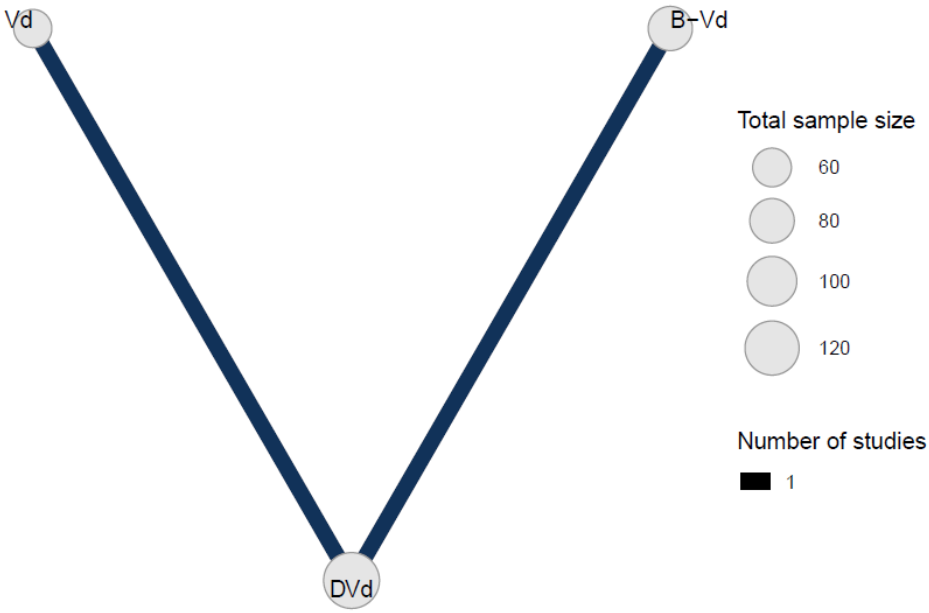
Figure 23. Relative effects for fitted fixed effect network meta-analysis model in progression-free survival secondary analysis for the lenalidomide-refractory population. Results summarised as posterior median hazard ratios and 95% credible intervals

[redacted]

Overall response rate:

The network of evidence for ORR, presented in Figure 24 comprised DREAMM-7 (99) and CASTOR (122) studies, since only those could be connected in a network of evidence.

Figure 24. Secondary analysis overall response rate network of evidence – Lenalidomide-refractory population



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; NMA, network meta-analysis; ORR, overall response rate; Vd, bortezomib and dexamethasone

The posterior estimates of the FE model are graphically illustrated in Figure 25. Results suggest that BVd leads to greater odds of ORR compared to DVd and Vd [redacted]

Figure 25. Relative effects for fitted fixed effect network meta-analysis model in overall response rate secondary analysis for the lenalidomide-refractory population. Results summarised as posterior median odds ratios and 95% credible intervals

[redacted]

B.2.9.5 Strengths and limitations

Findings of the conducted NMA are consistent with the efficacy results of the DREAMM-7 study (99), indicating the robustness and generalisability of the results to UK clinical practice and ensuring their relevance and applicability. The comparative efficacy of the treatments for patients with at least one prior LoT for RRMM was examined, using PFS, OS, and ORR endpoints, which are clinically important and relevant for the cost-effectiveness analysis.

The selection of studies for the NMA was based on a global SLR, aiming to summarise the efficacy and safety of treatments for RRMM in patients with at least one prior LoT, as detailed in Section B.2.1.To ensure the inclusion of relevant comparators, studies assessing any regimens likely to be considered relevant were examined during the NMA feasibility assessment.

In terms of disease characteristics, no significant imbalances were observed across the included studies. Where feasible, subgroup analyses were performed to account for any differences in the distribution of TEMs. It should be noted that the reporting of baseline characteristics within the primary analysis population was limited, which presents challenges in fully assessing the between-study heterogeneity. This limitation underscores the need for cautious interpretation of the NMA results, particularly when considering the potential impact of underlying trial differences on treatment effect estimates.

Standard NMA methodology requires that trial-reported HRs remain constant over time (that is, the assumption of PH holds). Please see Appendix D for supporting data to the conclusions that PH does hold for DREAMM-7. More broadly, PH NMAs have been used in the appraisals of relevant comparators in 2L RRMM (SVd and DVd) (29, 133). In addition, previously published ITCs in RRMM adopted a conventional NMA approach (21, 134-138). Therefore, a standard NMA approach that thoroughly explores heterogeneity was feasible and appropriate for the purposes of this appraisal.

The NMA models, which included both fixed- and RE models, were fit to the data in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) guidance (132). Similar model fit and relative treatment effect estimates across the different models attests to the robustness of the Bayesian NMA approach. A potential limitation of the implemented methodology is that NMAs do not account for imbalances in population characteristics that could influence treatment effects across studies. Beyond the thorough examination of studies to be included in the ITC to ensure comparability of populations results for the primary analysis for the ITT population were considered generalisable.

A limitation pertains to the immaturity of the survival data. For OS, the median survival times for DREAMM-7 study had not been reached at the data cut-off point of the analysis. An update to the NMA at a later data cut-off, when mature data will be

available for OS, may be necessary to enhance the interpretability of the posterior estimates.

B.2.10 Adverse reactions

B.2.10.1 Summary of adverse reactions

The safety and tolerability of BVd in DREAMM-7 was consistent with those previously described for belamaf, despite the longer time on treatment compared to the DREAMM-2 and DREAMM-3 trials (89, 90). The safety population included [redacted] patients ([redacted]), and all patients experienced ≥1 AE. Table 22 shows summary statistics for AEs experienced by this population, and further detail on adverse reactions is given in Appendix F.

The BVd vs DVd arm had higher overall rates of grade 3 or 4 AEs (95% vs 76%) and serious AEs (50% vs 37%). In the BVd and DVd arms, when adjusting for total treatment exposure (per 100 person-years), rates of grade 3 or 4 AEs were 68.8 and 62.4 and rates of serious AE were 36.3 and 30.0, respectively. In total, 64 patients (26%) in the BVd arm vs 36 (15%) in the DVd arm discontinued any trial treatment due to treatment-related AEs. Deaths from serious AEs were reported in 23 patients (10%) in the BVd arm and 19 (8%) in the DVd arm, with 7 (3%) and 2 (<1%), respectively, considered treatment-related.

The rates of infections, including opportunistic infections, a known risk with chimeric antigen receptor T-cell and bispecific T-cell engager BCMA-targeting agents (89, 91-94) was similar between treatment arms in the DREAMM-7 trial.

Eye-related side effects, a known risk with belamaf, were manageable and resolved with dose modifications (including delays and reductions). This therefore resulted in a low rate of overall discontinuations, but a significantly higher rate of dose interruptions and reductions in the BVd arm, which leads to a notably lower relative dose intensity (RDI) in actual clinical practice than might be inferred from the trial dosing schedule (see Section B.3.5.1.2). Despite the higher incidence of eye-related side effects in the BVd arm, overall HRQoL did not differ between arms over time (see Section B.2.6.1.7 and Appendix N).

There is some potential for bias (underreporting) in reporting of eye-related side effects in the DVd arm. Eye-related side effects were reported in 79% of patients in the BVd arm and 29% in the DVd arm, suggesting a background rate in the general MM population. For patients on treatment, eye examinations were performed less frequently in the DVd arm and the median duration of exposure of any trial drug was longer in the BVd arm ([redacted]) than the DVd arm ([redacted] potentially leading to reporting bias of eye-related events in the BVd arm.

Table 22. Summary of adverse events experienced during DREAMM-7 trial (safety population)

	BVd (N=243)	DVd (N=251)
Any AE	242 (100)	246 (100)
Related to any trial treatment[a]	242 (100)	234 (95)
Grade 3/4 AE	229 (95)	187 (76)
Exposure-adjusted rate[b]	68.8	62.4
Related to any trial treatment[a]	219 (90)	164 (67)
AEs leading to permanent discontinuation of any trial treatment	75 (31)	46 (19)
Exposure-adjusted rate[b]	22.5	15.4
Related to any trial treatment leading to permanent discontinuation of any trial treatment[a]	64 (26)	36 (15)
Belamaf discontinuation due to eye-related event	22 (9)	-
AEs leading to dose reduction	182 (75)	146 (59)
Belamaf dose reduction due to eye-related event	106 (44)	-
AEs leading to dose interruption / delay	228 (94)	185 (75)
Belamaf dose interruption / delay due to eye-related event	189 (78)	-
Any SAE	121 (50)	90 (37)
Exposure-adjusted rate[b]	36.3	30.0
Related to any trial treatment[a]	47 (19)	30 (12)
Fatal SAE	23 (10)	19 (8)
Related to any trial treatment[a]	7 (3)	2 (<1)

a "Related to any trial treatment" includes responses of 'Yes' and missing responses to the following question: "Is there a reasonable possibility that the AE may have been caused by the trial treatment?"
b Exposure-adjusted rates were calculated as the total number of patients with an event divided by the total exposure time in person-years (per 100 person-years). Total person-years is the sum of all patient exposure calculated as (last dose – first dose + 1) / 365.25
Abbreviations: AE, adverse events; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; SAE, serious adverse event
Source: DREAMM-7 primary analysis clinical study report (99).

B.2.10.2 Adverse reactions by system organ class

In both arms, the most common AEs by system organ class (SOC) included blood disorders and infections. In the BVd arm, the most frequently occurring grade ≥3 eye-related side effects included blurred vision, dry eyes, and cataract. Table 23 lists all-

grade treatment-emergent AEs (graded using the National Cancer Institute- Common Toxicity Criteria for Adverse Event [NCI-CTCAE] version 5.0) that occurred in ≥15% of patients in ≥1 treatment group, plus two broader AE categories of interest which GSK anticipates will be of interest, blood and lymphatic system disorders & infections and infestations. Further details on adverse reactions by SOC are given in Appendix F.

While rates of thrombocytopenia were higher with BVd than DVd (69% vs 50%; 50.2 vs 40.7 per 100 person-years), there was no difference between concomitant grade 3 or 4 platelet count decreases and grade ≥2 bleeding events ([redacted]). Anaemia was more frequent with DVd than BVd (26% vs 19%). Rates of infections (SOC) were similar between arms (70% vs 67%; 51.1 vs 55.4 per 100 person-years), with more grade ≥3 pneumonia reported with BVd than DVd (12% vs 4%; 8.4 vs 3.3 per 100 person-years). Opportunistic infections were not collected in a systemic way; however, when rates of infections (SOC) were analysed by the following AE preferred terms, aspergillus infection, cytomegalovirus infection reactivation, and pneumonia fungal, incidence of these 3 opportunistic infections were few and balanced between arms ([redacted]). Other non-eye-related side effects occurring in ≥20% of patients in either arm included diarrhoea, peripheral sensory neuropathy, neuropathy peripheral, constipation, and fatigue. Eye-related side effects were more frequent with BVd (all grades, 79% vs 29%; grade ≥3, 34% vs 3%).

Table 23. Adverse reactions by system organ class (safety population)

	BVd (n=242)		DVd (n=246)	
	All	**Grade ≥3**	**All**	**Grade ≥3**
Any adverse event, n (%)	242 (100)	230 (95)	246 (100)	192 (78)
Blood and lymphatic system disorders, n (%)	185 (76)	151 (62)	158 (64)	109 (44)
Thrombocytopenia[a]	167 (69)	134 (55)	122 (50)	87 (35)
Anemia[b]	46 (19)	20 (8)	65 (26)	25 (10)
Infections and infestations, n (%)	170 (70)	75 (31)	166 (67)	49 (20)
Pneumonia	44 (18)	28 (12)	22 (9)	10 (4)
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Eye-related event, n (%)[c]	191 (79)	82 (34)	72 (29)	7 (3)
Vision blurred	160 (66)	53 (22)	26 (11)	2 (<1)
Dry eye	123 (51)	17 (7)	17 (7)	0
Photophobia	[redacted]	[redacted]	[redacted]	[redacted]
Eye irritation	103 (43)	12 (5)	13 (5)	0

	BVd (n=242)		DVd (n=246)	
	All	Grade ≥3	All	Grade ≥3
Foreign body sensation in eye	[redacted]	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]	[redacted]
Other, n (%)				
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction[d]	[redacted]	[redacted]	[redacted]	[redacted]

a. If platelet count decrease is also included, percentage of thrombocytopenia events for all grades is [redacted] and [redacted] for BVd and DVd, respectively; percentage of thrombocytopenia events for grade ≥3 is [redacted] and [redacted] for BVd and DVd, respectively.
b. Red blood cells decreased was not reported.
c. Eye examination findings for patients in the BVd arm were assessed at screening/baseline and then every 3 weeks prior to dosing up to at least the sixth dose of belantamab mafodotin and then every 3 months if there were no eye-related findings. For patients in the DVd arm, Eye examinations were performed at screening/baseline, with on-treatment eye examinations performed at cycle 6 and then every 6 months.
d.Infusion-related reactions are based on a hybrid of terms identified in the electronic case report form and a list of terms identified by GSK internal review. The event must start within 24 hours of infusion and lead to dose interruption/delay or trial treatment withdrawal.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; COVID-19, coronavirus disease 2019; DVd, daratumumab in combination with bortezomib, and dexamethasone; GSK: GlaxoSmithKline.
Source: DREAMM-7 primary analysis clinical study report (99)

Treatment-related fatal AEs were <5% in both arms. In total in the BVd arm 23 patients experienced a fatal AE (of which 7 were considered treatment-related) and in the DVd arm 19 patients experienced a fatal AE (of which 2 were considered treatment-related). Table 24 summarises fatal and treatment-related fatal AEs by type of event. Further detail on fatal and treatment-related fatal AEs can be found in Appendix F.

Table 24. Fatal and treatment-related fatal adverse events (safety population)

	BVd (n=242)		DVd (n=246)	
	Fatal SAE	**Fatal TRSAE**	**Fatal SAE**	**Fatal TRSAE**
Total	23 (10)	7 (3)	19 (8)	2 (<1)
Pneumonia	[redacted]	[redacted]	[redacted]	
COVID-19	[redacted]		[redacted]	[redacted]
COVID -19 pneumonia	[redacted]		[redacted]	
Sepsis	[redacted]		[redacted]	
Respiratory failure	[redacted]			
Septic shock	[redacted]			
Acute myocardial infarction	[redacted]			
Acute respiratory failure			[redacted]	
Cerebral haemorrhage	[redacted]			
Cerebrovascular accident			[redacted]	
Colitis	[redacted]			
Coronavirus pneumonia	[redacted]			
Dyspnoea	[redacted]			
Fall			[redacted]	
Febrile neutropenia	[redacted]			
Gastrointestinal haemorrhage	[redacted]	[redacted]		
Haemorrhage intracranial			[redacted]	
Hyperkalaemia			[redacted]	
Hyperthermia			[redacted]	
Multiple organ dysfunction syndrome	[redacted]			
Peritonitis	[redacted]			
Respiratory tract infection	[redacted]			
Subdural haemorrhage	[redacted]	[redacted]		
Thrombosis mesenteric vessel	[redacted]	[redacted]		

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; COVID-19, coronavirus disease 2019; DVd, daratumumab in combination with bortezomib, and dexamethasone; SAE, serious adverse event; TRSAE, treatment-related serious adverse event.

Source: DREAMM-7 primary analysis clinical study report (99)

B.2.10.3 Eye-related side effects

As described in Section B.2.10.2 eye-related side effects were the most characteristic safety difference between the BVd and DVd arm. Although most eye-related side effects could be resolved with dose interruption / reduction, this led to a significantly lower RDI for BVd than DVd, which has implications for the cost-effectiveness of BVd in UK clinical practice (please see Section B.3.5.1.2) Since eye-related side effects are therefore an important consideration for the economic modelling as well as being clinically significant in their own right, they are described in more detail here (and in Appendix F) with an additional section on the impact of eye-related side effects on RDI in Section B.2.10.4

Table 25 summarises eye-related side effects that occurred on the BVd arm of the DREAMM-7 trial (eye-related events that occurred on the DVd arm would not usually lead to dose modification, so they are less relevant to the decision problem). Eye-related events did not always occur in both eyes. When an eye-related event occurred in both eyes, the grade of the event was based on the most severe event between the two eyes. The endpoint of relevance to eye-related events is best corrected visual acuity (BCVA), referring to the best vision achievable when the patient is wearing corrective lenses. A decrease in BCVA to 20/50 or worse represents 'blurred vision' (i.e., a change in visual acuity of clinical importance as it can affect activities of daily living), while a decrease in BCVA to 20/200 represents the level at which all patients will be 'vision impaired'. Figure 26 provides a reference image for the impact of BCVA at different levels on the patient.

Figure 26. Reference images for impact of best corrected visual acuity on patient

Abbreviation: BCVA, Best Corrected Visual Acuity

Among patients in the BVd arm with normal BCVA at baseline (defined as 20/25 or better in at least one eye), a worsening to bilateral BCVA of 20/50 or worse was reported in 34% of patients and a worsening to bilateral 20/200 was reported in 2%. For the first occurrence, nearly all patients (98%) with worsening to bilateral 20/50 and all patients with worsening to bilateral 20/200 improved to better than bilateral 20/50 and 20/200, respectively. The remaining 2% of patients reported as not resolved had discontinued treatment, with no follow-up available to assess for resolution. The median duration of the first occurrence was approximately three weeks regardless of how severe the initial impact on BCVA was.

Table 25. Summary of eye-related adverse events (safety population)

	BVd (N=242)	
	20/50	**20/200**
Patients, n/N (%)	82/242 (34)	5/242 (2)
Time to onset of first event, median (range), days	73.5 (16-753)	105 (47-304)
Duration of first event, median (range), days	22 (6-257)	19 (8-26)
First event resolved, n (%)[a]	80 (98)	5 (100)
Duration of last event, median (range), days	[redacted]	[redacted]
Last event resolved, n (%)[a]	[redacted]	[redacted]

a "Resolved" was defined as bilateral improvement to better than 20/50 (or 20/200).
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone
Source: DREAMM-7 primary analysis clinical study report (99)

Dose modifications of belamaf were based on overall Keratopathy Visual Acuity (KVA) grade. KVA events were reported in [redacted] of patients, with [redacted] grades 2 and [redacted] grade ≥3 events. These are summarised in Table 26. For the first occurrence of grade ≥2 KVA events, median time to onset was [redacted], and median duration was [redacted]; at data cut-off, [redacted] of patients had their first event resolved prior to or post end of treatment exposure. Eye-related events in the BVd arm led to belamaf dose reductions, delays, and discontinuations in [redacted], 78%, and 9% of patients, respectively. Patient-reported QOoL was similar between treated patients in both arms over time, as demonstrated by EORTC QLQ-C30 Global Health Status and QOL Domain Score, suggesting that there were minimal differences in the impact of AEs on patients' evaluation of their daily lives (see Section B.2.6.1.7 and Appendix N).

Table 26. Details of keratopathy visual acuity grade for patients in belamaf in combination with bortezomib arm (safety population)

	BVd (n=242)
Eye-related events per overall KVA scale	
Any event, n (%)	[redacted]
Grade 2, n (%)	[redacted]
Grade ≥3, n (%)	[redacted]
Time to onset of first occurrence (≥ grade 2), median (range) days	[redacted]
Duration of first occurrence (≥ grade 2), median (range) days	[redacted]

	BVd (n=242)
First event resolved, n/N (%)[a]	[redacted]
Eye-related events based on corneal examination findings	
Any event, n (%)	[redacted]
Grade 2, n (%)	[redacted]
Grade ≥3, n (%)	[redacted]
Time to onset of first occurrence (≥ grade 2), median (range) days	[redacted]
Duration of first occurrence (≥ grade 2), median (range) days	[redacted]
First event resolved, n/N (%)[a]	[redacted]
Eye-related events based on visual acuity changes	
Any event, n (%)	[redacted]
Grade 2, n (%)	[redacted]
Grade ≥3, n (%)	[redacted]
Time to onset of first occurrence (≥ grade 2), median (range) days	[redacted]
Duration of first occurrence (≥ grade 2), median (range) days	[redacted]
First event resolved, n/N (%)[b]	[redacted]

a "Resolved" was defined as achieving grade 1 or better
b "Resolved" was defined as bilateral improvement to better than 20/50 (or 20/200).
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KVA, Keratopathy Visual Acuity
Source: DREAMM-7 primary analysis clinical study report (99)

B.2.10.4 Relative dose intensity

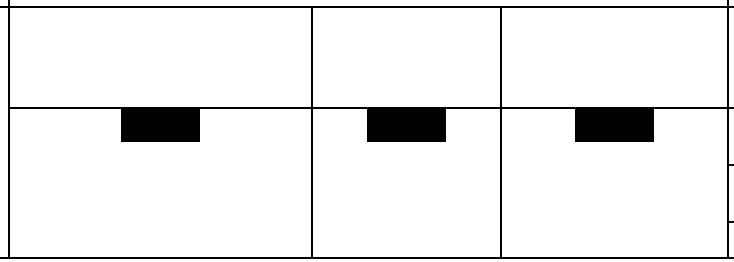
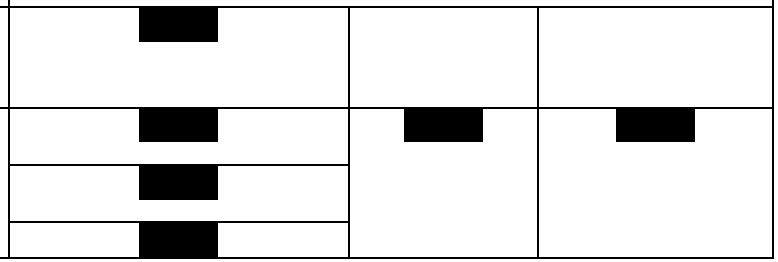
The impact of eye-related side effects on planned doses actually delivered has an important impact on the assessment of BVd's cost-effectiveness. This is because management of an eye-related side effects frequently involves a dose modification or delay, but rarely leads to total discontinuation of treatment. Table 27 summarises the impact that AEs have on median relative dose intensity. Note that due to the nature of the AEs experienced on BVd the median RDI may not be the most appropriate measure for use in a cost-effectiveness model; this section provides data supporting the claim made in B.2.10.3 that BVd and DVd have materially different relative dose intensities, while section discusses the most accurate way to implement these data into the model.

The median RDI of belamaf was [redacted] for the full treatment duration (post-hoc analysis showed [redacted] in the first [redacted] and [redacted] in the first [redacted]); the median RDI of daratumumab was [redacted] during each dosing period (e.g., cycles 1-3, 4-8, and 9+).

Median dose intensities of bortezomib and dexamethasone were similar between arms, with median dose intensities of [redacted] in the first [redacted].

Table 27. Summary of relative dose intensity data

	BVd (N=243)			DVd (N=251)		
Total duration of exposure, Median (range) months						
	Bela	**Bor**	**Dex**	**Dara**	**Bor**	**Dex**
Number of cycles, Median (range)[a], Mean (SD)						
Overall dose intensity, Measure, Median (range), Mean (SD)						
Relative dose intensity[e], Median (range), Mean (SD)						

	BVd (N=243)			DVd (N=251)		
						

a. Only includes cycles in which patients received a dose of the drug
b. Overall dose intensity is the cumulative actual dose divided by (duration of exposure in days / planned cycle length)
c. Dexamethasone dose intensity is calculated for 10mg and 20m based on the patient's starting dose
d. Overall dose intensity is the cumulative actual dose divided by (duration of exposure in days / planned cycle length). This is only calculated for daratumumab due to changes in dosing regimen at cycle 4 and an increase in cycle length to 28 days at cycle 9
e. Relative dose intensity is calculated as a percentage and defined as 100 x (overall dose intensity / planned dose intensity). For daratumumab, this is within the indicated cycles
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; Bela, belantamab mafodotin; Bor, bortezomib; Dex, dexamethasone; Dara, daratumumab; DVd, daratumumab in combination with bortezomib, and dexamethasone; SD, standard deviation
Source: DREAMM-7 primary analysis clinical study report (99).

B.2.11 Ongoing studies

DREAMM-7 (NCT04246047) is an ongoing phase III, open-label, randomised multicentre trial to evaluate the efficacy and safety of BVd compared with DVd in patients with RRMM who received at least 1 prior LoT. The study is being conducted in 20 countries in 151 sites, including 7 UK sites (86).

DREAMM-8 (NCT04484623) is a phase III clinical trial is a multicentre, open-label, randomised trial evaluating the efficacy and safety of head-to-head trial of belamaf, in combination with pomalidomide and dexamethasone (PomDex), compared to a combination of bortezomib plus PomDex in patients with RRMM previously treated with a least one prior LoT, including a lenalidomide-containing regimen, and who have documented disease progression during or after their most recent therapy. On 07 March 2024, GSK announced positive headline results for an interim analysis of this study. The trial met its primary endpoint of PFS at a prespecified interim analysis and was unblinded early (139).

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

B.2.12.1.1 Clinical effectiveness

The phase III, randomised, multicentre, open-label DREAMM-7 trial met its primary endpoint for PFS. BVd demonstrated a statistically significant and clinically meaningful PFS benefit (95% CI: 0.31, 0.53; HR, 0.41; p<0.00001; showing a 59% reduction in risk of disease progression or death) with a median PFS that was 23 months longer than that with DVd (36.6 vs 13.4 months) in the ITT population. PFS benefit consistently favoured BVd vs DVd across prespecified subgroups, including patients with lenalidomide-refractory or high-risk cytogenetic MM. These results were validated by clinical experts, who confirmed that the DREAMM-7 PFS for DVd generally aligns to clinical practice and noted that the PFS benefit for BVd was impressive (67).

The median PFS of [redacted] for BVd in the lenalidomide-refractory subgroup is markedly higher than that reported from the CASTOR, ENDEAVOR and BOSTON trials for lenalidomide-refractory populations (7.8 months, 8.6 months, and 10.2 months for DVd, Kd, and SVd, respectively) [CASTOR (19), ENDEAVOR (79) and BOSTON (28)] and the TTNTD (proxy-PFS) reported in emerging UK RWE for lenalidomide-refractory patients treated with DVd at 2L (10.3 months) (25, 26). As described in Section B.1.3.2, there is a high unmet need for lenalidomide-refractory patients at first relapse in the UK, as current treatment options are limited and corresponding outcomes are poor. Overall, this data suggests efficacy for this group is far improved with BVd over other options.

BVd was associated with greater depth of response with a ≥CR rate that was double that with DVd (34.6% vs 17.1%). MRD negativity rate (10^{-5}) in patients treated with BVd was more than double that in patients treated with DVd: 24.7% vs. 9.6% (p<0.00001; ≥CR). It was also reported that 65.8% and 46.2% of responders in BVd and DVd group achieved deep responses of VGPR or better with a median TTR of [redacted], respectively.

The median DoR (95%) was 35.6 months (30.5-NR) with BVd versus 17.8 months (13.8-23.6) with DVd. However, since more than half of responses were still ongoing in the BVd arm, the median DoR is not fully mature.

OS showed an early, strong, and clinically meaningful trend favouring the BVd arm (HR, 0.57; p=0.00049, 95% CI: 0.40, 0.80). Landmark analysis of OS at 18 months showed a higher survival rate in the BVd group compared with the DVd group (84% vs.73%). This was consistent in the lenalidomide-refractory subgroup ([redacted]). These results were validated by clinical experts, who noted that the OS data was immature, but that they expected to see a benefit (67).

The mean utility scores, based on EQ-5D-3L, were broadly similar between the two treatment arms across the study visits. However, there was a gradual increase in the utility scores (change from baseline) from Week 31 which became very noticeable from around 12 months onwards. Also, the utility scores before progression (i.e., progression-free state) were slightly higher than the scores after progression (progressed state). Moreover, in the fitted 2- and 3-health state model (adjusted for baseline utility score), patients in the BVd arm indicated higher improvement in utility scores compared to the DVd arm patients.

B.2.12.1.2 Safety

The safety and tolerability of BVd in the DREAMM-7 trial was consistent with those previously described for belamaf, despite the longer time on treatment compared to the DREAMM-2 and DREAMM-3 trials (89, 90). Eye-related side effects, a known risk with belamaf, were manageable, resolved with dose modifications including delays and reductions, and led to a low rate of discontinuations. Eye-related side effects were reported in 79% of patients in the BVd arm and 29% in the DVd arm, suggesting a background rate in the general MM population. On-treatment eye-related examinations were performed less frequently in the DVd arm, potentially leading to reporting bias of eye-related events in the BVd arm. Despite the higher incidence of eye-related side effects in the BVd arm, overall HRQoL did not differ between arms over time. Finally, the rates of infections, including opportunistic infections, a known risk with chimeric antigen receptor T-cell and bispecific T-cell engager BCMA-targeting agents (91-94) was similar between treatment arms in the DREAMM-7 trial.

B.2.12.2 Strengths and limitations of the clinical evidence base

B.2.12.2.1 Strengths of the clinical evidence base

- The principal strength of the clinical evidence base is the very strong signal that BVd is superior to the existing NHS SoC in a head-to-head clinical trial. BVd demonstrated a statistically significant PFS benefit, with a 59% reduction in the risk of progression or death (HR, 0.41; 95% confidence limit (CL) 0.31-0.53; p<0.00001), in patients at first relapse or later. All outcomes included in the NMA were consistent with the head-to-head trial, suggesting superior outcomes of BVd versus all other relevant comparators.

- Related to this, the findings are highly consistent across endpoints and subgroups. BVd was associated with greater depth and DoR including sCR/CR rate, MRD negativity, and DoR, and early OS trends also favour BVd. The marked PFS benefit favouring BVd was consistent across prespecified subgroups, including those with high-risk cytogenetic abnormalities and disease that is refractory to lenalidomide.

- The results of the DREAMM-7 trial are highly transferrable to the NHS. Patients were recruited from seven centres in the UK, and all patients had received at least one prior LoT. More than half had prior exposure to lenalidomide in the 1L, which is SoC in the UK. All the key outcomes relevant for decision making were assessed in the DREAMM-7 trial and were used in the economic analysis (PFS, OS, AEs, HRQoL).

- A key potential concern decision makers may have had around belamaf – the resolvability of eye-related side effects – appears to have been conclusively resolved by the DREAMM-7 trial. Results are consistent with a manageable safety profile, with most eye-related side effects resolving within three weeks or less. Other AEs, including the rate of infections, was similar between BVd and DVd.

B.2.12.2.2 Limitations of the clinical evidence base

- Due to the different methods of administering the study treatments, it was not possible to blind the study. This could have led to performance bias, where patients and clinicians adjust their behaviour due to knowledge about which treatment they are receiving. This was expected to be of limited concern; DVd was well known as a highly effective treatment for 2L MM, so any performance bias would likely be against BVd. However, to minimise this risk as far as possible the primary end point was assessed by IRC to ensure impartiality. This risk of bias should be contextualised against the gains in generalisability from designing DREAMM-7 as a head-to-head against UK SoC, which would not be possible if the study had to be double blinded.

- In common with most MM studies, OS is immature in DREAMM-7 (median survival times had not been reached at the data cut-off point of the analysis). Although there is a clear apparent trend of the curves separating over time, an update to the NMA using a later data cut-off could improve interpretability of these results. This was thought to be a minor limitation given the well-known association between PFS and OS, and the extensive clinical validation of the OS extrapolation curves eventually selected for use in the economic model.
- Although the population of the DREAMM-7 trial is highly generalisable to the NHS, it is not clear if studies of competitor drugs have the same high level of validity given, they were carried out on historic populations. Since NMAs do not account for imbalances in population characteristics that could influence treatment effect across studies, it is possible that imbalances in population characteristics could introduce uncertainty into the NMA results. This limitation is less concerning for BVd than it might be in other circumstances, as the NMA produces clear and consistent results favouring BVd under all combinations of subgroups and comparators, including comparators of no relevance to NHS practice (indicating that imbalances in population characteristics are unlikely to be decision-relevant for the NHS).

B.2.12.3 Conclusion

Despite the availability of treatment options for RRMM patients at first relapse, there is a high unmet need for patients for whom lenalidomide is unsuitable, because options are limited and data suggests that corresponding efficacy is suboptimal. Therefore, a new and effective therapy with a unique MoA is needed, and if approved, belamaf would be the first BCMA targeted option within the NICE pathway.

Belamaf has been evaluated in combination with Vd in the DREAMM-7 phase III trial and this trial provides the most robust source of evidence generalisable to the UK population. Belamaf has demonstrated significant superiority to current SoC in the randomised controlled trials (RCT) and existing 2L treatment options where the NMA results suggest that BVd is more efficacious compared to all comparators (hKd, DVd and SVd), for all populations in terms of PFS, OS, and ORR. Finally, the results from the comparison of BVd vs DVd were aligned between the DREAMM-7 analyses and the NMA.

Taken together, the broad efficacy benefit observed in this appraisal, manageable safety profile, and utility of belamaf as an off-the-shelf, outpatient BCMA therapy, strongly support BVd as the new SoC at first relapse for patients who are refractory to lenalidomide or are patients for whom lenalidomide is unsuitable. Should BVd be approved for routine commissioning for this group, it has the potential to redefine the NICE treatment paradigm, offering new hope for myeloma patients and their families in the UK.

B.3 Cost-effectiveness

Summary of cost-effectiveness analysis

- A *de novo* partitioned survival model (PSM) was developed to evaluate the cost-effectiveness (CE) of BVd versus DVd in adult patients with RRMM who have had one prior therapy, 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 and the structure is the standard approach taken in oncology HTA submissions which has been validated by experts.
- Clinical outcomes, AEs, incidence, and subsequent treatments for belamaf were derived from the ITT population of the final analysis of the DREAMM-7 trial.
- Health state utilities for the PFS and PD health states were informed by the DREAMM-7 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 based on clinical opinion and previous NICE submissions.

Summary of cost-effectiveness results

- The base-case cost-effectiveness model (CEM) indicates that BVd Patient Access Scheme (PAS) extendedly dominates DVd (a mix of BVd and SVd is both cheaper and more effective than DVd), and BVd could become more CE over time as the use of daratumumab increases in 1L.
- The base-case cost-effectiveness estimate (BVd PAS vs other list) was £8,190 / quality-adjusted life year (QALY) versus SVd, and the hKd comparator was dominated in the incremental analysis. By conventional cost-effectiveness criteria, BVd would be a highly CE use of NHS resources.
- Sensitivity and scenario analysis confirms this result is highly likely to be seen in plausible RW settings. The model also presents evidence on a subpopulation of patients who are refractory to daratumumab, in whom the CE will always be either the same or superior. This subpopulation is likely to become proportionally larger over time as 1L treatment evolves. GSK argues that this creates a case for approval above the £30,000 / QALY incremental cost-effectiveness ratio (ICER) threshold in any scenario versus DVd, as cost-effectiveness of BVd will be aligned to this subgroup in the future.
- As BVd substantially decreases subsequent treatment costs, there is a net resource saving for the NHS over the first five years of BVd's approval ([redacted]). Nevertheless, the ICER demonstrates that BVd is an effective use of NHS resources regardless of the budget impact.
- Taken together, the broad benefit observed in this appraisal and utility of the regimen as an off-the-shelf, outpatient therapy strongly support BVd as the new SoC at 2L for patients unsuitable to lenalidomide. If approved for routine commissioning, belamaf has the potential to redefine the NICE treatment paradigm, offering new hope for patients and their families.

B.3.1 Published cost-effectiveness studies

An economic SLR was first conducted in January 2023 and then updated again in January 2024 using the same methodology to identify relevant cost-effectiveness (CE), cost, and resource use, and HRQoL studies from the published literature. The population considered in this submission is patients with 2L RRMM (140).

This SLR was conducted according to the NICE guidelines, the PRISMA statement, and the Cochrane Handbook for Systematic Reviews of Interventions, to ensure methodological quality (141-144).

In the economic SLR, 72 publications that described cost-effectiveness analyses conducted for RRMM were identified (140):

- 19 publications were conducted for the UK settings (England, Wales, Scotland, UK),
- 53 publications were conducted for other countries including: US, Canada, France, Germany, Italy, China, Japan, and other countries.

In the 19 publications conducted for UK settings :

- 10 publications used a partitioned survival approach (22, 79, 145-152).
- Four publications used Markov or semi-Markov approaches (145, 153-155).
- One publication compared outputs from Markov and partitioned survival approaches (156).
- Three publications used individual simulation or discrete simulation approaches (157, 158).
- One publication (conference abstract) did not specify the model structure used. (159)

Full details of the SLR strategy, study selection process and results are presented in Appendix G.

B.3.2 Economic analysis

In anticipation of the potential launch of BVd for the treatment of adult patients with RRMM who have had one prior LoT, GSK developed a *de novo* cost-effectiveness model (CEM) for the purpose of this appraisal, as described in the following sections (141). This economic model was used to estimate the total costs and quality-adjusted life years (QALYs) associated with BVd compared to relevant comparators as described in B.1.1, that have the potential to be displaced with recommendation of BVd in 2L in England and Wales (i.e., DVd, hKd, and SVd) (141). In this section, hKd refers to high-dose carfilzomib (56mg/m^2) plus dexamethasone which aligns to Kd treatment recommended in the NICE pathway. The NMA conducted provided results

for hKd in order to differentiate between another Kd trial, and therefore, the model nomenclature aligns with the NMA (see B.2.9).

The model adopts the UK NHS and Personal Social Services (PSS) perspective for the UK base-case, in line with the NICE reference case requirements (160). This approach includes all direct health-related resource use and health outcomes for patients.

B.3.2.1 Patient population

The population entering the model is largely aligned with the DREAMM-7 (88, 99, 161) trial population: adults (aged ≥18 years) with documented MM, previously treated with one prior LoT, and with documented disease progression during or after their most recent therapy. The overall ITT population from the DREAMM-7 trial is included within the model as it is reflective of clinical practice, has a large sample size and more robust data available from the NMA analysis given data availability. Given stronger evidence of outcomes benefit of BVd over DVd in the lenalidomide refractory and exposed population, use of the ITT data provides a conservative estimate of the true cost-effectiveness of the population proposed by GSK (patients in 2L for whom lenalidomide is unsuitable).

B.3.2.2 Baseline characteristics

Baseline characteristics for the modelled cohort are based on the statistical analysis of the ITT population of DREAMM-7 trial and are presented in Table 28.

Table 28. Patient baseline characteristics for the base-case economic analysis

Characteristic	ITT
Baseline mean age (years)	64
Baseline weight (kg)	[redacted]
Baseline BSA (m^2)	[redacted]
% of males	55%

Abbreviations: BSA, body surface area; ITT, intention-to-treat.
Source: DREAMM-7 (162)

B.3.2.3 Model structure

A *de novo* health economic model was constructed in Microsoft Excel to evaluate the CE of BVd versus DVd, hKd and SVd in patients with 2LMM. The model adopts the structure of a cohort-based partitioned survival model (PSM), where health state occupancy over time is governed by parametric models fitted to PFS, OS, and TTD data from the DREAMM-7 trial and hazard ratios derived from the NMA. This structure

is the standard approach used in oncology HTA submissions, due to its intuitiveness, allowing state occupancy to be estimated directly from trial-based estimates of OS, PFS and TTD. The model structure has been validated by clinical experts in a recent Scientific Committee Meeting held by GSK (67) and is also aligned with all of the precedent Technology Appraisals in MM (Table 29).

Table 29. Relevant published models

Factor	NICE TA974 (29)	NICE TA897 (22)	NICE TA870 (48)	NICE TA783 (151)	NICE TA695 (163)	NICE TA658 (149)	NICE ID4014 (164)	ICER appraisal 061016V3 (165)	ICER appraisal 040521-1 (166)
Intervention	SVd	DVd	IxaRd	Daratumumab	KRd	IsaPd	DRd	KRd, daratumumab, ERd, IxaRd, FVd, and Pd	Ide-cel, cilta-cel, and belamaf
Line of therapy	2L, 3L	2L	3L, 4L	4L	2L+	4L	1L	2L+	4L+
Model structure	Three state PSM	Three state PSM	Three state PSM	Four state PSM	Three state PSM	Three state PSM	Three state PSM	Three state PSM	Initial decision tree followed by three state PSM
Time horizon	Lifetime (35 years)	Lifetime (30 years)	Lifetime (25 years)	Lifetime (15 years)	Lifetime (40 years)	Lifetime (20 years)	Lifetime (26 years)	Lifetime	Lifetime
Cycle length	One week	One week	One week	One week	28 days	One week	Four weeks	One week	One month
PFS and OS modelling	PFS and OS extrapolated directly from observed trial KM data	PFS and OS extrapolated directly from observed trial KM data	PFS and OS extrapolated directly from observed trial KM	PFS and OS extrapolated directly from observed trial KM	PFS extrapolated directly from observed trial KM data. OS	PFS and OS extrapolated directly from observed trial KM data. Estimation	PFS and OS extrapolated directly from observed trial KM data and validated	PFS extrapolated directly from observed trial KM data for	Intervention PFS and OS and comparator OS extrapolated

Factor	NICE TA974 (29)	NICE TA897 (22)	NICE TA870 (48)	NICE TA783 (151)	NICE TA695 (163)	NICE TA658 (149)	NICE ID4014 (164)	ICER appraisal 061016V3 (165)	ICER appraisal 040521-1 (166)
					extrapolated from real-world data	of OS using a PFS:OS relationship was explored as a scenario analysis	with real-world data	lenalidomide and dexamethasone. Hazard ratios from NMA used to derive PFS curves for other interventions. OS estimated from treatment-specific PFS:OS relationships	directly from observed trial KM data. Comparator PFS estimated from PFS:OS relationship derived from NMA

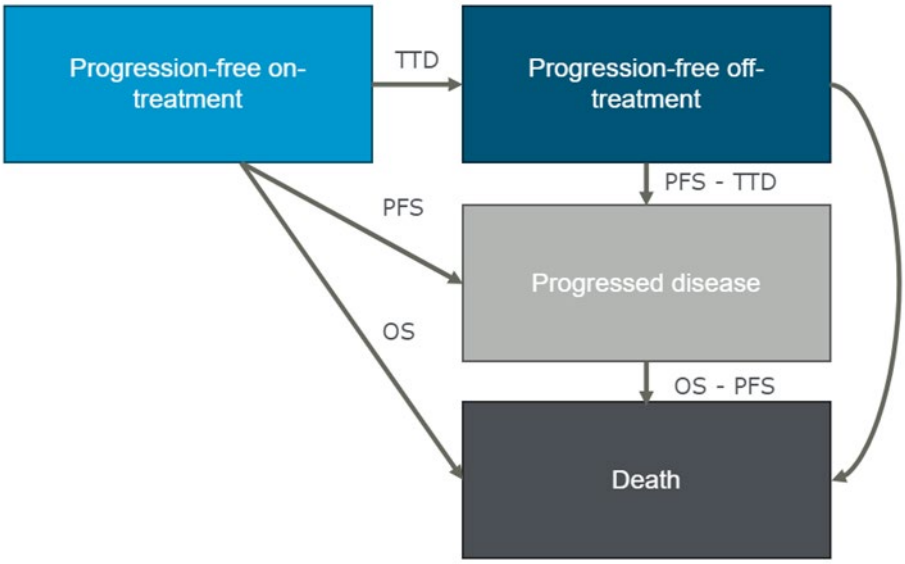
Abbreviations: 1L, first line, 2L second line; 2L+, second line and onwards 3L, third line; 4L, fourth line; 4L+, fourth line onwards; cilta-cel, ciltacabtagene autoleucel; DRd, daratumumab in combination with lenalidomide and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; ERd: elotuzumab in combination with lenalidomide, and dexamethasone ; FVd, panobinostat in combination with bortezomib, and dexamethasone; ICER, Institute for Clinical and Economic Review; ide-cel, Idecabtagene vicleucel; IsaPd, isatuximab in combination with pomalidomide, and dexamethasone; IxaRd, ixazomib in combination with lenalidomide, and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; SVd, selinexor in combination with bortezomib, and dexamethasone; TA, , technology appraisal.

The model is composed of four mutually exclusive health states:

- Progression-Free Disease (PF) on treatment (on-tx),
- PF off treatment (off-tx),
- Progressed Disease (PD)
- Death

A visual representation of the model structure is presented in Figure 27.

Figure 27. Diagram of model structure



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

The proportion of patients occupying each health state over time is estimated from parametric distributions fitted to the PFS, OS and TTD data from the DREAMM-7 trial for BVd and DVd.

State membership for each health state is calculated as follows:

- PF on-tx – estimated from the extrapolated TTD KM curves,
- PF off-tx – estimated by subtracting the TTD curve from the extrapolated PFS KM curve for each treatment (i.e., PFS off-tx = PFS-TTD),
- PD – estimated by subtracting PFS KM curve from the OS KM curve (PD=OS-PFS),
- Death – estimated using the extrapolated OS KM curves (Death=1-OS)

The PF health state was split into on- and off-tx on the basis that some patients in DREAMM-7 withdrew from active treatment before disease progression. 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 (acquisition and administration), monitoring, and AEs, whilst PD captures the costs and consequences of subsequent treatments, monitoring. The death state captures end of life care. Therefore, the model captures the key elements of care for patients with 2L MM from the time they initiate treatment, to when they complete subsequent treatment and finally when patients enter terminal care.

For each weekly cycle, costs, and QALYs are calculated based on the state membership of patients across the modelled health states and death. Costs and QALYs are accumulated over the lifetime model time horizon to calculate total costs and QALYs for BVd and its comparators, with the data used to calculate incremental results and the cost per QALY for BVd versus each comparator. In addition, the cost per life year gained is calculated.

B.3.2.4 Model settings

A summary of the model features and justification is presented in Table 30 alongside a comparison with models included in previous NICE appraisals of treatments for RRMM as these were used to inform the DREAMM-7 model base-case.

Table 30. Comparing recent appraisals with a population of 2L MM patients with DREAMM-7

Parameter		Previous appraisals			DREAMM-7	
Factor	**NICE TA974 (29)**	**TA897 (22)**	**TA695 (163)**	**TA657 (79)**	**DREAMM-7 (99, 167)**	**Justification**
Population and treatment	RRMM patients who have received one or two lines of prior therapy Intervention: Selinexor in combination with bortezomib, and dexamethasone	Previously treated MM patients Intervention: Daratumumab in combination with bortezomib, and dexamethasone	RRMM patients who have received one to three lines of prior therapy Intervention: carfilzomib in combination with lenalidomide, and dexamethasone	Patients with MM who have received at least one prior therapy Intervention: Carfilzomib and dexamethasone	Patients with MM who have received one prior therapy Intervention: Belamaf in combination with bortezomib, and dexamethasone	In line with the current decision problem for this submission
Time horizon	35 years (lifetime)	30 years (lifetime)	40 years (lifetime)	40 years (lifetime)	36 years (lifetime)	Sufficiently long to be considered a lifetime horizon for 1L+ MM patients with a mean age of 64 years and aligned with NICE reference case (160)
Perspective	NHS & PSS	NHS & PSS	NHS & PSS	NHS	NHS & PSS	In line with NICE reference case (160)
Discounting	3.5%					In line with NICE reference case

Parameter		Previous appraisals			DREAMM-7	
Factor	**NICE TA974 (29)**	**TA897 (22)**	**TA695 (163)**	**TA657 (79)**	**DREAMM-7 (99, 167)**	**Justification**
Cycle length	1 week	1 week	28 days	4 weeks	1 week	This allows the model to capture the differences in treatment cycle length across BVd and comparators since 1 week is a common denominator. In addition, a short cycle length captures the rapid progression of TCR MM.
Health states	PSM – progression-free, progressed, dead	PSM- pre-progression (on and off treatment), post-progression (on and off treatment), dead	PSM – progression-free, progressed, death	PSM - pre-progression, post-progression, death	PSM – progression-free (on and off treatment), progressed disease, death	Health states aligned with previous NICE appraisals and are consistent with the natural disease progression in MM patients.
Source of utilities	Utilities derived from BOSTON (mapped from the EQ-5D-5L to EQ-5D-3L),	Utilities derived based on ENDEAVOR (TA457)	EORTC QLQ-C30 from ASPIRE mapped to EQ-5D	Mapping analysis using change from baseline from clinical trial applied to van Agthoven (2004)	Utility scores derived from DREAMM-7, as well as based on TA897, TA695,TA369	Aligned with previous approaches in NICE Appraisals

Parameter		Previous appraisals			DREAMM-7	
Factor	**NICE TA974 (29)**	**TA897 (22)**	**TA695 (163)**	**TA657 (79)**	**DREAMM-7 (99, 167)**	**Justification**
Source of costs	National Schedule of Reference Costs 2021-2022, Unit Costs of Health and Social Care, British National Formulary, Department of Health eMIT	MIMS UK Drug Database, National Schedule of Reference Costs 2020-2021	MIMS UK Drug Database, Department of Health eMIT	MIMS UK Drug Database, Department of Health eMIT	National Schedule of Reference Costs 2021-2022, Unit Costs of Health and Social Care, British National Formulary, and TA897	In line with NICE reference case (160)

Abbreviations: 1L+, one line and onwards; 2L, second line; BVd, belamaf in combination with bortezomib, and dexamethasone; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; eMIT, Electronic Market Information Tool; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D, EuroQol 5-Dimension questionnaire; EQ-5D-3L, EuroQol 5-Dimension questionnaire 3 Level; MIMS, Monthly Index of Medical Specialties; MM, multiple myeloma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSM, Partitioned survival model; PSS, Personal Social Services; RRMM, relapsed refractory multiple myeloma; SVd, 99elinexor in combination with bortezomib, and dexamethasone TA, technology appraisal; TCR MM, triple-class refractory multiple myeloma; UK, United Kingdom

B.3.2.5 Intervention technology and comparators

The intervention being considered in the CEM is BVd. Belamaf is available in 100mg and 70mg vials which are administered as an IV infusion. The dosage used in the CEM is 2.5mg/kg of belamaf Q3W with dose reductions and delays accounted for via a parameter for 'relative dose intensity' in the model. Bortezomib is given in 1.3mg/m^2 doses administered through a SC injection, four times every three weeks. Dexamethasone is given as 20mg oral tablets (eight times every three weeks). This aligns with the DREAMM-7 CSR (99, 167) and the Summary of Product Characteristics (SmPC) (168).

In line with insights from clinical experts and relevant NICE-approved treatments in the 2L pathway of care, the model compares BVd with:

- DVd,
- hKd,
- SVd

Where 'hKd' refers to the carfilzomib and dexamethasone comparator in the NICE treatment pathway (called Kd in B.1 but hKd here to differentiate it from low-dose carfilzomib and align it to the NMA output in Section B.2.9).

The comparator treatments are also implemented as per their respective marketing authorisations and are given according to their licensed dosing regimens (e.g., bortezomib is implemented for up to eight treatment cycles).

An ITC has been conducted to provide comparative efficacy and safety between BVd and relevant comparators as identified in the decision problem. See section B.2.9 and appendix D for additional details.

B.3.3 Clinical parameters and variables

B.3.3.1 Data sources for survival endpoints

The key outcomes used in the economic model are PFS, OS and TTD. Efficacy data for BVd and DVd are sourced from the DREAMM-7 trial (99). Estimates for the relative treatment effect of BVd or DVd versus the remaining comparators have been informed by a NMA (B.2.9) Table 31 summarises the clinical efficacy input data used in the CEM.

Table 31. Clinical inputs for CEM

Endpoint	Source of clinical effectiveness		
	BVd	**DVd**	**Non-trial comparators**
PFS	Base-case: DREAMM-7 direct extrapolation Scenario: DREAMM-7 HRs applied to DVd baseline curve	Base-case: DREAMM-7 direct extrapolation Scenario: DREAMM-7 HRs applied to BVd baseline curve	Base-case: NMA with DVd as baseline
OS	Base-case: -Unadjusted DREAMM-7 extrapolation Scenarios: - IPCW adjusted DREAMM-7 extrapolation (Appendix O) - PFS: OS surrogacy	Base-case: DREAMM-7 extrapolation using informative priors from CASTOR trial Scenarios: - IPCW adjusted DREAMM-7 extrapolation (Appendix O) - PFS: OS surrogacy	
TTD	Base-case: DREAMM-7 extrapolation	Base-case: DREAMM-7 extrapolation	Base-case: NMA with DVd as baseline using PFS HRs as proxy Scenarios: - TTD=PFS - DVd TTD KM data as proxy and cap this by respective PFS HRs

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CEM, cost-effectiveness model; DREAMM, Driving Excellence in Approaches to Multiple Myeloma; DVd, daratumumab in combination with bortezomib, and dexamethasone; HR, hazard ratio; IPCW, inverse-probability of censoring weighting; KM, Kaplan-Meier; NMA, network meta analysis; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.3.2 Parametric survival modelling

Parametric survival modelling has been implemented to extrapolate DREAMM-7 survival curves over a lifetime horizon of the CEM. These analyses have been carried out in line with the NICE TSD 14 (160). In brief:

- Six standard parametric distributions have been fitted to KM data using R software (Exponential, Weibull, Gompertz, log-logistic, log-normal and Generalised Gamma). The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) are used to estimate the goodness of fit for each parametric distribution. The use of parametric distributions is justified through assessment of the PH assumption (Appendix O)
- UK external clinical experts (EEs) have been consulted to validate the clinical plausibility and visual goodness of fit of the long-term extrapolations generated by each of the distributions, specifically proportions of patients who would be on treatment, progression-free, or alive following treatment with BVd and DVd at 5-, 10-, and 15- year landmarks. EEs also validated the most plausible curves fitted to the data, only after landmarks were elicited to reduce bias in these estimates.
- For the comparators that are not included in the DREAMM-7 trial (i.e., hKd and SVd), PFS, and OS curves were estimated by applying the NMA HRs for each comparator to the extrapolated DVd or BVd data of the corresponding outcome. Due to unavailability of published data to inform an NMA for TTD, assumptions were made to fit plausible TTD estimations for hKd and SVd (Section B.3.9.2).

Table 32 summarises the selection of curves used in the CEM.

Table 32. Choice of curve selection for each major parameter in the CEM

Endpoint	Curve selection	Brief justification	Comparison between extrapolation and trial data at 2 years
PFS	Exponential	Good agreement between AIC, BIC and EE for both comparators	[redacted]
OS	Weibull	For BVd, there was a disagreement between statistical fit and EE believed all curves but one too optimistic. As this curve did not have good statistical fit, aligned to least optimistic curve with adequate statistical fit For DVd, all curves roughly similar as an informative prior approach was taken to reduce uncertainty, so Weibull chosen to align with BVd.	[redacted]
TTD	Weibull	For DVd, good agreement between AIC, BIC and EE. For BVd, there was a disagreement between statistical fit and EE. Use of statistical fit resulted in incoherent extrapolation, so EE aligned to DVd curve choice was preferred.	[redacted]

For non-DVd comparators, curves were estimated by applying the NMA HRs for each comparator to the extrapolated data of the corresponding outcome
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; EE, external clinical experts; HR, hazard ratio; NMA, network meta analysis; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation.

B.3.3.2.1 BVd - Progression-free survival

In the DREAMM-7 ITT population, there is a statistically significant and clinically meaningful PFS benefit with BVd compared with DVd, as demonstrated by an HR of 0.41 (95% CI: 0.31, 0.53; p <0.00001) (refer to B.2.6.1.1 for more details). Six parametric distributions have been fitted to the PFS KM curves collected from DREAMM-7 to extrapolate PFS in the economic model. The AIC/BIC statistical goodness of fit for these six distributions is shown in Table 33, in addition to the landmark survival estimates. Extrapolations of PFS using each model up to 20 years are presented in Figure 28 to facilitate the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

Table 33. PFS – BVd goodness of fit statistics for parametric distributions

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	-	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; PFS, progression-free survival.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Figure 28. PFS – BVd KM and parametric distributions, long term fit

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; PFS, progression-free survival.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

According to the AIC and BIC, the exponential distribution appeared to provide the best statistically fitting model for BVd PFS (Table 33). Within the observed trial period, all extrapolated parametric models yield similar visual predictions. It is also worth noting that the Weibull, Gompertz and log-logistic are considered a comparable fit due to being within three points of each other for their AIC scores (169). Based on the AIC and BIC, assessment of diagnostic plots, long-term assessment of visual fit and clinical expert opinion (Appendix M), the exponential has been selected for BVd PFS in the base-case.

B.3.3.2.2 DVd - Progression-free survival

The same approach has been adopted to extrapolate PFS data from the DVd arm from DREAMM-7. The AIC/BIC statistical goodness of fit for the six distributions are shown in Table 34, in addition to the landmark survival estimates. Extrapolations of PFS using each model up to 20 years is presented in Figure 29 to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

Table 34. PFS – DVd goodness of fit statistics for parametric distributions

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	-	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; DVd, daratumumab in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; PFS, progression-free survival.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Figure 29. PFS – DVd KM and parametric distributions, long term fit

[redacted]

Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; PFS, progression-free survival.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

In TA897, the exponential curve was selected as the best fitting curve to extrapolate DVd beyond 4 years, based on AIC and BIC, evolution of empirical hazards as well as clinical expert opinion. This was deemed appropriate by the external assessment group (EAG) as company's choice of curve (KM up to four years followed by the exponential distribution) provides the lowest estimate at 10 years in the DVd arm. Scenarios using SACT data were also performed, with the Weibull curve fitted to the SACT data to extrapolate (133).

Based on the AIC and BIC, and assessment of diagnostic plots, the log-logistic and Generalized gamma are the best statistically fitting curves for DVd PFS, although there is little difference between all fits. It is also worth noting that exponential, and log-normal could also be considered comparable as they are within three points of each other for their AIC scores (169). Expert opinion suggested that 10% PFS at five years seems reasonable given that the percentage of long-term responders is typically small at a maximum of 10% (Appendix O). Based on long-term assessment, assessment of diagnostic plots, precedent use of the exponential curve to model PFS in DVd, the exponential model is selected for extrapolation for base-case. Sufficient evidence is also seen in the diagnostic plots to assume PH between BVd and DVd.

B.3.3.2.3 Other - Progression-free survival

HRs are derived from the DREAMM-7 NMA for the key comparators of interest. In the base-case of the model these HRs are applied to the DVd PFS parametric survival curve to estimate the PFS for hKd and SVd. A scenario is explored where NMA HRs are applied to the BVd PFS parametric curve. The HRs versus both BVd and DVd are presented in Table 35.

Table 35. PFS HRs for comparators derived from NMA

	Vs BVd (95% CrI)	Vs DVd (95% CrI)
hKd	[redacted]	[redacted]
SVd	[redacted]	[redacted]
DVd	[redacted]	-
BVd	-	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; SVd, selinexor in combination with bortezomib, and dexamethasone.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.3.2.4 BVd - Overall survival

A strong and clinically meaningful OS benefit favoured the BVd group vs. the DVd group with a nominal p-value of 0.00049 (HR=0.57; 95% CI: 0.40, 0.80). Refer to section B.2.6.1.2 for more details.

Six parametric distributions have been fitted to the OS KM curves collected from DREAMM-7 to extrapolate OS in the economic model. The AIC/BIC statistical goodness of fit for these six distributions are shown in Table 36, in addition to the landmark survival estimates. Extrapolations of OS using each model up to 20 years is presented in Figure 30 to facilitate the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

Table 36. OS – BVd goodness of fit statistics for parametric distributions

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	-	-	-	-	NR	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; NR, not reached; OS, overall survival.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Figure 30. OS – BVd KM and parametric distributions, long term fit

Abbreviations: BVd, belamaf in combination with bortezomib; KM, Kaplan Meier; OS, overall survival.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162).

Based on the AIC and BIC, lognormal is the best statistically fitting curve for BVd OS, however, Gompertz, log-logistic, generalized gamma and Weibull could all be considered comparable as their AIC values are within three points (169). Gompertz has been excluded because the tail is unusually high. Experts suggested that the exponential curve might provide plausible predictions for 5, 10, and 15-year OS for BVd followed by the Weibull model.

There is a disparity in the data between the landmark survival estimations elicited from external experts and the fitting of the curves to the early trend seen in the OS of the BVd arm. The statistically best fitting curves suggest an optimistic continuation of strong survival outcomes for patients in the BVD arm of the trial. Experts, however, suggest that these curves are implausible in the long term.

Observation of the KM data in Figure 30 and the fit of the exponential curve shows a misalignment to the early positive trend seen in the BVd OS and would suggest that given more follow-up for a severe drop off in overall survival would be seen. This suggestion is also counterintuitive with the IPCW OS adjustment outlined in Appendix O where adjusting for subsequent therapies not available in the UK is estimated to improve OS outcomes for patients in the BVd arm.

There is therefore a lack of clarity in how the highly efficacious outcomes in PFS seen from DREAMM-7 translates into OS in the long run. Analysis of surrogacy between PFS and OS both shows a strong relationship between the two outcomes, but also highlights the lack of particularly efficacious treatments historically being used in the RRMM space (170). Based on a combination of assessing statistical fit and diagnostic plots, while aligning to the conservative long-term OS outcomes experienced by clinicians in RRMM, the Weibull was chosen as the best fitting curve for base-case.

B.3.3.2.5 DVd – Overall survival

NICE TSD 14, a NICE recommended source of methodological advice for HTA, states where external data is available, such as from a separate clinical trial with longer follow-up, it would represent a strong source of information (171). Compared with standard parametric survival, which is based only on the available follow-up data, a Bayesian approach can provide more robust survival estimates by using an informative prior distribution for the shape parameter of the OS curve estimated from external sources.

The method of using informative priors in MM has been previously applied by Soikkeli et al. and more recently by Palmer et al. specifically for MM outcomes and has been

shown to improve survival extrapolations (172, 173). This additional information is expected to improve survival extrapolations and reduce uncertainty.

Mature OS data for DVd (59% events over a maximum follow-up of 79.8 months) are available from the multicenter, randomized, open-label, phase III CASTOR study (NCT02136134), a strong source of information which can be used to obtain an informative prior for the control arm of DREAMM-7 (86). Feasibility assessment concluded that CASTOR had a similar trial design and treatment as DREAMM-7 with a longer follow-up period, and therefore, the assumption that the shape parameter of OS is exchangeable between studies is expected to hold (174, 175).

Frequentist survival analyses for DREAMM-7 using informative priors from CASTOR were therefore performed for DVd. The parameter estimates for different distributions using Bayesian informative prior analysis are presented in (174, 175). As the exponential model does not have a shape parameter, it could not be considered within this analysis. Additionally, Gompertz has been excluded due to clinically infeasible long-term projections resulting from a negative shape parameter which is not supported by the survHE R package in which the analysis was conducted.

The AIC/BIC statistical goodness of fit for these distributions are shown in Table 37 in addition to the landmark survival estimates. Extrapolations of OS using each model up to 20 years is presented in Figure 31 to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

Table 37. OS – DVd goodness of fit statistics for parametric distributions

Distribution	AIC	Rank	BIC	Rank	Median	Years					
	Months					1	2	5	10	15	20
KM	-	-	-	-	NR	[redacted]	[redacted]	-	-	-	-
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; DVd, daratumumab in combination with bortezomib, and dexamethasone; KM, Kaplan-Meier; NA, not applicable; OS, overall survival.

Figure 31. OS – DVd KM and parametric distributions, within trial fit

Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; OS, overall survival.

All AIC and BIC values are within three points of each other, and can therefore be considered comparable with regards to statistical fit (169). The lognormal is the best fitting curve based on AIC and BIC, however visually all models show a similar short-term fit. While the long-term curve shapes are visually similar, the landmark estimates of survival at different time points show differences. Experts considered that on average approximately 5-10% of patients would be alive at 15 years, with Weibull distribution reflecting these estimates. Based on long-term assessment, and expert opinion, Weibull is selected for DVd OS extrapolation.

B.3.3.2.6 Other - Overall survival

The HRs estimated from the NMA versus both BVd and DVd are presented in Table 38.

Table 38. OS HRs for comparators derived from NMA

	Vs BVd (LB and UB)	Vs DVd (LB and UB)
hKd	[redacted]	[redacted]
SVd	[redacted]	[redacted]
DVd	[redacted]	-
BVd	-	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; HR, hazard ratio; LB, lower bound; NMA, network meta-analysis; OS, overall survival; SVd, selinexor in combination with bortezomib, and dexamethasone; UB, upper bound
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.3.2.7 BVd - Time to treatment discontinuation

Six parametric distributions have been fitted to the TTD KM curves collected from DREAMM-7 to extrapolate TTD in the economic model. The AIC/BIC statistical goodness of fit for these six distributions are shown in Table 39, in addition to the landmark survival estimates. Extrapolations of TTD using each model up to 20 years are presented in Figure 32 to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

Table 39. TTD – BVd goodness of fit statistics for parametric distributions

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	-	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; TTD, time to treatment discontinuation.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Figure 32. TTD – BVd KM and parametric distributions, long term fit

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; TTD, time to treatment discontinuation.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

As can be seen from Figure 32, the extrapolation curves broadly divide themselves into two groups – a 'higher TTD' group consisting of lognormal, log-logistic and generalized gamma, and a 'lower TTD' group consisting of exponential and Weibull (the Gompertz was excluded given the tail is implausibly high). In general, the 'higher TTD' group had better measures of statistical fit but the 'lower TTD' group were preferred by a majority of clinicians.

Selecting a curve from the 'higher TTD' group leads to a significant face validity issue, namely that the TTD curve will cross the PFS curve at around 10 years. This is logically impossible, since patients must be pre-progression in order to be receiving a treatment which is treat-to-progression. Although this would not lead to invalid CEM results (as the CEM will automatically prevent illogical results like PFS>OS or TTD>PFS), it will violate many of the assumptions which justify the use of parametric curves in the first instance.

For this reason, curves from the 'higher TTD' group were rejected, and the Weibull curve selected from within the pair of 'lower TTD' choices. The reason for preferring Weibull to exponential were:

- Aligns to curve choice for DVd TTD (which is valuable as there is ambiguity regarding the PH assumption)
- Slightly better statistical fit than the exponential
- Landmarks suggested by clinicians and landmarks used in previous appraisals (TA897 (22)) align to using the Weibull curve

B.3.3.2.8 DVd - Time to treatment discontinuation

Six parametric distributions have been fitted to the TTD KM curves collected from DREAMM-7 to extrapolate TTD in the economic model. The AIC/BIC statistical goodness of fit for these six distributions are shown in Table 40, in addition to the landmark survival estimates. Extrapolations of TTD using each model up to 20 years is presented in Figure 33 to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

Table 40. TTD – DVd goodness of fit statistics for parametric distributions

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	-	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; DVd, daratumumab in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; TTD, time to treatment discontinuation.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Figure 33. TTD – DVd KM and parametric distributions, long-term fit

Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; KM, Kaplan Meier; TTD, time to treatment discontinuation.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Based on the AIC and BIC, exponential and Weibull are the best statistically fitting curves for DVd TTD, however, all distributions other than the log-normal can be considered comparable as they are within three AIC points (169). Gompertz has been excluded because the tail is unusually high. Both the Weibull and exponential were well aligned to the landmarks suggested by clinicians. In TA897 (CASTOR), the company and the EAG agreed with the shape of the Weibull curve to appropriately model the shape of DVd discontinuation over time (22). Based on statistical fit, long-term assessment, assessment of diagnostic plots, expert opinion, the Weibull was selected for extrapolation of DVd TTD in the base-case.

B.3.3.2.9 Other - Time to treatment discontinuation

Due to unavailability of publicised data to inform an NMA for TTD, assumptions were made to fit plausible TTD estimations for hKd and SVd. This is a common problem found in HTA, since trial TTD data is rarely publicised outside of the confidentiality of the HTA process for oncology treatments. Given the issue of data availability, three approaches were taken to modelling TTD in the CEM:

- Non-trial comparator HRs are applied to DVd TTD extrapolation using PFS HRs from the NMA versus DVd as a proxy, assuming PH of comparator TTD to DVd TTD
- PFS=TTD for non-trial comparators
- DVd TTD as a proxy for non-trial comparators; DVd KM data is used as a proxy and capped by their respective PFS HRs

GSK aligned with the first approach following advice from external clinical and economic experts that the relationship between comparator PFS and extrapolated PFS from the DREAMM-7 DVd trial arm estimated from the NMA analysis is a plausible estimation of non-trial comparator TTD versus the TTD extrapolated from the arms of the trial.

In a recent appraisal TA897 (DVd 2L) a similar approach was taken and agreed with by the EAG, while in TA917 (DRd 1L) the company assumed the second approach listed above and were prompted by the EAG to run the first approach as a scenario as TTD equivalence to PFS likely overestimates comparator TTD given some patients would have discontinued treatment but remain progression free. (22, 74) Out of the three scenarios, the most conservative option with regards to comparator TTD was assumed for base-case.

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

B.3.3.3 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.

The DREAMM-7 safety data was used to inform the AEs associated with BVd in the economic model (see Section B.2.10). For hKd and SVd, the incidence of AEs were sourced from Usmani 2023 and Bahlis 2018, respectively (176, 177).

The AEs included within the base-case CEA for BVd and DVd are presented in Table 41.

Table 41. Incidence of Grade ≥3 adverse events reported in ≥5% of patients in either the BVd and DVd from DREAMM-7

Adverse event	BVd	DVd
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Peripheral neuropathy	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Keratopathy	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]
Dry eyes	[redacted]	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DREAMM, Driving Excellence in Approaches to Multiple Myeloma; DVd, daratumumab in combination with bortezomib, and dexamethasone
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

The sum product of these incidence rates and disutilities or costs associated with AEs, described in Sections B.3.5.4, 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 (149).

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life systematic literature review

A SLR was conducted to identify HRQoL studies of patients with MM who have received at least one prior LoT. The SLR was conducted in January 2023 and updated in January 2024. Please see Appendix H for the methods used to identify relevant studies, and detailed description and of identified studies.

Overall, 146 HRQoL publications reporting patients reported outcomes and utility data for RRMM patients with at least one prior treatment were identified. A total of 100 publications reported patient reported outcome (PRO) data, of which four were from a UK perspective, with most of these studies using the EORTC QLQ-C30 questionnaire. A total of 34 publications reported utility data, of which 11 were from a UK perspective, with most eliciting values from the EQ-5D tool.

Utilities/disutilities were reported mostly for model states and adverse events, with utilities for pre-progression ranging between 0.68 to 0.78 and for post-progression health state between 0.61 to 0.72 (79). Ten publications were identified containing both PRO and utility data, of which three were from a UK perspective and used the following questionnaires: EQ-5D, EORTC QLQ-MY20, and EORTC QLQ-C30.

Out of the 146 identified in the SLR, three were selected to inform HRQoL in the economic assessment, either to inform disutilities associated with AEs or health state utilities in scenario analyses. Note that DREAMM-7 health state utility analysis results are not published and there were not captured in the SLR results. The sources selected from the SLR to inform the model were deemed the most relevant to the decision problem based on population, interventions, and recentness of publication. TA695 (163) reported pre-progression and post-progression utility values for KRd and Rd. TA897 (22) reported utility values for progression-free survival and post-progression survival for DVd, Vd and hKd. DVd and hKd values are used to inform heath state utility value scenarios in the CEM and are summarised in Table 46. TA695 (163), TA897 (22) and Brown 2013 (157) all reported adverse events utilities. These adverse event utility decrements were used to inform the CEM base-case.

B.3.4.2 Health-related quality of life data used in the cost-effectiveness analysis

Utility values were assigned to each health state in the model to capture patient HRQoL associated with treatment and outcomes. In the base-case utility values were derived from an analysis of EQ-5D-3L from DREAMM-7. 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.

The EQ-5D-3L utility data were analysed using mixed-effects linear regression, incorporating all available EQ-5D-3L measurements across all visits. The estimated regression coefficients obtained from the best fitting model were used as an estimate of the disutility resulting from progression, relative to the mean utility associated with the 'baseline profile' of progression-free patients, allowing progression-free and progressed disease health state utility values to be derived.

The utility scores before progression (i.e., progression-free state) were slightly higher than the utility scores after progression (i.e., progressed state) (Table 42). Moreover, in the fitted 2- and 3-health-state model (adjusted for baseline utility score), patients in the BVd arm indicated higher improvement in utility scores compared to DVd arm patients (Table 43 and Table 44).

Table 42. Summary of Two-State EQ-5D-3L Utility scores Model - All Visits- UK Value Set

		Estimate	SE	95% CI (lower)	95% CI (Upper)	Z-Value	P-Value	QIC
Model Estimates								
Intercept		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Utility Score		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Progression (IRC)	Progression Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Progressed	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Least Square Mean Estimates								
Progression (IRC)	Progression Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Note: EQ-5D-3L is the EuroQol-Five Dimensions Three Levels questionnaire.
Note: Intercept effect refers to effect associated with the reference category in each covariate.
Abbreviations: CI, confidence interval, EQ-5D-3L, European Quality of life-5 Dimensions 3 levels; IRC, Independent Review Committee; QIC, Quasi-likelihood under the Independence model Criterion, SE, standard error.

Table 43. Summary of Two-State EQ-5D-3L Utility scores Model with Treatment Arms - All Visits-UK Value Set

		Estimate	SE	95% CI (lower)	95% CI (Upper)	Z-Value	P-Value	QIC
Model Estimates								
Intercept		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Utility Score		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Progression (IRC)	**Progression Free**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Progressed	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Treatment	**BVd**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	DVd	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Least Square Mean Estimates								
Progression (IRC)	**Progression (IRC)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Progression (IRC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Treatment	**BVd**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Note: EQ-5D-3L is the EuroQol-Five Dimensions Three Levels questionnaire.
Note: Intercept effect refers to effect associated with the reference category in each covariate
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval, DVd, daratumumab in combination with bortezomib, and dexamethasone; EQ-5D-3L, European Quality of life-5 Dimensions 3 levels; EuroQol, European Quality of life; IRC, Independent Review Committee; QIC, Quasi-likelihood under the Independence model Criterion; SE, standard error.

Table 44. Summary of Three-State EQ-5D-3L Utility scores Model with Treatment Arms - All Visits-UK Value Set

		Estimate	SE	Lower CL	Upper CL	Z-Value	P-Value	QIC
Model Estimates								
Intercept		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Utility Score		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Progression & Response (IRC)	Progression free, in-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Progression free, no-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Progressed	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Treatment	BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	DVd	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Least Square Mean Estimates								
Progression & Response (IRC)	Progression free, in-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Progression free, no-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Treatment	BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Note: EQ-5D-3L is the EuroQol-Five Dimensions Three Levels questionnaire.
Note: Intercept effect refers to effect associated with the reference category in each covariate.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CL, Confidence Limit; DVd, Daratumumab in combination with bortezomib, and dexamethasone; EQ-5D-3L, European Quality of life-5 Dimensions 3 levels; EuroQol, European Quality of life; IRC, Independent Review Committee; QIC, Quasi-likelihood under the Independence model Criterion; SE, Standard Error.

In the base-case treatment-specific health state utility values were used for the progression-free state derived from DREAMM-7. As the DREAMM-7 trial collected utility values for BVd and DVd only, the model assumes the utility value of hKd and SVd is equal to DVd utility values derived from DREAMM-7. A scenario analysis was conducted where health state utility was assumed equal across all treatments. A summary of treatment specific health state utility values is presented in Table 45.

Table 45. Progression-free treatment-specific health-state utilities sourced from DREAMM-7

Health state	Utility	Source
PFS on-tx/off-tx *		
BVd	[redacted]	DREAMM-7 (99)
DVd	[redacted]	DREAMM-7 (99)
hKd	[redacted]	Assumed to be equal to DVd
SVd	[redacted]	Assumed to be equal to DVd
Pd	[redacted]	DREAMM-7 (99)

Note: *PFS off treatment utility values are assumed to be the same as on treatment.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; Pd, pomalidomide, and dexamethasone; PFS, progression-free survival; SVd, selinexor in combination with bortezomib, and dexamethasone;
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Additionally, the model considers the reduction in QoL of patients due to ageing by applying age-adjustment factors to health state utilities. Age-adjusted utility values are calculated by applying the general population EQ-5D weights published by Hernández Alava et al.(178). Where trial-based utility values exceed the general population age- and sex-adjusted utility values, the age-adjusted utility value are used.

There are differences amongst the DREAMM-7 utilities and previous TAs and published literature. Thus, scenario analyses were conducted where, values from TA695 (163) and TA897 (22) were used in the model (see Table 46) to account for the uncertainty characterizing the health state utility inputs. These analyses assumed equal health state utilities across all treatments.

Table 46. Model health state utility values

Source	TA695 (163)	TA897 (22)
Data Source	ASPIRE	ENDEAVOR
PFS, on treatment	0.75	0.74
PFS, off treatment	0.75	0.74
PD	0.70	0.67
Death	0.00	0.00

Abbreviations: PD, Progressed disease; PFS, Progression-free survival; TA, Technology appraisal

B.3.4.3 Adverse events

The impact of treatment-related AEs on HRQoL is incorporated in the model as a one-off QALY loss for each AE and applied on an absolute (rather than relative) basis.

AE disutilities are applied in the first cycle of treatment for patients entering the model, under the assumption that AEs are likely to occur very soon after treatment initiation and only require acute care.

Given the regularity of eye-related events in the BVd arm of DREAMM-7, the QoL measures taken in the trial are highly likely to account for HRQoL associated with these events. The EQ-5D-3L evidence from DREAMM-7 (B.2.6.1.7) show a higher QoL profile than the trial comparator arm DVd. Therefore, for eye-related events the model accounts for only the cost of ophthalmologist visits and one-off AEs costs.

A summary of the AE disutility estimates are presented in Table 47.

Table 47. Adverse events disutilities

Adverse event	Disutility	Source
Neutropenia	0.15	TA695 (163)
Anaemia	0.31	TA695 (163)
Thrombocytopenia	0.31	TA695 (163)
Lymphopenia	0.07	TA897 (22)
Pneumonia	0.19	TA695 (163)
Peripheral neuropathy	0.07	TA897 (22)
Hypertension	0.00	TA695 (163)
Leukopenia	0.07	TA510 / TA783 (151)
Nausea	0.10	TA510 / TA783 (151)
Diarrhoea	0.10	TA510 / TA783 (151)
Fatigue	0.12	TA695 (163)
Dyspnoea	0.12	TA510 / TA783 (151)

Adverse event	Disutility	Source
Back pain	0.09	Sullivan et al. (2011) (179)
Hypokalaemia	0.20	TA695 (163)

Note: A small implementation error is in the CEM for eye-related disutilities. It is applied as a one-off event in the first cycle. GSK intended to remove this from the model, however, it has no impact on results.
Abbreviations: CEM, cost-effectiveness model; GSK, GlaxoSmithKline; TA, Technology appraisal
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

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. Costs in the model included:

- Treatment costs, including drug acquisition and administration costs for both 2L (applied for the duration of active treatment) and subsequent lines of treatment
- Costs of disease management and monitoring
- Costs of adverse event
- Terminal care costs

Unit costs were obtained from routinely collected evidence sources, such as NHS reference costs 2021/22 (180), the British National Formulary (BNF) (181-188), and Personal Social Services Research Unit (PSSRU) 2023 (189). The economic SLR described in Section B.3.1 and Appendix I also identified relevant cost and resource use studies from the published literature.

B.3.5.1 Drug acquisition and administration costs

B.3.5.1.1 Drug unit costs

Belamaf is available as 100mg and 70mg powder for concentration for solution for infusion at a list price of £[redacted] and £[redacted], respectively, pending confirmation with the Department of Health and Social Care. For comparators, the unit size, pack size and cost per pack are sourced from the BNF (182-188). Where multiple unit costs/sizes are available, the available formulations were checked for consistency across price per mg. If treatment costs were inconsistent across per mg price, the pack size and dose most aligned to the comparator dosing regimen were selected.

Drug acquisition costs are applied in line with the treatment cycle length for each comparator as per the dosing schedule (Section B.3.5.1.2) until treatment discontinuation.

Unit costs applied for each drug are presented in Table 48.

Table 48. Drug acquisition costs (List)

Drug	Unit size (mg)	Pack size (number of units)	Cost per pack (£)	Unit cost (list price) (£)	Source
Belamaf (100mg vial)	100	1	[redacted]	[redacted]	GSK
Belamaf (70mg vial)	70	1	[redacted]	[redacted]	GSK
Bortezomib	1	1	217.82	217.82	BNF (182)
Dexamethasone	20	10	20.00	2	BNF (183)
Daratumumab	100	1	360.00	360.00	BNF (184)
High-dose carfilzomib	60	1	1,056.00	1,056.00	BNF (185)
Selinexor	20	8	3,680.00	460.00	BNF (186)
Pomalidomide	4	21	8,884.00	423.05	BNF (187)
Isatuximab	100	1	506.94	506.94	BNF (188)

Abbreviations: BNF, British National Formulary; GSK, GlaxoSmithKline.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.5.1.2 Dosing

For all treatments, the model is flexible to include or exclude treatment wastage. In the model base-case, wastage is included to resemble UK clinical practice. The model does not, however, allow for vial sharing due to the difficulties in quantifying how this may reduce wastage in real world practice. Wastage in the model is therefore likely to be overestimated, and so a scenario without wastage is included in the scenario analysis. When wastage is considered, method of moments (MoM) calculations derive the number of vials needed per treatment cycle based on the distribution of patients' weight or body surface area (BSA) from individual patient-level weight data from DREAMM-7. Wastage was applied to 100% of administrations. SmPC aligned dosing for each drug included in the drug acquisition costs are presented in Table 49.

Table 49. Details of treatment administration of BVd and its comparators, based on the Summary of product characteristics (SmPC)

Regimen	Drug	Treatment cycle	Dose
BVd	Belamaf	All treatment cycles	2.5mg/kg
	Bortezomib	Treatment cycles 1-8	1.3mg/m^2
	Dexamethasone	Treatment cycles 1 - 8 (days 1,2, 4, 5, 8, 9, 11 and 12)	20mg
hKd	High-dose carfilzomib	Treatment cycle 1 (days 1 and 2)	20mg/m^2
		Treatment cycle 1 (days 8, 9, 15 and 16)	56mg/m^2
		Treatment cycle 2+ (days 1, 2, 8, 9, 15 and 16)	56mg/m^2
	Dexamethasone	All treatment cycles (1, 2, 8, 9, 15, 16, 22 and 23)	20mg
SVd	Selinexor	All treatment cycles (days 1, 8, 15, 22, 29)	100mg
	Bortezomib	All treatment cycles (days 1, 8, 15, 22)	1.3mg/m^2
	Dexamethasone	All treatment cycles (days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30)	20mg
DVd	Daratumumab	Treatment cycles 1-3 (days 1, 8 and 15)	16mg/kg
		Treatment cycles 4-8 (day 1 only)	16mg/kg
		Treatment cycles 9+ (day 1 only)	16mg/kg
	Bortezomib	Treatment cycles 1-8 (days 1, 4, 8 and 11)	1.3mg/m^2
	Dexamethasone	Treatment cycles 1-8 (days 1, 2, 4, 5, 8, 9, 11 and 12)	20mg

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, High-dose carfilzomib and dexamethasone; IhKd, Isatuximab in combination with high-dose carfilzomib, and dexamethasone; m, metre; mg, milligram; SmPC, Summary of product characteristics; SVd, selinexor in combination with bortezomib, and dexamethasone
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Dose delays and reductions are key modifications in clinical practice to manage toxicity and tolerability of active MM therapies. For all comparators in the model besides BVd, a constant RDI was used to capture the impact of dose alterations in the model and align treatment costs to actual doses received by patients. For BVd, individual patient-level data (IPD) was used to track the doses received by patients over time (see Section B.3.5.1.2.1).

For BVd and DVd, RDI is sourced from DREAMM-7. For all other comparators, RDI is sourced from publications of key clinical trials. If not available, it was assumed that the actual dose patients receive is equal to labelled doses presented in Table 50 (i.e., RDI = 100%). RDI values are applied by multiplying the RDI by the dose recommended in the administration schedule. RDI values are presented in Table 50.

Table 50. Relative dose intensity

Drug	RDI	Source
Belamaf (100mg vial)	[redacted]	DREAMM-7 CSR (99)
Belamaf (70mg vial)	[redacted]	
Bortezomib	[redacted]	
Dexamethasone	[redacted]	
Daratumumab	[redacted]	
High-dose carfilzomib	91%	TA695 (148)
Selinexor	100%	Assumed as 100%
Pomalidomide	90%	STRATUS (MM-010) (190)
Isatuximab	92%	ICARIA-MM

Abbreviations: CSR, Clinical study report; mg, milligram; RDI, Relative dose intensity
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.5.1.2.1 Belamaf IPD dosing

Belamaf dosing in BVd is based on IPD from the DREAMM-7 trial. This was due to the time-variable trend identified for the RDI of belamaf. Figure 34 outlines how the RDI of belamaf changes over time, with a strong indicator that dose delays and dose reductions increase over time the longer patients are on treatment. Figure 34 shows that when accounting for patients dropping out during the time intervals, the trend is still clear.

Using the standard mean RDI approach would therefore artificially inflate the costs of belamaf by assuming the average actual doses during the trial period are extrapolated over the remainder of the time horizon for patients on-treatment. IPD was therefore directly modelled to account for this time variable trend and more accurately depict the actual doses of belamaf administered to patients. For comparators treatments, RDI was high (>90%, closely aligning to SmPC dosage) and so time variation of RDI would likely not impact treatment costs.

Figure 34. DREAMM-7 - Dose intensity by 6-month time interval (Restricted to subjects who are not dropping out during a time interval)

[redacted]

In the base-case, IPD provided weekly data for belamaf dosage detailing the number of patients on treatment, the number of patients receiving any belamaf dose and number of patients receiving each belamaf dose. For each weekly cycle, the cost of the distribution of doses received from patients on treatment from DREAMM-7 is applied to the proportion of patients on-treatment estimated from the TTD extrapolation to inform the belamaf acquisition cost per cycle. When patients on treatment in DREAMM-7 was reduced to 50 patients, an assumption was taken that the distribution of doses received was extrapolated through the remainder of the model time horizon. This assumption avoids destabilised estimates when the number of

patients on treatment is low. It is, however, a conservative assumption, since this assumes a capping of the downwards trend in RDI over time seen in the trial.

The belamaf dosing calculations also use the same MoM as the other comparators with constant dose and RDI, to appropriately model wastage with each received dose (<1.7mg/kg – 2.7mg/kg). Administration costs for belamaf are also aligned to the patients receiving treatment in the IPD.

In the absence of data to inform the belamaf acquisition cost for doses <1.7 mg/kg and >2.7 mg/kg, the model assumes patients incur the same acquisition cost as 1.7 mg/kg and 2.7 mg/kg, respectively, although this assumption has little impact given a very small amount of these doses were given in the IPD.

As mentioned in section B.3.5.1, the model includes the functionality to use the SmPC doses instead of the actual dose received. In this scenario, the belamaf acquisition cost for each dose is as per the closest labelled doses from the belamaf SmPC of 1.9 mg/kg and 2.5 mg/kg. Costing as per the SmPC assumes actual doses of 1.7-2.1 mg/kg and 2.2-2.7 mg/kg incur the acquisition cost of 1.9 mg/kg and 2.5 mg/kg doses, respectively.

B.3.5.1.2.2 Wastage

For all interventions and comparators, the model includes functionality to include or exclude wastage, defining the proportion of administrations with wastage. When wastage is assumed, MoM calculations derive the number of vials needed per cycle based on weight or BSA. Wastage is included in the model base-case. In the base-case, wastage is applied to 100% of administrations.

For oral treatments, when wastage is not included, the acquisition cost is calculated by multiplying the cost per unit (capsule) by the unrounded number of capsules per dose without RDI applied. When wastage is included, the acquisition cost is calculated by multiplying the cost per unit (capsule) by the number of capsules per dose without RDI applied rounded up to the nearest whole capsule.

For IV and SC treatments, when wastage is not included the acquisition cost is calculated by multiplying the cost per unit (vial) by the unrounded number of vials required per dose. When wastage is included, the model uses MoM. This uses the distribution of patients' weight and BSA from the DREAMM-7 trial (99, 167), and dose to determine the number of vials required for treatment. In the base-case, the dose for belamaf is not adjusted by RDI as IPD are used to inform dosing, but for comparators the dose is adjusted by RDI prior to MoM calculations.

The MoM calculation assumes the patients' weight and BSA are normally distributed to calculate the distribution of the dose received per cycle. The cost of vials dose is calculated by multiplying the number of whole vials required by the unit cost. The weighted cost of vials is calculated by multiplying the cost of vials by the distribution for each dose of each dose. The sum of the weighted cost per vial calculated the MoM Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

acquisition cost per administration. An example of the belamaf (2.5 mg/kg dose) MoM calculation with only the 100mg vial available is presented in Table 51 at belamaf Patient Access Scheme (PAS) price without accounting for RDI.

Table 51. Belamaf (2.5 mg/kg dose) method of moments example calculation

Dosing (mg)	Distribution	Number of 100 mg vials	Cost of vials (£)
100	0.001	1	[redacted]
200	0.607	2	[redacted]
300	0.378	3	[redacted]
400	0.014	4	[redacted]
500	0.000	5	[redacted]
Method of moments acquisition cost per administration			[redacted]

Abbreviations: kg, kilogram; mg, milligram
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

The acquisition cost per treatment cycle is calculated as follows:

Acquisition cost per treatment cycle = method of moments acquisition cost per administration administrations per cycle*

For belamaf only, both 70mg and 100mg vials are available. The MoM therefore optimises the dosage between these vial sizes to decrease the wastage to align with clinical practice.

The total treatment cost per cycle is calculated as follows:

Treatment cost per treatment cycle = acquisition cost per treatment cycle + administration cost per treatment cycle

In the model trace, the cost per treatment cycle is applied in the first model cycle of each treatment cycle, besides BVd where IPD accounts for delays to dosage continuously throughout the model.

B.3.5.1.3 Drug administration costs

Treatments can be administered orally, via a SC or IV. For an IV administration, the administration unit cost depends on whether it is a first administration in a treatment cycle, or a subsequent administration, and on the complexity of the infusion.

IV administration complexity was defined as per the Department of Health reference costs and guidance 2011/12 (191) as follows:

- Simple infusion: 30-60 minutes of chair time.
- Complex infusion is defined as 60-120 minutes of chair time.

- Complex prolonged infusion as over 120 minutes of chair time.

For oral treatments, no treatment administration costs are assumed. For drugs that are administered intravenously or subcutaneously, administration unit costs are included based on the NHS reference costs 2021/2022 (180). Costs of administration are presented in Table 52.

Table 52. Unit cost of administration

Treatment	Admin cost (£)	Source
Subcutaneous administration: Specialist Nursing, Cancer Related, Adult, Face to face	119.00	NHS reference code: N10AF
IV treatment: First administration in a treatment cycle (simple infusion)	286.71	NHS reference code: SB12Z
IV treatment: First administration in a treatment cycle (complex infusion)	353.64	NHS reference code: SB13Z
IV treatment: First administration in a treatment cycle (complex prolonged infusion)	474.94	NHS reference code: SB14Z
IV treatment: Subsequent administrations in a treatment cycle	368.44	NHS reference code: SB15Z
Oral treatment	0.00	Assumed to be 0

Abbreviations: IV, Intravenous; NHS, National health services.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

Administration schedules are sourced from the DREAMM-7 CSR for BVd and DVd as well as relevant clinical trials for other comparator regimens. The administration schedules for the intervention regimen and its comparators are presented in Table 53.

Table 53. Administration schedules

Regimen	Drug	Treatment cycle	Treatment cycle duration (days)	Dose	Admin method	Admins per treatment cycle
BVd	Belamaf	All treatment cycles	21	2.5mg/kg	IV-Simple	1
	Bortezomib	Treatment cycles 1-8	21	1.3mg/m^2	SC	4
	Dexamethasone	Treatment cycles 1 - 8 (days 1,2, 4, 5, 8, 9, 11 and 12)	21	20mg	Oral	8
hKd	High-dose carfilzomib	Treatment cycle 1 (days 1 and 2)	28	20mg/m^2	IV-Simple	2
		Treatment cycle 1 (days 8, 9, 15 and 16)	28	56mg/m^2	IV - Simple	4
		Treatment cycle 2+ (days 1, 2, 8, 9, 15 and 16)	28	56mg/m^2	IV - Simple	6
	Dexamethasone	All treatment cycles (1, 2, 8, 9, 15, 16, 22 and 23)	28	20mg	Oral	8
SVd	Selinexor	All treatment cycles (days 1, 8, 15, 22, 29)	35	100mg	Oral	5
	Bortezomib	All treatment cycles (days 1, 8, 15, 22)	35	1.3mg/m^2	SC	4
	Dexamethasone	All treatment cycles (days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30)	35	20mg	Oral	10

Regimen	Drug	Treatment cycle	Treatment cycle duration (days)	Dose	Admin method	Admins per treatment cycle
DVd	Daratumumab	Treatment cycles 1-3 (days 1, 8 and 15)	21	16mg/kg	SC	3
		Treatment cycles 4-8 (day 1 only)	21	16mg/kg	SC	1
		Treatment cycles 9+ (day 1 only)	28	16mg/kg	SC	1
	Bortezomib	Treatment cycles 1-8 (days 1, 4, 8 and 11)	21	1.3mg/m^2	SC	4
	Dexamethasone	Treatment cycles 1-8 (days 1, 2, 4, 5, 8, 9, 11 and 12)	21	20mg	Oral	8

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, High-dose carfilzomib and dexamethasone; IV, Intravenous; kg, kilogram; m, meter; mg, milligram; SC, Subcutaneous; SVd, selinexor in combination with bortezomib, and dexamethasone
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.5.1.4 Drug acquisition and administration summary

A summary of the total acquisition and admin costs used in the model for the comparators is included in the Table 54 below for each combinations relevant treatment cycle. For cycles 2+, BVd acquisition and admin costs dependent on dose delays and reductions in the IPD.

Table 54. Summary of acquisition and administration costs

Intervention	Treatment cycle	Cost per treatment cycle (£) (No wastage)			Cost per treatment cycle (£) (Wastage)		
		Acquisition	Admin	Total	Acquisition	Admin	Total
BVd	1 (Q3W)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2+ (Q3W)	Variable based on IPD					
hKd	1 (Q4W)	8,024.09	2128.93	10,153.02	10,754.58	2,128.93	12,883.52
	2+ (Q4W)	10,208.66	2128.93	12,337.59	12,955.84	2,128.93	15,084.78
SVd	All cycles (Q5W)	12,416.66	476.02	12,892.67	13,623.03	476.02	14,099.05
DVd	1-3 (Q3W)	14,683.94	595.02	15,278.96	15,617.40	595.02	16,212.42
	4-8 (Q3W)	6,042.45	476.02	6,518.46	6,618.49	476.02	7,094.50
	9+ (Q4W)	4,320.75	119.00	4,439.75	4,499.46	119.00	4,618.46

Note:IPD is used for belamaf dosing, therefore the costs presented are the average cost across all treatment cycles.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone;; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, High-dose carfilzomib and dexamethasone; Q(X)W, X week cycle length; SmPC, Summary of product characteristics; SVd - Selinexor plus bortezomib and dexamethasone;.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.5.2 Subsequent Treatments

Given that patients with MM receive multiple LoTs, and prior therapies received have an impact on the future treatment pathway, subsequent treatments are an important aspect to capture in cost-effectiveness assessments. This dependency creates a challenge, as given the global scope of the trial, subsequent treatments are based on differing MM treatment pathways.

Given the lacking information for detailed modelling approaches of subsequent treatment, a simplified approach was taken in the cost-effectiveness analysis. Patients progressing from the initially modelled treatment continue in the model to use a basket of potential treatment options, which are applied as a one-off cost, similar to previous MM submissions (22, 74). The distribution of subsequent treatment options was elicited from external expert feedback.

Cost of subsequent treatments were captured for up to two lines of subsequent therapy. The one-off subsequent treatment cost is calculated using the proportion of patients who received a first and second subsequent line of treatment, the distribution of first and second subsequent treatments required for each treatment arm, and the treatment cost of each subsequent treatment.

Relevant costs of regimens used in subsequent lines of treatments are sourced from the BNF for patients who received subsequent treatments upon progression to manage their disease. As patients with MM typically receive treatment until death, median OS of 9 months for third and later line patients was assumed to be a reasonable proxy for the median duration of subsequent treatments, sourced from Kumar et al. (192) as per TA897 (22). The treatment costs for each subsequent treatment are summarised in Appendix K.

The proportion of patients on BVd and DVd who progress and start a subsequent treatment was collected in the DREAMM-7 study. However, results of the study showed that despite an improved PFS and OS observed in DREAMM-7 only [redacted]% of patients in the BVd arm received a first line of subsequent treatment, while the equivalent proportion of patients in the DVd arm was [redacted]%, which can be potentially attributed to the immaturity of this data. Hence, the proportion of patients who received a first and second line of subsequent treatment was informed by Raab (2019) (47) in the base-case, while a scenario was conducted using estimates from Yong (2016) (46). The proportion of patients who received a first and second line of subsequent treatment was assumed to be the same across all comparators in the model.

The proportion of patients requiring subsequent treatment is summarised in Table 55.

Table 55 . Proportion of patients who require subsequent treatment, as included in the base case of the cost-effectiveness model

Treatment arm	Proportion of patients (first subsequent treatment)	Proportion of patients (second subsequent treatment)
BVd	81%	34%
hKd	81%	
SVd	81%	
DVd	81%	

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, High-dose carfilzomib and dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone
Source: Raab (2019) (47)

Choice of treatment is dependent on prior treatments received as well as a multitude of other patient characteristics such as frailty, ability to tolerate treatment toxicity, aggressiveness of the disease and patient choice (72). The diversity of the feedback elicited from the EEs on the estimations of subsequent treatment distributions following 2L therapy characterises the complexity of the MM pathway and the fast-evolving SoC.

Treatment with BVd versus DVd will benefit the future treatment pathway, increasing the availability of treatment options following 2L therapy. Patients who have not yet received treatment with an anti-CD38 targeting therapy are more likely to receive isatuximab in combination with pomalidomide, and dexamethasone (IsaPd) or Daratumumab monotherapy in 4L.

Analysis of the discussions with each clinician showed the EEs aligned to three scenarios for distribution of subsequent treatments following 2L:

- EE1 identified the likely future pathway with patients who receive DRd in 1L filtering down throughout the pathway. Hence, due to increased usage of an anti-CD38 in 1L, there will be limited and reduced use of isatuximab and daratumumab in subsequent therapy. Use of subsequent pomalidomide following 2L therapy highlighted the real-world UK practice of line-skipping of 3L therapies to treat patients with 4L treatments where more choices are available for patients for whom lenalidomide treatment is unsuitable.
- EE2 aligned their feedback to current patients in the pathway, with use of daratumumab monotherapy and IsaPd evident in subsequent therapy. Use of 4L therapy subsequent to 2L treatments again highlighted evidence of bridging of 3L treatments.
- EE3 aligned their feedback to precisely the NICE pathway guidance. For patients for whom lenalidomide is unsuitable, only PanoVd is available at 3L and so 100% of patients receive this combination, disregarding any real-world practice of line skipping.

B.3.5.2.1 First subsequent treatment

Given the three scenarios provided by clinicians, GSK have included the subsequent treatments estimations from EE2 in the cost-effectiveness model base case, as these values closely align with the NICE HTA guidance of centring the evidence on current clinical practice (160). The two other scenarios are included as scenario analyses.

These values were adjusted to fit the target population of patients for whom lenalidomide treatment is unsuitable. A limitation of these estimates is that SVd was not NICE approved at the time of the expert elicitation, and so subsequent SVd in 3L is not present. The distribution of the subsequent treatments population in the model are outlined in Table 56 below.

Table 56. Distribution of first subsequent treatments across treatment arms, as included in the base case of the cost-effectiveness model

Subsequent treatment	Treatment arm			
	BVd	hKd	SVd	DVd
Dara	8.6%	8.6%	8.6%	1.1%
IxaRd	0%	0%	0%	0%
Pd	16.1%	16.1%	16.1%	61.3%
IPd	43.0%	43.0%	43.0%	5.4%
PanoVd	32.3%	32.3%	32.3%	32.3%
Palliative chemotherapy	0%	0%	0%	0%
Kd	0%	0%	0%	0%
Rd	0%	0%	0%	0%

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; Dara, Daratumumab; DVd, daratumumab in combination with bortezomib, and dexamethasone; IPd, Isatuximab + pomalidomide + dexamethasone; IxaRd, Ixazomab + lenalidomide +dexamethasone; hKd, high dose carfilzomib + dexamethasone; Kd, carfilzomib and dexamethasone PanoVd, Panobinostat + bortezomib + dexamethasone; Pd, Pomalidomide + dexamethasone; Rd, Lenalidomide +dexamethasone; SVd, Selinexor in combination with bortezomib, and dexamethasone

Source: Porteous et al. (2023) (193)

B.3.5.2.2 Second subsequent treatment

The three EEs closely aligned with their estimated treatment distributions following 3L, with the majority of patients receiving pomalidomide-based therapies. A weighted average of the three clinicians was used to estimate treatment distribution of subsequent therapies after 3L.

Due to some clinicians recommending 4L treatments following 2L (after bridging therapy at 3L due to lack of suitable treatment options), assumptions were made to estimate treatments received for patients who had now received 4L therapy after 2L (and are thus receiving therapies approved in 5L as a second subsequent treatment): Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

- In the NICE guidance, only Pd and PanoVd are available in 5L. Selinexor plus dexamethasone (Sd) was only approved by NICE after the expert engagement took place and so it was not included in the discussions with clinicians.
- Patients receiving IsaPd after 2L treatment are unlikely to receive another pomalidomide regimen, and so 100% of these patients receive the only option available; PanoVd. This assumption is replicated with patients receiving Pd in 4L.
- Patients receiving 4L Daratumumab monotherapy following 2L can only receive either PanoVd or Pd as per the NICE guidance. The distribution of treatment received was assumed to be a reweighted average of the split between PanoVd and Pd from the available post-3L estimations from 3L treatments which do not contain pomalidomide with the following rationale:
    - Patients receiving 2L therapy and bridging to 4L Daratumumab mono could not yet have received a pomalidomide-based therapy as per NICE guidance.
    - Preference for pomalidomide treatment when available was evident from the EE feedback.
    - These estimates have face validity with the treatment choice logic expressed by the EEs, that if patients at 5L have not yet received pomalidomide-based treatment the vast majority would then then receive Pd.

Distributions are included in Table 57 below for subsequent treatments following 3L/4L.

Table 57. Distribution of subsequent treatments following 3L (of 4L if bridging)

Subsequent treatments	Treatments received			
	IsaPd (4L)	Dara mono (4L)	Pd (4L)	PanoVd (3L)
Rd	0.0%	0%	0.0%	0%
PanoVd	100.0%	6.4%	100.0%	0%
Pd	0.0%	93.6%	0.0%	81.4%
Dara mono	0.0%	0.0%	0.0%	11.8%
IsaPd	0.0%	0.0%	0.0%	6.8%

Abbreviations: 3L, third-line; 4L, fourth-line; Rd, Lenalidomide plus dexamethasone; IsaPd, Isatuximab in combination with pomalidomide, and dexamethasone; Dara mono, Daratumumab monotherapy; Pd, Pomalidomide plus dexamethasone; PanoVd, Panobinostat plus bortezomib and dexamethasone; BVd, belamaf in combination with bortezomib, and dexamethasone;

For the second line of subsequent treatment experts' responses were averaged and normalised based on the first line of subsequent treatment received in the model. The distributions for the second subsequent treatments are presented in Table 58.

Scenario analyses are conducted informing the distribution of treatments in the first and second line of subsequent treatment based on responses from clinical expert 1, clinical expert 3, and estimates reported by Porteous et al (2023) (193). The latter reports the proportion of patients receiving individual subsequent (3L+) lines of treatment for DVd and Kd. The DVd results inform the DVd distributions for first and second subsequent treatments. The Kd results inform the distributions for all other comparators for first and second subsequent treatments.

Table 58. Distribution of second subsequent treatments across treatment arms, as included in the base case of the cost-effectiveness model

Subsequent treatment	Treatment arm			
	BVd	hKd	SVd	DVd
D	3.8%	3.8%	3.8%	3.8%
IxaRd	0.0%	0.0%	0.0%	0.0%
Pd	34.3%	34.3%	34.3%	27.3%
IPd	2.2%	2.2%	2.2%	2.2%
PanoVd	59.7%	59.7%	59.7%	66.7%
Palliative chemotherapy	0.0%	0.0%	0.0%	0.0%
Kd	0.0%	0.0%	0.0%	0.0%
Rd	0.0%	0.0%	0.0%	0.0%

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; D, Daratumumab; DVd, daratumumab in combination with bortezomib, and dexamethasone; IPd, Isatuximab + pomalidomide + dexamethasone; IxaRd, Ixazomab + lenalidomide +dexamethasone; hKd, high dose carfilzomib + dexamethasone; Kd, carfilzomib and dexamethasone; PanoVd, Panobinostat + bortezomib + dexamethasone; Pd, Pomalidomide + dexamethasone; Rd, Lenalidomide +dexamethasone; SVd, Selinexor in combination with bortezomib, and dexamethasone
Source: Porteous et al. (2023) (193)

A summary of one-off subsequent treatment costs applied in the model is presented in Table 59.

Table 59. Summary of subsequent treatment costs

Treatment arm	First subsequent treatment cost (£)	Second subsequent treatment cost (£)
BVd	85,702.58	79,412.48
hKd	85,702.58	79,412.48
SVd	85,702.58	79,412.48
DVd	84,441.02	78,815.62

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, High-dose carfilzomib + dexamethasone; SVd, Selinexor + bortezomib + dexamethasone
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.5.3 Disease management costs

Patients receiving RRMM treatments require symptom management and frequent monitoring, including outpatient visits, imaging procedures, and diagnostic procedures. Treatment-specific symptom management and monitoring resource use is informed based on clinical expert opinion elicited from three EEs for the frequency of follow-up care for progression-free patients (on and off treatment) and post-progression. All three EEs aligned on that the almost all resource use is bound to the respective treatment cycles of the comparators (Appendix O). Ophthalmologist visits, however, are exclusive to patients receiving belamaf in the BVd treatment arm and were additionally assumed to be required for the first four treatment cycles as per the draft SmPC (5).

Given the commonality of dose delays for the belamaf component of BVd, there is the likelihood this would result in reduced disease management costs for long-term patients on-treatment who are only treated with the belamaf component after 8 treatment cycles. In addition, clinical expert opinion stated resource use may be less frequent after the first six months. Three-weekly resource use for BVd was therefore a conservative assumption for the model base-case. A scenario analysis was therefore conducted in which frequency of symptom management and monitoring resources were assumed sourced from TA897 (22) and were assumed to be equal across all comparators.

Unit costs for each resource are derived from NHS reference costs (180). All relevant symptom management and monitoring costs were included in the model.

The monitoring cost for each treatment are 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 The unit costs of identified monitoring and symptom management resources were derived from NHS reference costs 2021/22 (180).

Table 60 below summarises the health-state-specific disease management costs per cycle applied in each model cycle for each treatment arm.

Table 60. Costs associated with routine monitoring and management of MM

Healthcare resource	Unit cost (£)	Health state	Resource use per model cycle				Unit cost Source
			BVd	hKd	SVd	DVd	
Haematologist visit	209.41	PFS (on-tx)	0.33	0.25	0.20	0.25	NHS code WF01A (180)
		PFS (off-tx)	0.25	0.25	0.25	0.25	
		PD	0.25	0.25	0.25	0.25	
Full blood count	2.96	PFS (on-tx)	0.33	0.25	0.20	0.25	NHS code DAPS05 (180)
		PFS (off-tx)	0.25	0.25	0.25	0.25	
		PD	0.25	0.25	0.25	0.25	
Biochemistry	1.55	PFS (on-tx)	0.33	0.25	0.20	0.25	NHS code DAPS04 (180)
		PFS (off-tx)	0.25	0.25	0.25	0.25	
		PD	0.25	0.25	0.25	0.25	
Protein electrophoresis	1.55	PFS (on-tx)	0.33	0.25	0.20	0.25	NHS code DAPS04 (180)
		PFS (off-tx)	0.25	0.25	0.25	0.25	
		PD	0.25	0.25	0.25	0.25	
Immunoglobin	1.55	PFS (on-tx)	0.33	0.25	0.20	0.25	NHS code DAPS04 (180)
		PFS (off-tx)	0.25	0.25	0.25	0.25	
		PD	0.25	0.25	0.25	0.25	
Serum-free light chain	1.55	PFS (on-tx)	0.33	0.25	0.20	0.25	NHS code DAPS04 (180)
		PFS (off-tx)	0.25	0.25	0.25	0.25	

Healthcare resource	Unit cost (£)	Health state	Resource use per model cycle				Unit cost Source
			BVd	hKd	SVd	DVd	
		PD	0.25	0.25	0.25	0.25	
Ophthalmologist	143.93	PFS (on-tx)	0.33	0.00	0.00	0.00	WF01A (180)
		PFS (off-tx)	0.00	0.00	0.00	0.00	
		PD	0.00	0.00	0.00	0.00	
Total health state cost per model cycle (£)		PFS (on-tx)	72.85 (+47.98 for the first 4 treatment cycles)	54.64	43.71	54.64	
		PFS (off-tx)	54.64	54.64	54.64	54.64	
		PD	54.64	54.64	54.64	54.64	

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab; hKd, high-dose carfilzomib and dexamethasone; MM, Multiple myeloma; NHS, National Health Services; PD, Progressed disease; PFS, Progression-free survival; SVd, Selinexor in combination with bortezomib, and dexamethasone; tx, treatment.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

B.3.5.4 Adverse events costs

The model considers how treatment-related AEs impact the costs and QoL of patients receiving all relevant comparators. In line with existing cost-effectiveness analyses in MM (for example, NICE TA897, the CEM considered Grade ≥3 AEs only (22). AE incidence data for BVd and DVd are sourced from DREAMM-7. AE incidence data for comparator treatments are sourced from their respective RCTs, as identified in the clinical SLR, and are presented in Table 61.

Table 61. Grade ≥3 AE incidence

Adverse event	Incidence			
	BVd	hKd	SVd	DVd
Neutropenia	[redacted]	7%	19%	[redacted]
Anaemia	[redacted]	16%	4%	[redacted]
Thrombocytopenia	[redacted]	16%	31%	[redacted]
Lymphopenia	[redacted]	7%	0%	[redacted]
Pneumonia	[redacted]	9%	0%	[redacted]
Peripheral neuropathy	[redacted]	1%	0%	[redacted]
Hypertension	[redacted]	18%	0%	[redacted]
Leukopenia	[redacted]	0%	0%	[redacted]
Nausea	[redacted]	1%	0%	[redacted]
Diarrhoea	[redacted]	1%	4%	[redacted]
Fatigue	[redacted]	5%	23%	[redacted]
Dyspnoea	[redacted]	3%	0%	[redacted]
Back pain	[redacted]	1%	0%	[redacted]
Hypokalaemia	[redacted]	3%	0%	[redacted]

Abbreviations: AE, Adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, High-dose carfilzomib and dexamethasone; SVd, Selinexor in combination with bortezomib and dexamethasone.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) (162)

As AEs have a minor impact on the cost-effectiveness results, a simple naïve comparison of AEs was conducted. Treatment-related AEs (Grade ≥3) are incorporated as one-off events and the impact is attributed to the first cycle of treatment for patients entering the model, under the assumption that AEs are likely to occur very soon after treatment initiation and only require acute care. The unit costs Grade ≥3 AEs were sourced from the NHS reference costs 2021/2022 (180) and are presented in Table 62.

Table 62. Grade ≥3 AE unit costs

Adverse event	Unit cost (£)
Neutropenia	1,772.97
Anaemia	1,439.66
Thrombocytopenia	2,163.16
Lymphopenia	1,772.97
Pneumonia	2,505.31
Peripheral neuropathy	1,342.94
Hypertension	781.13
Leukopenia	1,772.97
Nausea	824.90
Diarrhoea	1,446.84
Fatigue	824.90
Dyspnoea	241.01
Back pain	1,118.92
Hypokalaemia	2,639.41

Abbreviation: AE, Adverse event

Source: NHS reference costs 2021/2022 (180)

Grade ≥3 Eye-related side effects are also included, however, given the specificity of corneal events to belamaf, these AEs are applied only to the BVd arm as a one-off cost.

The eye-related side effects considered are keratopathy, blurred vision and dry eyes. Incidence and units costs for keratopathy is informed by DREAMM-7 (161) and NHS reference costs (180), respectively. Incidence and units costs for blurred vision and dry eyes are assumed to be the same as keratopathy. Incidence and unit costs for Grade ≥3 are presented in Table 63 and Table 64, respectively.

Table 63. Eye-related side effects incidence

Eye-related adverse event	Grade ≥3 incidence	Source
Keratopathy	[redacted]	DREAMM-7 (161)
Blurred vision	22%	
Dry eyes	7%	

Abbreviations: AE, Adverse event

Table 64. Eye-related side effects unit costs

Eye-related adverse event	Grade ≥3-unit cost (£)	Source
Keratopathy	29.18	NHS code WF01B (180)
Blurred vision	29.18	Assumed the same as keratopathy
Dry eyes	29.18	Assumed the same as keratopathy

Abbreviations: AE, Adverse event; NHS, National Health Services

A summary of AEs costs is presented in the Table 65 below.

Table 65. Summary of total AE costs

Total AE costs	BVd	hKd	SVd	DVd
AE (non-ocular) - One-off costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
AE (ocular) one-off cost (£)	[redacted]	-	-	-

Abbreviations: AE, Adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; SVd, Selinexor in combination with bortezomib, and dexamethasone

B.3.5.5 End-of-life costs

Terminal care costs are applied as a one-off cost of £12,397.00 to all patients who transition to the death health state (189).

B.3.6 Severity

A severity weighting was not applicable for this submission based on the expected total QALYs for the general population and for those living with the condition with current treatment.

To calculate the absolute QALY shortfall, the total QALYs that individuals living with a condition would be expected to have with current treatment were subtracted from the expected total QALYs for the general population, based on NICE's health technology evaluation guidance development manual. For the calculation of expected total QALYs for the general population, survival data from the 2018-20 National life tables for England and Wales from the Office for National Statistics (ONS) (194) were used, while population EQ-5D-3L data by age and sex were derived from the HSE 2014 dataset, as recommended in the NICE DSU report by Hernández Alava et al. (2022) (178). QALYs were discounted using the reference case annual discount rate of 3.5% for health outcomes.

The features of the population used in the QALY shortfall analysis are summarized in Sections B.3.2.2 and B.3.2.4. Health state benefits and utility values used for the QALY shortfall analysis were derived directly from the model calculations. Based on the absolute and proportional shortfalls of comparator treatments being less than 12 and 0.85, respectively, the QALY weighting for severity assigned was '1' (Table 66). No QALY shortfall was reported in TA897, TA974, so a comparison with previous submissions was not completed (Table 67) ((22, 29).

Table 66. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to Section in submission
Sex distribution	55% male	B.3.2.2
Starting age	64	B.3.2.2

Table 67. Summary of QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
SVd	[redacted]	[redacted]	[redacted]	[redacted]
DVd	[redacted]	[redacted]	[redacted]	[redacted]
hKd	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; QALY, quality adjusted life year; SVd, selinexor in combination with bortezomib, and dexamethasone.

B.3.7 Uncertainty

Due to the nature of MM and the necessity for successive treatments to be planned based on patients' experience with previous exposure to treatments and their tolerance of side effects, treatment pathways are complex and highly individualized. Additionally, treatment decisions are influenced not only by the relative efficacy at the current line of treatment but also by how this exposure might impact opportunities for effective treatments later in the pathway. This submission aims to address uncertainties in subsequent treatments received in the treatment pathway following 2L treatment.

Considering that head-to-head comparative efficacy evidence were available only between BVd and DVd based on a median follow-up of 28.24 follow-up, there is also pronounced uncertainty in the projection of OS in the longer-term, as well as in the comparative efficacy compared to SVd and hKd. A set of methods have been considered within this submission to minimize this uncertainty as described in Section B.3.11 and Appendix O.

Finally, there was paucity of evidence in terms of the types and frequency of resource use and distribution of subsequent treatments received. UK EE opinion was sought to inform assumptions around these model parameters.

Uncertainty around the aforementioned model parameters is explored in Section B.3.11 to determine the impact of different scenarios related to these parameters on the cost-effectiveness of BVd for treating patients with MM who had one previous LoT. The limitations associated with these aspects are described in Section B.3.15.

B.3.8 Managed access proposal

Managed access could be considered if this was an appropriate route to ensure patient access.

B.3.9 Summary of base-case analysis variables 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 68.

Table 68. Summary of variables applied in the base-case economic analysis

Parameter	Mean Value	SE	Lower bound	Upper bound	PSA distribution	Reference to location in submission
Model settings						
Cohort size	1000	-	-	-	-	-
Time horizon (years)	36	-	-	-	-	B.3.2.4
Age (years)	64	-	-	-	-	
Discount rate costs (%)	3.5	-	-	-	-	
Discount rate outcomes (%)	3.5	-	-	-	-	
Survival inputs						
BVd PFS	Exponential					B.3.3.1
BVd OS	Weibull – Unadjusted					
BVd TTD	Weibull					
DVd PFS	Exponential					
DVd OS	Weibull – informative prior					
DVd TTD	Weibull					
hKd PFS HR	[redacted]	[redacted]	[redacted]	[redacted]	LOG-NORMAL	
hKd OS HR	[redacted]	[redacted]	[redacted]	[redacted]	LOG-NORMAL	
hKd TTD HR	[redacted]	[redacted]	[redacted]	[redacted]	LOG-NORMAL	
SVd PFS HR	[redacted]	[redacted]	[redacted]	[redacted]	LOG-NORMAL	
SVd OS HR	[redacted]	[redacted]	[redacted]	[redacted]	LOG-NORMAL	
SVd TTD HR	[redacted]	[redacted]	[redacted]	[redacted]	LOG-NORMAL	
Drug acquisition costs						
BVd cost per treatment cycle 1-8 (£)	[redacted]	-	-	-	-	B.3.5.1.1
BVd cost per treatment cycle 9+ (£)	[redacted]	-	-	-	-	
BVd Belamaf RDI (%)	[redacted]	[redacted]	[redacted]	[redacted]	BETA	

Parameter	Mean Value	SE	Lower bound	Upper bound	PSA distribution	Reference to location in submission
BVd Bortezomib RDI (%)	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
BVd Dexamethasone RDI (%)	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
hKd cost per treatment cycle 1 (£)	10,754.58	-	-	-	-	
hKd cost per treatment cycle 2+ (£)	12,955.84	-	-	-	-	
hKd Carfilzomib RDI (%)	91%	0.18	31%	100%	BETA	
hKd Dexamethasone RDI (%)	82%	0.16	40%	100%	BETA	
SVd cost per treatment cycle (£)	13,623.03	-	-	-	-	
SVd Selinexor RDI (%)	100%	0.20	61%	100%	BETA	
SVd Bortezomib RDI (%)	79%	0.16	41%	99%	BETA	
SVd Dexamethasone RDI (%)	82%	0.16	40%	100%	BETA	
DVd cost per treatment cycle 1-3 (£)	15,617.40	-	-	-	-	
DVd cost per treatment cycle 4-8 (£)	6,618.49	-	-	-	-	
DVd cost per treatment cycle 9+ (£)	4,499.46	-	-	-	-	
DVd Daratumumab RDI (%)	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
DVd Bortezomib RDI (%)	79%	0.16	41%	99%	BETA	
DVd Dexamethasone RDI (%)	82%	0.16	40%	100%	BETA	
Drug administration costs						
Administration cost per treatment cycle with BVd treatment cycle 1-8 (£)	762.73	152.55	493.60	1089.48	GAMMA	B.3.5.1.3
Administration cost per treatment cycle with BVd treatment cycle 9+ (£)	286.71	57.34	185.54	409.54	GAMMA	
Administration cost per treatment cycle with hKd treatment cycle 1 (£)	2,128.93	425.79	1377.73	3040.98	GAMMA	
Administration cost per treatment cycle with hKd treatment cycle 2+ (£)	2,128.93	425.79	1377.73	3040.98	GAMMA	
Administration cost per treatment cycle with SVd treatment cycle 1 (£)	476.02	95.20	308.05	679.94	GAMMA	
Administration cost per treatment cycle with SVd treatment cycle 2+ (£)	476.02	95.20	308.05	679.94	GAMMA	
Administration cost per treatment cycle with DVd treatment cycle 1-3 (£)	595.02	119.00	385.06	849.93	GAMMA	

Parameter	Mean Value	SE	Lower bound	Upper bound	PSA distribution	Reference to location in submission
Administration cost per treatment cycle with DVd treatment cycle 4-8 (£)	476.02	95.20	308.05	679.94	GAMMA	
Administration cost per treatment cycle with DVd treatment cycle 9+ (£)	119.00	23.80	77.01	169.99	GAMMA	
Subsequent treatments						
BVd one-off subsequent treatment cost (£)	85,703	17141	55,462	122,418	GAMMA	B.3.5.2
hKd one-off subsequent treatment cost (£)	85,703	17141	55,462	122,418	GAMMA	
SVd one-off first subsequent treatment cost (£)	85,703	17141	55,462	122,418	GAMMA	
DVd one-off first subsequent treatment cost (£)	84,441	16888	54,646	120,616	GAMMA	
BVd one-off second subsequent treatment cost (£)	79,412	15882	51,392	113,433	GAMMA	
hKd one-off second subsequent treatment cost (£)	79,412	15882	51,392	113,433	GAMMA	
SVd one-off second subsequent treatment cost (£)	79,412	15882	51,392	113,433	GAMMA	
DVd one-off second subsequent treatment cost (£)	78,816	15763	51,005	112,581	GAMMA	
BVd first subsequent treatment, % patients	81%	0.16	40%	100%	BETA	
hKd first subsequent treatment, % patients	81%	0.16	40%	100%	BETA	
SVd first subsequent treatment, % patients	81%	0.16	40%	100%	BETA	
DVd first subsequent treatment, % patients	81%	0.16	40%	100%	BETA	
Second subsequent treatment, % patients	34%	0.07	22%	48%	BETA	
Disease management costs						
BVd PFS on tx disease management total cost (£)	73	15	47	104	GAMMA	B.3.5.3
BVd PFS off tx disease management total cost (£)	55	11	35	78	GAMMA	
BVd PD disease management total cost (£)	55	11	35	78	GAMMA	
BVd PFS on tx disease management - ophthalmologist cost	48	10	31	69	GAMMA	
hKd PFS on tx disease management total cost (£)	55	11	35	78	GAMMA	
hKd PFS off tx disease management total cost (£)	55	11	35	78	GAMMA	

Parameter	Mean Value	SE	Lower bound	Upper bound	PSA distribution	Reference to location in submission
hKd PD disease management total cost (£)	55	11	35	78	GAMMA	
SVd PFS on tx disease management total cost (£)	44	9	28	62	GAMMA	
SVd PFS off tx disease management total cost (£)	55	11	35	78	GAMMA	
SVd PD disease management total cost (£)	55	11	35	78	GAMMA	
DVd PFS on tx disease management total cost (£)	55	11	35	78	GAMMA	
DVd PFS off tx disease management total cost (£)	55	11	35	78	GAMMA	
End of life costs						
End of life cost (£)	12,397.00	2,479.40	8,022.68	17,707.92	GAMMA	B.3.5.5
Quality of life						
Utility: PFS on-tx	[redacted]	[redacted]	[redacted]	[redacted]	BETA	B.3.4.2
Utility: PFS off tx	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
Utility: PD	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
BVd treatment utility	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
hKd treatment utility	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
SVd treatment utility	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
DVd treatment utility	[redacted]	[redacted]	[redacted]	[redacted]	BETA	
BVd adverse event total disutility	0.28	0.06	0.18	0.39	BETA	B.3.4.3
hKd adverse event total disutility	0.15	0.03	0.10	0.21	BETA	
SVd adverse event total disutility	0.17	0.03	0.11	0.24	BETA	
DVd adverse event total disutility	0.19	0.04	0.12	0.27	BETA	

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, Daratumumab + bortezomib + dexamethasone; hKd, High-dose carfilzomib + dexamethasone; PD, progressed disease; PFS, progression-free survival; PSA, probability sensitivity analysis; RDI, relative dose reduction; OWSA, one-way sensitivity analysis; SE, standard error; SVd, Selinexor in combination with bortezomib, and dexamethasone; tx, treatment

B.3.9.2 Assumptions

A summary of modelling assumptions is provided, divided by aspect of the cost-effectiveness model, in Table 69.

Table 69. List of assumptions for the base-case cost-effectiveness analysis

Category	Assumption	Justification
Population and comparators	The DREAMM-7 trial is representative of patients with RRMM in the 2L setting in the UK	The clinical trial population for DREAMM-7 assessed belamaf in patients with RRMM, with several clinical trials sites located in the UK.
Comparators	Clinical expert opinion	Only lenalidomide-sparing comparators at 2L are considered given the proposed population of patients for whom lenalidomide is unsuitable.
Model structure and settings	The key costs and outcomes associated with RRMM are captured using a PSM model structure.	A PSM considers estimates for each clinical endpoint separately (i.e. PFS, OS and TTD are modelled independently) and, as such, maintains consistency between the endpoints used in the cost-effectiveness analysis and the published clinical data. Additionally, the use of a PSM structure is widely accepted in oncology by HTA bodies across the globe and the application is well understood by clinician experts and health economists alike (195).
	The key costs and outcomes associated with RRMM are captured by PF and PD and death health states.	The choice of modelling PF and PD health states is intended to capture important differences in costs and quality of life within RRMM in a similar fashion to other models in MM. PF captures the costs and consequences of active treatments, monitoring, and treatment-related AEs, whilst PD captures the costs and outcomes of subsequent treatment and monitoring, while death captures end-of-life care.
	The progression-free health state was divided into on- and off-treatment in order to differentiate costs based on treatment status. Drug acquisition and admin costs are only included in PF on-tx	The PF on- and off-treatment split was chosen based on the observation that in MM some patients withdraw from active treatment before disease progression, which was also aligned with previous NICE TAs (151), and this has an impact to treatment and monitoring costs.
	Lifetime horizon of 36 years	The mean age of the population is 64 years (based on the mean age in DREAMM-7) therefore a 36-year time horizon was considered long enough to capture the clinical and economic impacts of RRMM in a 2L setting.
	Discount rate of 3.5%	This is in line with the NICE reference case.
	No half cycle correction applied	The one-week cycle length was assumed to be sufficiently short to capture model transitions.

Category	Assumption	Justification
	The model looks at the perspective of the NHS & PSS	This is in line with the NICE reference case (195).
Clinical effectiveness	In the absence of TTD data for non-trial comparators, PFS HRs from the NMA applied to DVd TTD are used as a proxy for treatments given until progression.	PFS HRs applied to DVd TTD was determined to be the most conservative assumption to estimate non-trial comparator TTD.
	Grade 3+ AE incidences occurring with <5% in either the BVd or DVd arms of DREAMM-7 are not included	Grade 3+ AEs occurring in small amounts of patients are not likely to impact cost-effectiveness since with <5% incidence in both arms, small incremental difference is seen between the BVd and DVd.
Cost and resource use inputs	Belamaf dosing is informed by the actual DREAMM-7 dose received.	Dose delays / interruptions were frequent, as a consequence of managing eye-related side effects. To model the relationship more accurately between time on treatment and dose intensity, an individual patient level analysis of dose intensity was conducted (embedded in the model). This methodology accurately depicts the dosing and management of eye-related side effects with BVd treatment that is expected to be reflective in clinical practice.
	RDI is assumed to be constant throughout treatment for all other comparators than BVd.	Dose delays and reductions for all other comparators to BVd in the model were limited (all treatments included in combinations with large cost impact were estimated to have >90% RDI). Limited cost-effectiveness impact is expected from constant RDI methods for daratumumab (DVd) versus IPD usage. Paucity of IPD dosage data for all non-trial comparators means constant RDI assumptions were necessary.
	RDI data was unavailable for Selinexor and a rate of 100% has been assumed.	In the absence of RDI, the dose received is the same as the administration schedule.
	Wastage is assumed on 100% of administrations. For IV and SC administrations, dosing is calculated using method of moments.	Although vial sharing is practiced, it is uncertain what is the proportion of administrations to which vial sharing is practiced. Hence, the analysis follows a conservative approach, assuming that wastage is applied to 100% of administrations. The impact of this assumption on the ICER is explored in scenario analysis where no wastage is applied.
	No administration costs for oral first-line or subsequent treatments.	Oral treatments can be taken at home without assistance from a health care professional.
	TRAEs (Grade ≥3) are incorporated as one-off events and the impact is attributed to the first cycle of treatment for patients entering the model.	AEs are likely to occur very soon after treatment initiation and only require acute care.

Category	Assumption	Justification
	Unit costs associated with treatment of different types of eye-related side effects are assumed to be the same.	Non-admitted face to face outpatient service with a Consultant has been assumed for the treatment of eye-related AEs.
	The proportion of patients receiving subsequent treatment is informed by the literature.	DREAMM-7 was not considered an appropriate source to inform the proportion of patients who continued to subsequent treatment therapy due to immaturity of patients entering subsequent treatment. Hence, the proportion of patients who received a first and second line of subsequent treatment was informed by Raab (2019) (47) in the base-case, while a scenario was conducted using estimates from Yong (2016) (46).
	The distribution of patients in each subsequent treatment is informed by clinical expert opinion.	Expert opinion was selected as the preferred approach to inform the number of patients who continued to subsequent treatment. Given the three scenarios provided by clinicians, GSK have included the subsequent treatments estimations from EE2 in the cost-effectiveness model base case, as these values closely align with the NICE HTA guidance of centring the evidence on current clinical practice (160). The two other scenarios are included as scenario analyses.
	Subsequent treatments are being modelled through a one-off cost upon disease progression.	In line with previous HTA appraisals, a one-off cost upon disease progression is applied for up to two lines of subsequent therapy.
	Costs associated with the delivery of second subsequent treatment were assumed to incur at the same time as costs related to the first subsequent line of treatment (i.e., upon disease progression)	Patients were assumed to incur a one-off cost associated with both first and second line of subsequent treatment, upon disease progression. The rationale for this assumption was based on the structural limitations of PSMs and the limitation in available evidence to map the timing of subsequent treatments

Category	Assumption	Justification
		across two subsequent treatment lines for all included comparators. Hence, a simplified approach was taken to assume that costs associated with second line of subsequent treatment incur at the same time as costs of first line of subsequent treatment.
	End-of-life care costs is applied as a one-off cost in the cycle in which patients die.	Patients will accrue end-of-life care costs before they die and therefore, they are applied within the cycle of death.
Health-related quality of life	EQ-5D utility scores from DREAMM-7, are sufficiently robust to inform HRQoL of patients with RRMM whether PF or with PD.	In line with the NICE and ICER reference cases by using data directly from the DREAMM-7 clinical trial. The model also includes scenarios with alternative sources for utilities.
	Eye-related side effects QALYs	Eye-related side effects were extremely common in the DREAMM-7 trial, so that assigning a specific QALY decrement to the occurrence of an eye-related side effects would likely double count the utility decrement (since these would have been captured in the EQ-5D-3L data).
	Health specific utilities are applied in each cycle to the differing health states (PF and PD). PF utility was also assumed to differ between treatments (for SVd and hKD utilities were assumed to be equal to DVd).	EQ-5D-3L change from baseline data was collected in the DREAMM-7 trial, supporting there is a difference between HRQoL in patients in PF and PD health states, as well as in PF utility between treatment arms. A number of scenario analyses were conducted to assess the impact of this assumption in the model, assuming the same utilities across treatments, and using different sources of evidence to inform health state utilities.
	Age-related utility decrements are applied in every cycle.	Age-related utility decrements are applied in the model to incorporate the natural decline in HRQoL associated with increasing age and to ensure the utility of 2L MM patients does not exceed that of the general population.

Abbreviations: AE, Adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, High-dose carfilzomib and dexamethasone; HR, Hazard ratio; HRQoL, Health-Related Quality of Life; HTA, Health Technology Assessment; ICER, Incremental Cost-Effectiveness ratio; IV, Intravenous; MM, Multiple Myeloma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, Progression-free; QALY, Quality adjusted life year; RDI, relative dose intensity; SC, Subcutaneous; SVd, Selinexor in combination with bortezomib, and dexamethasone; TDD, time to treatment discontinuation; TTRAE, Treatment-related adverse event; 2L, second line

B.3.10 Base-case results

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

As described in Section B.1.3.2, this submission effectively covers two 'subpopulations' which differ only by their relevant comparators:

- DVd eligible subpopulation - Patients who were eligible for transplant at 1L or who were ineligible for transplant before the approval of DRd as a 1L treatment can be compared against any approved lenalidomide-sparing 2L treatment.
- DVd ineligible subpopulation – Patients in 2L who were ineligible for transplant following the approval of DRd, will almost certainly be refractory to daratumumab and therefore BVd cannot be compared against DVd (but can be compared against any other approved lenalidomide-sparing regimen).

This section presents the base-case summary results for the CEA comparing BVd to hKd, SVd for both DVd eligible and ineligible subpopulations, and DVd for DVd eligible subpopulation.

Due to the confidential nature of the PAS for comparator treatments (including subsequent treatments), the base-case results are presented using the list price for all treatments and the confidential simple PAS price of £[redacted] for belamaf. It is therefore challenging to determine the actual cost-effectiveness of BVd, but based on the information available to GSK, results with PAS discount for belamaf only are presented below. Results using the list price for belamaf are provided in Appendix K.

DVd eligible subpopulation

Total costs, life years gained (LYG), QALYs, and the incremental cost-effectiveness ratio (ICER) for BVd versus DVd, hKd and SVd are presented in Table 70. In the deterministic base case analysis, BVd resulted in the highest average QALYs ([redacted]) and LYs (9.24) compared to all other treatments. In the fully incremental analysis hKd is dominated by BVd (i.e., resulting in QALY gains and cost savings). DVd is extendedly dominated by BVd, meaning that a combination of treating patient with SVd and BVd are estimated to provide both cheaper and more effective care than treating with DVd alone. Finally, results of the base case analysis show that BVd is a cost-effective option compared with SVd with an ICER of £8,190 per QALY. In the assessment of the incremental net health benefit (INHB), the INHB of BVd compared to SVd is [redacted] and [redacted] for a WTP threshold of £20,000 and £30,000 per QALY, respectively.

Additional clinical outcomes and disaggregated base-case results are presented in Appendix J.

DVd ineligible subpopulation

Total costs, LYG, QALYs, and the ICER for BVd versus hKd, SVd are presented in Table 71. In the base-case, the distinction between DVd eligible and ineligible subpopulations does not affect the results as BVd extendedly dominates DVd in the DVd eligible subpopulation. Similar to the analysis of the DVd eligible subpopulation, in the fully incremental analysis of DVd ineligible subpopulation hKd is dominated by BVd, and BVd is a cost-effective option compared with SVd with an ICER of £8,190 per QALY. In the assessment of the incremental net health benefit (INHB), the INHB of BVd compared to SVd is [redacted] and [redacted] for a WTP threshold of £20,000 and £30,000 per QALY, respectively.

Table 70. DVd eligible subpopulation – fully incremental analysis (PAS vs list, deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000	INHB at £30,000
SVd	[redacted]	4.17	[redacted]	-	-	-	-	-	-
DVd	[redacted]	4.97	[redacted]	-	-	-	Extendedly dominated	-	-
hKd	[redacted]	4.58	[redacted]	-	-	-	Dominated	-	-
BVd	[redacted]	9.24	[redacted]	[redacted]	5.07	[redacted]	8,190 (vs. SVd)	[redacted](vs. SVd)	[redacted] (vs. SVd)

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SVd, Selinexor in combination with bortezomib, and dexamethasone
Note: Incremental results are presented versus non-dominated options

Table 71. DVd ineligible subpopulation – fully incremental analysis (PAS vs list, deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000	INHB at £30,000
SVd	[redacted]	4.17	[redacted]	-	-	-	-	-	-
hKd	[redacted]	4.85	[redacted]	-	-	-	Dominated	-	-
BVd	[redacted]	9.24	[redacted]	[redacted]	5.07	[redacted]	8,190 (vs. SVd)	[redacted](vs. SVd)	[redacted] (vs. SVd)

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SVd, Selinexor in combination with bortezomib, and dexamethasone
Note: Incremental results are presented versus non-dominated options

B.3.11 Exploring uncertainty

Probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWSA) have been conducted 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, treatment costs (including subsequent treatment costs), and utility inputs. 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

PSA was conducted to estimate the uncertainty in the key model input parameters. The PSA involved varying the inputs by assigning values to each parameter included in this analysis from predefined uncertainty distributions.

This sampling process was performed in an iterative process for each parameter, and the resulting incremental cost and QALY predictions were recorded. The PSA was run for 1,000 iterations, following a visual assessment of convergence of the mean ICER estimates.

The choice of distribution (e.g., normal, beta, gamma, log-normal) applied to parameters was selected based on recommendations outlined in Briggs et al. (2006) (196). Where available, standard errors (SEs) were sourced from available evidence or calculated based on published standard deviations (SD) or 95% CIs. When none of the above were available, the SE was estimated as 20% of the mean parameter value.

Table 68 presents the uncertainty distributions that were drawn from for each variable, along with the corresponding standard errors. 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.

B.3.11.1.1 DVd eligible subpopulation

Results of the probabilistic analysis for the DVd eligible subpopulation are presented in tabulated form in Table 72. The incremental cost-effectiveness plane scatter plot (Figure 35), cost-effectiveness acceptability curve (CEAC) (Figure 36), and cost-effectiveness acceptability frontier (CEAF) (Figure 37) were also reported to provide a graphical illustration of the level of variability and uncertainty in the results.

Results of the PSA were highly consistent with results from the deterministic base-case analysis, with hKd being dominated by BVd, DVd being extendedly dominated by BVd, and an estimated probabilistic ICER (no severity modifier applied) for BVd versus SVd of £9,652. Consistent with the deterministic analysis, hKd is dominated by BVd. In the assessment of the incremental net health benefit (INHB), the INHB of BVd compared to SVd is [redacted] and [redacted] for a WTP threshold of £20,000 and £30,000 per QALY, respectively.

The incremental cost-effectiveness plane (Figure 35) demonstrates that in the vast majority of simulations BVd is more effective and more costly than SVd and DVd. When compared to hKd, the majority of simulations showed that BVd is less costly and more effective (i.e., dominant). The CEAC and CEAF show that at a WTP threshold of £30,000, BVd has a 99% probability of being a cost-effective treatment option (Figure 36, Figure 37).

Table 72. DVd eligible subpopulation - probabilistic fully incremental analyses (PAS vs list)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000	INHB at £30,000
SVd	[redacted]	4.45	[redacted]				-	-	-
DVd	[redacted]	5.13	[redacted]	-	-	-	Extendedly dominated	-	-
hKd	[redacted]	4.85	[redacted]	-	-	-	Dominated	-	-
BVd	[redacted]	9.21	[redacted]	[redacted]	4.76	[redacted]	9,652 (vs. SVd)	[redacted] (vs. SVd)	[redacted] (vs. SVd)

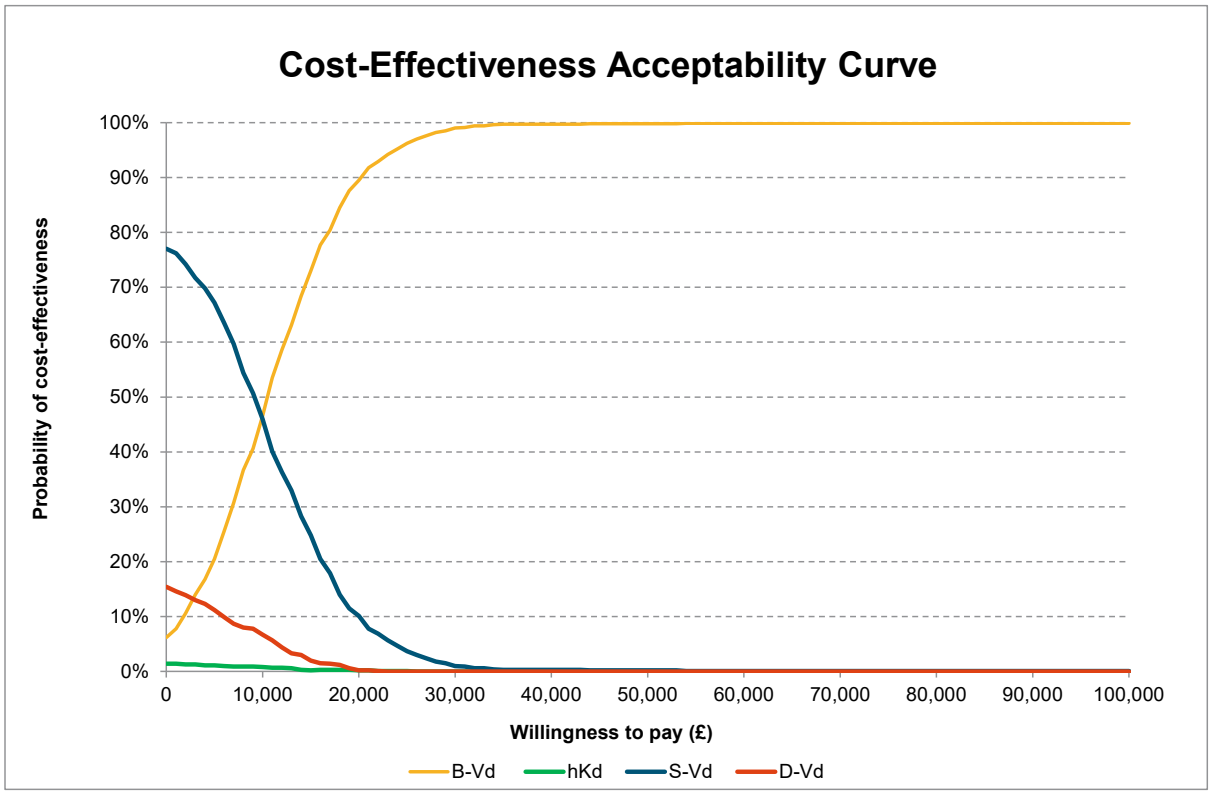
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INHB, incremental net health benefit; SVd, Selinexor in combination with bortezomib, and dexamethasone
*Incremental results are presented versus non-dominated options

Figure 35. DVd eligible subpopulation - Incremental cost-effectiveness plane

[redacted]

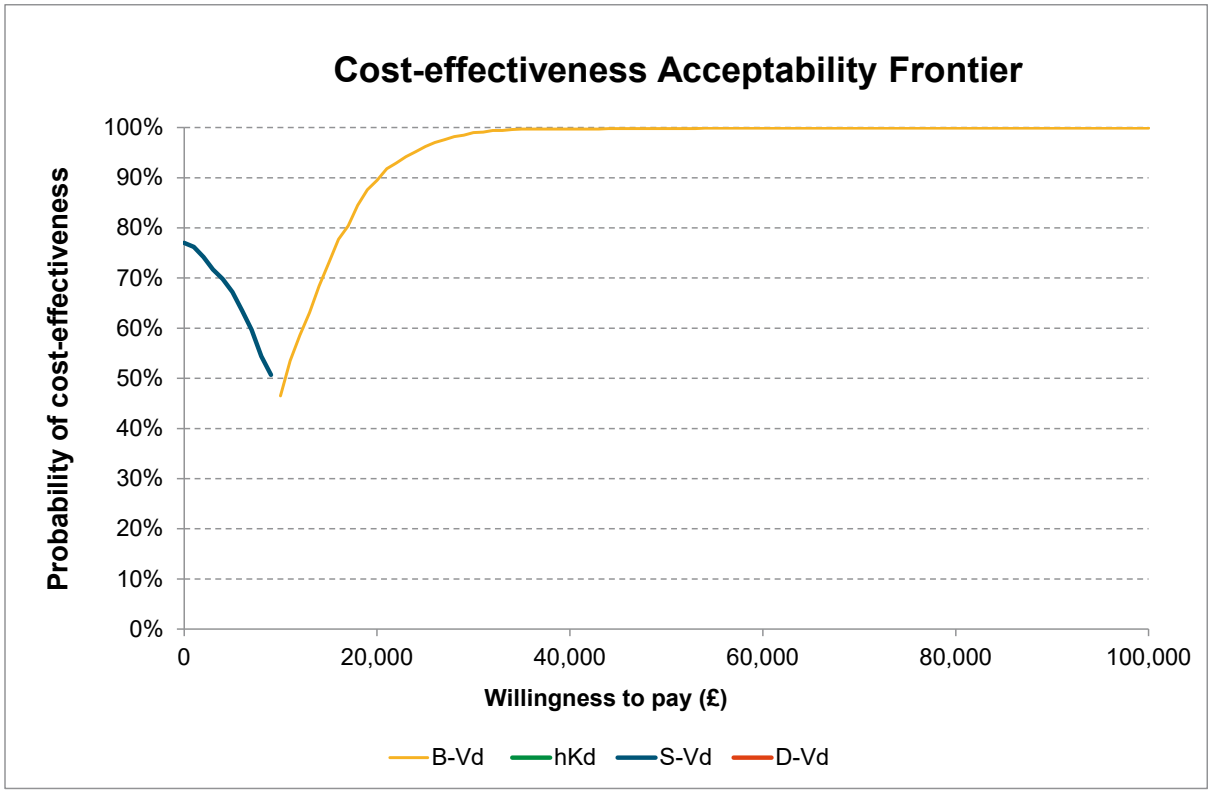
Abbreviations: B-Vd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; S-Vd, Selinexor in combination with bortezomib, and dexamethasone; WTP, willingness-to-pay.

Figure 36. DVd eligible subpopulation - Cost-effectiveness acceptability curve



Abbreviations: B-Vd, belamaf in combination with bortezomib, and dexamethasone; D-Vd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; S-Vd, Selinexor in combination with bortezomib, and dexamethasone.

Figure 37. DVd eligible subpopulation - Cost-effectiveness acceptability frontier



Abbreviations: B-Vd, belamaf in combination with bortezomib, and dexamethasone; D-Vd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; S-Vd, Selinexor in combination with bortezomib, and dexamethasone.

B.3.11.1.2 DVd ineligible subpopulation

Similar to the deterministic analysis, the distinction between DVd eligible and ineligible subpopulations does not affect the probabilistic results between DVd eligible and DVd ineligible patients, as DVd is extendedly dominated by BVd in the DVd eligible subpopulation. Results of the PSA were highly consistent with results from the deterministic base case analysis, with hKd being dominated by BVd, and an estimated probabilistic ICER (no severity modifier applied) for BVd versus SVd of £9,652. Consistent with the deterministic analysis, hKd is dominated by BVd. In the assessment of the incremental net health benefit (INHB), the INHB of BVd compared to SVd is [redacted] and [redacted] for a WTP threshold of £20,000 and £30,000 per QALY, respectively (Table 73).

The incremental cost-effectiveness plane (Figure 38) demonstrates that in the vast majority of simulations BVd is more effective and more costly than SVd. When compared to hKd, the majority of simulations showed that BVd a dominant treatment option. The CEAC and CEAF show that at a WTP threshold of £30,000, BVd has a 99% probability of being a cost-effective treatment option (Figure 39, Figure 40).

Table 73. DVd ineligible subpopulation - probabilistic fully incremental analyses (PAS vs list)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000	INHB at £30,000
SVd	[redacted]	4.45	[redacted]				-	-	-
hKd	[redacted]	4.85	[redacted]	-	-	-	Dominated	-	-
BVd	[redacted]	9.21	[redacted]	[redacted]	4.76	[redacted]	9,652 (vs. SVd)	[redacted] (vs. SVd)	[redacted] (vs. SVd)

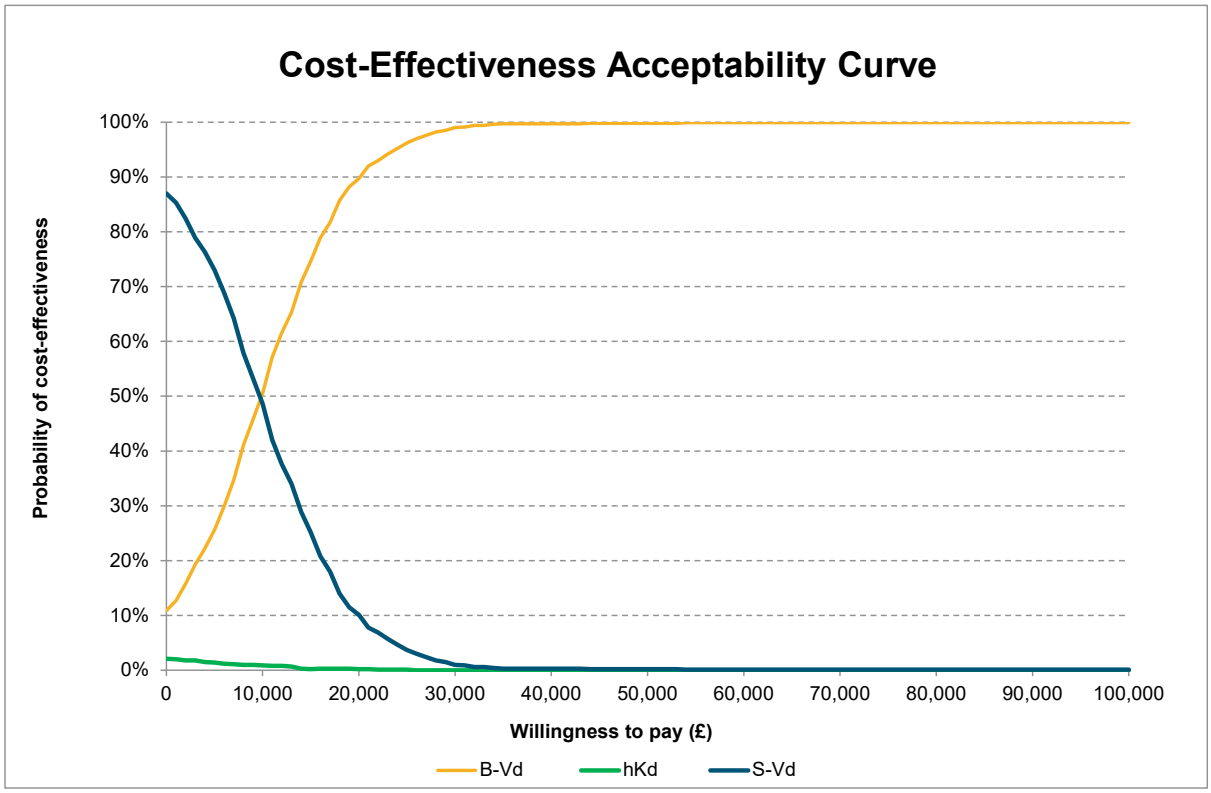
Abbreviations: : BVd, belamaf in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INHB, incremental net health benefit; SVd, Selinexor in combination with bortezomib, and dexamethasone
*Incremental results are presented versus non-dominated options

Figure 38. DVd ineligible subpopulation - Incremental cost-effectiveness plane

[redacted]

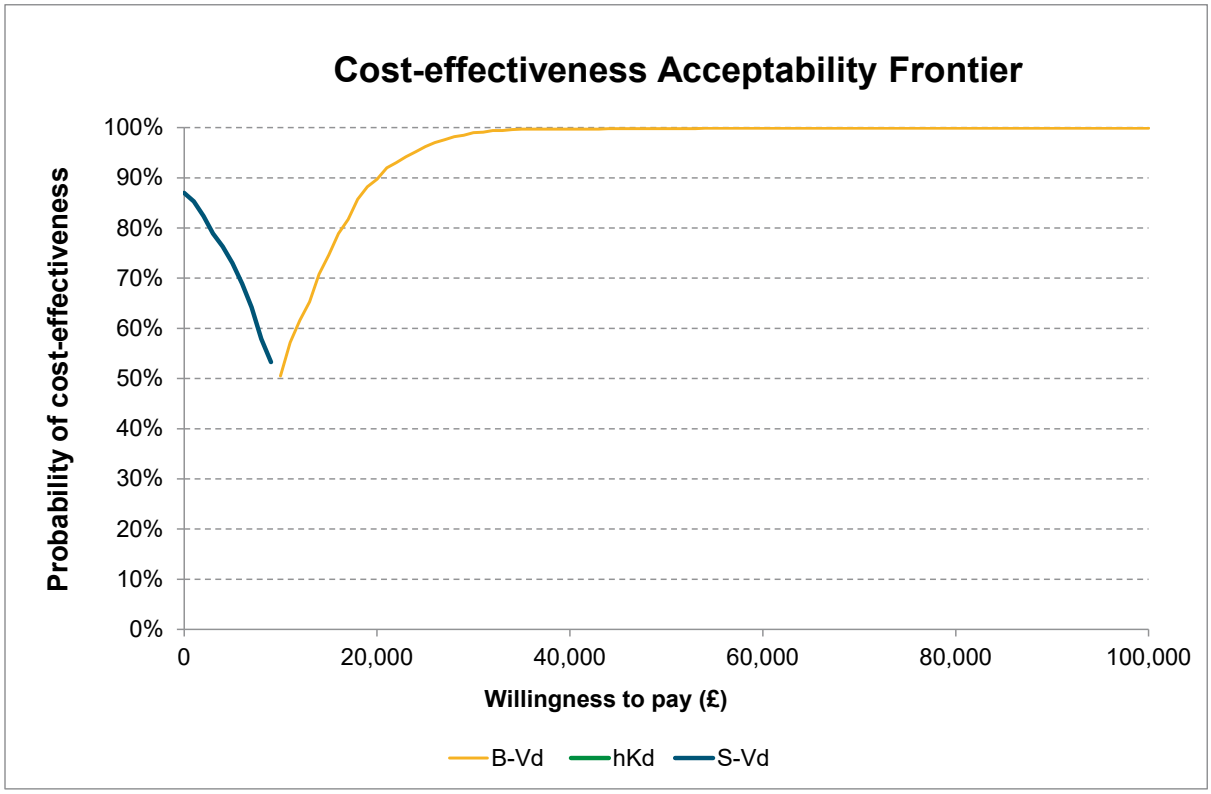
Abbreviations: B-Vd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; S-Vd, Selinexor in combination with bortezomib, and dexamethasone; WTP, willingness-to-pay.

Figure 39. DVd ineligible subpopulation - Cost-effectiveness acceptability curve



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; S-Vd, Selinexor in combination with bortezomib, and dexamethasone.

Figure 40. DVd ineligible subpopulation - Cost-effectiveness acceptability frontier



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; SVd, Selinexor in combination with bortezomib, and dexamethasone.

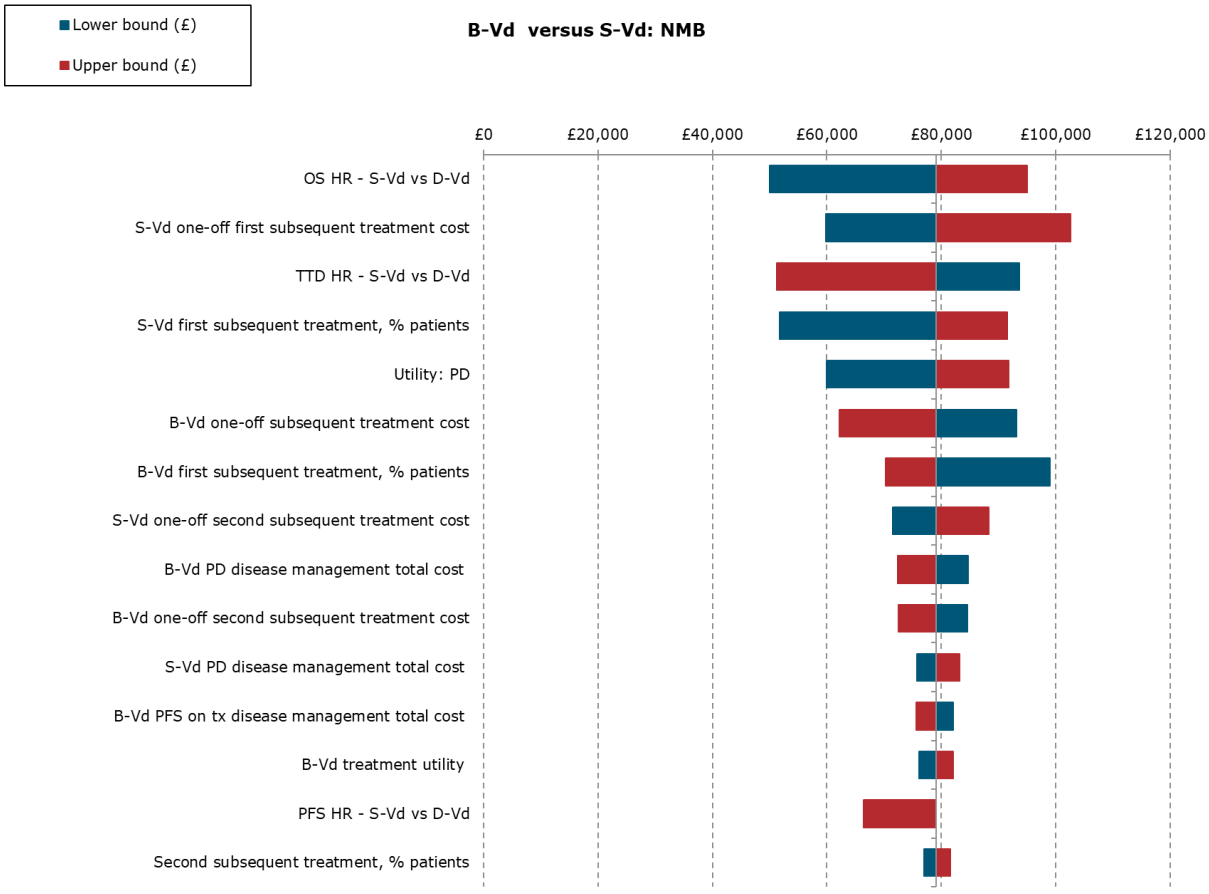
B.3.11.2 Deterministic sensitivity analysis

A one-way deterministic sensitivity analysis (OWSA) was performed to test the robustness of the model and identify key model drivers. Parameters were varied one at a time between their upper and lower 95% CIs, while others were kept constant at their base case values. For the OWSA, 95% CIs were determined based on SEs when available, and when not available SEs were estimated as 20% of the mean parameter value. Parameters related to survival outcomes were excluded from the OWSA due to the covariance between these parameters, which would lead to misleading results when varied individually.

Individual tornado diagrams for the comparison between BVd against SVd, DVd, and hKd were developed to graphically present the parameters for variables that have the greatest effect on the NMB, at a WTP threshold of £30,000 per QALY. The NMB was used as an alternative to the ICER in order to avoid negative or SW ICERs within the OWSA (e.g., when BVd dominates hKd). The top 15 most influential parameters on the ICER from the OWSA for BVd compared with SVd, DVd, and hKd are presented in the form of tornado diagrams in Figure 41, Figure 42, Figure 43. Results of the OWSA are also presented in tabulated form in Appendix O, Section 5.

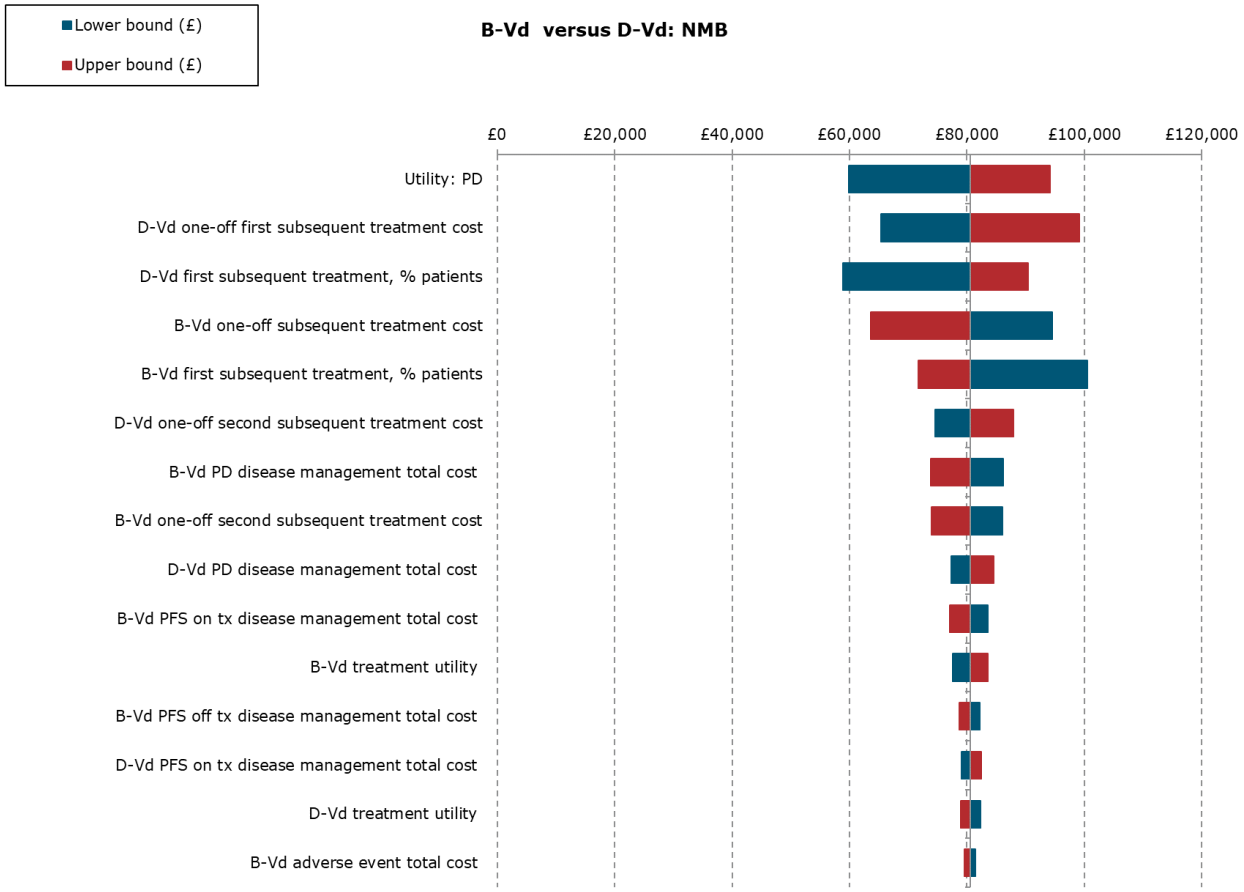
Given that OWSA considers a pairwise comparison, this analysis was not conducted separately for the DVd eligible and DVd ineligible subpopulations. Results in all three comparisons are most sensitive to the total cost of subsequent treatments, the percentage of patients receiving subsequent treatment, and the PD health state utility. For SVd and hKd for which treatment efficacy was modelled based on HRs (instead of individually fitted curves used for DVd based on DREAMM-7 data) results were also sensitive to relative treatment efficacy for TTD and OS. All variations in model parameters resulted in INMBs which indicated that BVd was cost-effective vs. all comparators. Specifically, INMB estimates for all OWSA conducted did not fall below £55,000.

Figure 41. OWSA tornado diagram (BVd vs. SVd)



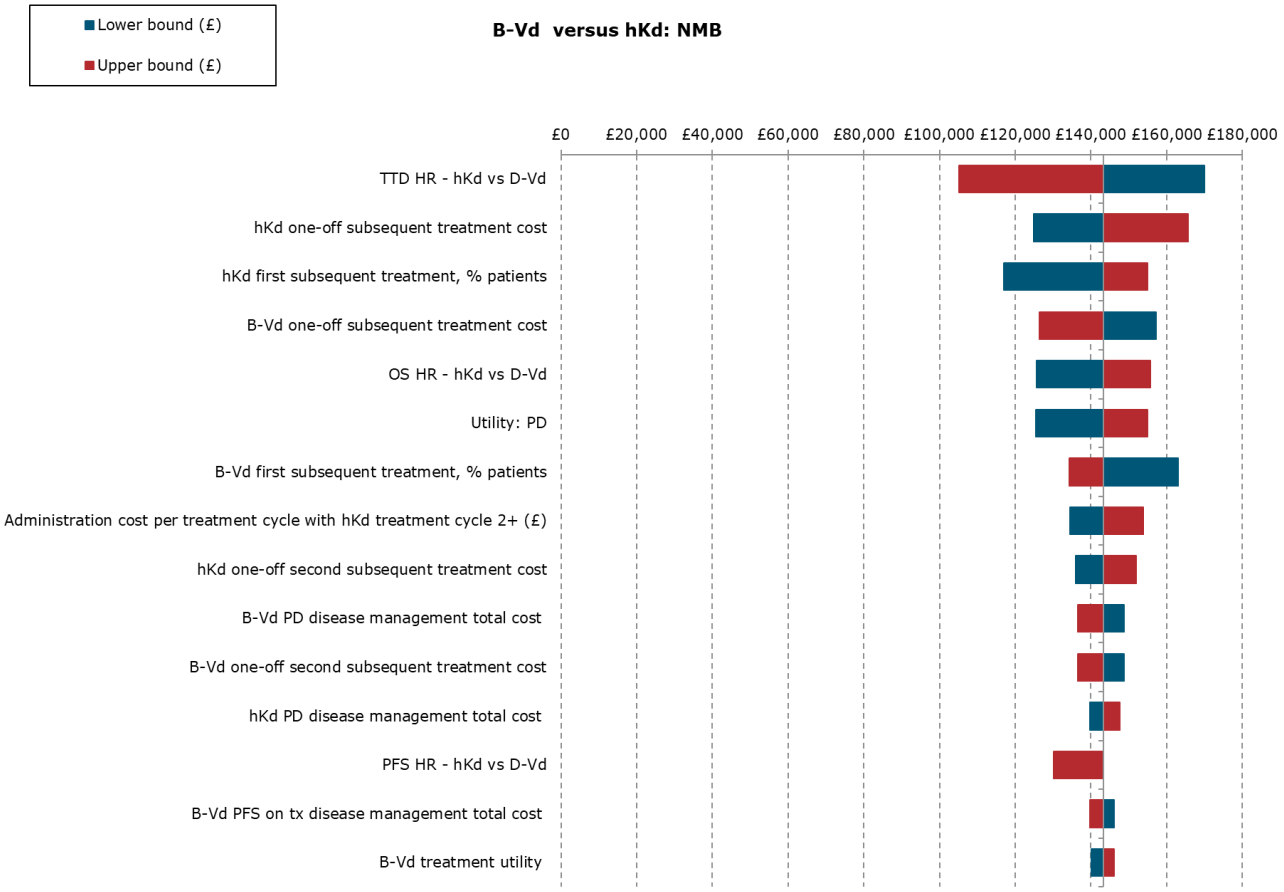
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; HR, hazard ratio; NMB, net monetary benefits; OS, overall survival; OWSA, one-way deterministic sensitivity analysis; PD, progressed disease; PFS, progression-free survival; S-Vd, Selinexor in combination with bortezomib, and dexamethasone; TTD, time to treatment discontinuation.

Figure 42. OWSA tornado diagram (BVd vs. DVd)



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; NMB, net monetary benefits; OWSA, one-way deterministic sensitivity analysis; PD, progressed disease; PFS, progression-free survival; tx, treatment.

Figure 43. OWSA tornado diagram (BVd vs. hKd)



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; HR, hazard ratio; NMB, net monetary benefits; OS, overall survival; OWSA, one-way deterministic sensitivity analysis; PD, progressed disease; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.11.3 Scenario analysis

A number of scenario analyses was conducted to estimate the impact of structural and model input model assumptions on the cost-effectiveness of BVd. The list of scenarios explored in the model, and the corresponding rationale are presented in Table 74. The inputs used for each scenario are presented in Appendix O, Section 6.

Table 74. Scenario analyses explored in the model

Model setting	Base case	Scenario analysis	Rationale
Time horizon	36 years	30 years	36 years represents lifetime horizon (see Table 68). Scenarios are explored to test the impact of shorter time horizons.
		20 years	
Discount rates for costs and outcomes	3.5%	0%	3.5% as per NICE reference case. Values of 0% and 6% are tested to explore the impact of discounting.
		6%	
Parametric survival modelling for OS and PFS	BVd PFS using direct extrapolation from parametric model	BVd PFS extrapolated using a HR applied to DVd baseline	In the base case, PFS was modelled independently for BVd and DVd treatment arms, because it was not possible to conclusively determine whether the PH assumption holds (Appendix O.2.1). Two scenario analyses were conducted assuming that the PH assumption holds and HRs from the NMA were assigned for all comparators to: - The DVd PFS curve from DREAMM-7 - The BVd PFS curve from DREAMM-7
	DVd PFS using direct extrapolation from parametric model; DVd as baseline	DVd PFS extrapolated using a HR applied to BVd baseline	
	OS curves using direct extrapolation from parametric model; DVd as baseline	OS extrapolated using PFS:OS surrogacy (DVd baseline curve)	In the base case, OS was modelled using direct extrapolation in OS from DREAMM-7 trial. Considering the immaturity of OS data in DREAMM-7, in the base case informative priors from CASTOR study have been used to model OS for DVd. However, alternative approaches have been explored in scenario analysis. Two scenario analyses are conducted in which OS was extrapolated assuming a surrogacy between PFS and OS outcomes (Appendix O.4.2, (170)). In these two scenarios HRs for each comparator are applied to the baseline PFS curve to estimate OS for each comparator. The two
	OS curves using direct extrapolation from parametric model; BVd as baseline	OS extrapolated using PFS:OS surrogacy (BVd baseline curve)	

Model setting	Base case	Scenario analysis	Rationale
			scenarios assumed the following for PFS for non-trial comparators: - DVd PFS curve was used as the baseline treatment curve - BVd PFS curve was used as the baseline treatment curve
	BVd OS curve: Weibull -unadjusted for treatment switching	BVd OS curve: Weibull -adjusted for treatment switching	In the base case OS curve for BVd was modelled based on DREAMM-7 with no further adjustments, while OS curve for DVd was modelled based on DREAMM-7 using informative priors from the CASTOR trial. To test the structural uncertainty around this decision two separate scenario analyses are conducted using parametric curves for BVd and DVd fitted to the IPCW adjusted OS KM curves data.
	DVd OS curve: Weibull - using informative prior from CASTOR study	DVd OS curve: Weibull adjusted for treatment switching	
	BVd PFS curve: Exponential	BVd PFS curve: Weibull	In the base case, an exponential extrapolation is assumed for BVd PFS. In this scenario, a Weibull curve is selected to offer a more optimistic view of BVd PFS over time.
	DVd PFS curve: Exponential	DVd PFS curve: Log-logistic (DVd only scenario due to PH model)	In the base case, an exponential extrapolation is assumed for DVd PFS. Three scenario analyses were conducted based on statistical fit or expert opinion to offer a more optimistic view of DVd PFS over time, by assuming a Log-logistic, Lognormal, and Generalized Gamma model, respectively.
		DVd PFS curve: Lognormal (DVd only scenario due to PH model)	
		DVd PFS curve: Generalised Gamma (DVd only scenario due to PH model)	

Model setting	Base case	Scenario analysis	Rationale
Treatment duration	PFS HRs applied to DVd TTD using direct extrapolation from parametric model	TTD equal to PFS for hKd & SVd comparators	Due to unavailability of publicised data to inform an NMA for TTD, PFS HRs for SVd and hKd were applied to the DVd TTD curve, based on clinical and health economic expert opinion. This is the most conservative assumption and is consistent with TA897 (22). Two scenario analyses were conducted: - The first assuming that TTD is equal to PFS for hKd and SVd, which is consistent with TA197 (74) - The second scenario assumed that DVd TTD from DREAMM-7 can be used as a proxy for hKd and SVd TTD curves.
		DVd TTD as a proxy for hKd & SVd TTD	
Wastage	Wastage included	No wastage costs included	In the base case, no vial sharing is assumed. However, as some treatments included in the model may allow for vial sharing to be implemented in practice, a scenario has been conducted to assess the impact of assuming no wastage on the results.
Dosing	IPD off-label dosing: Per actual dose received in DREAMM-7	IPD off-label dosing: Per SmPC dose	In the base case belamaf dosing in BVd is based on individual patient data (IPD) from the DREAMM-7 trial. The use of IPD-based dosing as per actual dose received in DREAMM-7 was implemented to reflect the time-variable trend identified for the RDI of belamaf, which is expected to be seen in clinical practice. A scenario analysis is conducted using the SmPC doses instead of the actual dose received in DREAMM-7, while still accounting for the time-variable trend in RDI observed in DREAMM-7. In this scenario, the belamaf acquisition cost for each dose is as per the closest labelled doses from the belamaf SmPC of 1.9 mg/kg and 2.5 mg/kg. Costing as per the SmPC assumes actual doses of 1.7-2.1 mg/kg and 2.2-2.7 mg/kg incur the acquisition cost of 1.9 mg/kg and 2.5 mg/kg doses, respectively.
Health care resource use	Clinical expert opinion	Sourced from TA897	Clinical expert opinion was used in the base to inform the frequency of use of various monitoring and disease management costs (Table 60) in different model health states. In a scenario analysis the impact of

Model setting	Base case	Scenario analysis	Rationale
			informing health care resource use based on TA897 (22) was explored. An assumption was made that frequency of use was equal among all treatment arms. Inputs for this scenario are presented in Appendix O, Section 6.
Subsequent treatment	Subsequent Tx distribution: clinical expert 2 (Current practice)	Subsequent Tx distribution: clinical expert 1 (Future treatment pathway)	Clinical expert opinion was used in the base case analysis to inform the distribution of subsequent treatments (Appendix M). EE2 opinion was used in the base case (Table 68) as their feedback was aligned with the NICE HTA guidance of centring the evidence on current clinical practice (160). Three scenario analyses were conducted to explore the impact on the ICERs when using different sources to inform the distribution of subsequent treatment: - Scenario using EE1 opinion (aligned to the future pathway with DRd approval) - Scenario using EE 3 opinion (aligned to the exact NICE pathway) - Estimates were informed based on Porteous et al. 2023 (193) using inputs from TA897 (22). Inputs for these three scenarios can be found in Appendix O, Section 6.
		Subsequent Tx distribution: clinical expert 3 (NICE treatment pathway aligned)	
		Subsequent Tx distribution: TA897	
	Subsequent Tx distribution: clinical expert 2 (Current practice) Health care resource use: Clinical expert opinion	Subsequent Tx distribution: TA897 Health care resource use: TA897	This scenario was conducted to reflect the joint impact of the assumptions described in the two scenarios above, when using inputs from TA897 (22) to inform the distribution of subsequent lines of treatment, and healthcare resource utilisation.

Model setting	Base case	Scenario analysis	Rationale
	Application of subsequent Tx costs: Upon progression	Application of subsequent Tx costs: First cycle	In the base case it is assumed that the costs of subsequent treatment lines are applied as one-off costs upon disease progression. The percentage of patients who received subsequent treatment lines is sourced from Raab (2019) (47), which provides estimates of patients on the proportion of patients receiving active treatment, by line of treatment. There is some uncertainty as to what proportion of patients would go on to receive subsequent treatment at any given time point. Hence, a scenario analysis was conducted, simplifying this calculation and assuming that subsequent treatment costs are applied as a one-off cost in the first cycle of the model.
	Source for % of patients continuing to subsequent Tx Lines: Raab et al. 2019	Source for % of patients continuing to subsequent Tx Lines: Yong et al. 2016	In the base case evidence, Raab (2019) (47) was used to inform the percentage of patients receiving subsequent lines of treatment. The proportion of patients who received a first and second line of subsequent treatment was assumed to be the same across all comparators in the model. To reflect the uncertainty in these model input parameters, a scenario analysis is conducted where the percentage of patients receiving subsequent lines of treatment is informed by Yong (2016) (46).
Utilities	Treatment specific utilities sourced from DREAMM-7	Equal health state utility for all comparators sourced from DREAMM-7	In the base case utility values for health states were informed from an analysis of EQ-5D-3L collected in DREAMM-7, using a mixed-effects linear regression. The fitted models (adjusted for baseline utility score), demonstrated higher improvement in utility scores in the BVd arm compared to DVd arm patients. Hence treatment specific health state utilities were used for BVd and DVd in the base case, with utilities for hKd and SVd assumed to be equal to DVd. To test the impact of this assumption three scenarios were conducted to inform utility inputs from different sources, assuming no treatment effect on health state utlities:
		Health state utility sourced from TA897	
		Health state utility sourced from TA695	

Model setting	Base case	Scenario analysis	Rationale
			- In the first scenario evidence from DREAMM-7 was used assuming no differential effect of treatment on health state utilities - In the second scenario health state utilities were informed from TA897 - In the third scenario health state utilities were informed from TA695 Inputs for these scenarios are presented in Appendix O, Section 6.
	AE disutilities included	AE disutilities not included	In the base case, AE disutilities were informed by TA695 and TA897. However, considering that the impact of AE may be already captured by the DREAMM-7 EQ-5D-3L data, a scenario is conducted assuming no additional impact of AE on health state utilities.
	Source of AE disutilities: TA695 & TA897	Source of AE disutilities: TA695	In the base case TA897 and TA695 were used to inform disutilities associated with AEs. To assess the impact of using AE inputs, a scenario was conducted where AE disutilities reported only TA695 was used.

Abbreviations: AE, adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; HR, hazard ratio; HTA, Health Technology Assessment; IPD, individual patient data; OS, overall survival; PH, proportional hazards; PFS, progression-free survival; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics; SVd, Selinexor in combination with bortezomib, and dexamethasone

B.3.11.3.1 Scenario results: BVd vs. SVd

The results of the scenario analyses with BVd discounted price for BVd vs. SVd are presented in Table 76.

Table 75. Scenario analyses: ICERs for BVd vs. SVd (BVd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	Change relative to base-case ICER
Base-case	[redacted]	[redacted]	**8,190**	**0.0%**
30 years	[redacted]	[redacted]	8,024	-2.0%
20 years	[redacted]	[redacted]	7,698	-6.0%
Discount (costs and benefits) 0%	[redacted]	[redacted]	9,842	20.2%
Discount (costs and benefits) 6%	[redacted]	[redacted]	6,027	-26.4%
BVd PFS extrapolated using a HR applied to DVd baseline	[redacted]	[redacted]	7,661	-6.5%
DVd PFS extrapolated using a HR applied to BVd baseline	[redacted]	[redacted]	7,878	-3.8%
OS extrapolated using PFS:OS surrogacy (DVd baseline curve)	[redacted]	[redacted]	10,211	24.7%
OS extrapolated using PFS:OS surrogacy (BVd baseline curve)	[redacted]	[redacted]	10,066	22.9%
BVd OS curve: Weibull adjusted for treatment switching	[redacted]	[redacted]	8,527	4.1%
DVd OS curve: Weibull adjusted for treatment switching	[redacted]	[redacted]	8,339	1.8%
BVd PFS curve: Weibull	[redacted]	[redacted]	7,578	-7.5%
TTD equal to PFS	[redacted]	[redacted]	4,203	-48.7%
DVd TTD as a proxy for comparator TTD	[redacted]	[redacted]	4,203	-48.7%
No wastage costs included	[redacted]	[redacted]	7,381	-9.9%
IPD off-label dosing: Per SmPC dose	[redacted]	[redacted]	8,314	1.5%
Health care resource use sourced from TA897	[redacted]	[redacted]	6,187	-24.5%
Subsequent Tx distribution: clinical expert 1 (Future treatment pathway)	[redacted]	[redacted]	6,330	-22.7%
Subsequent Tx distribution: clinical expert 3 (NICE treatment pathway aligned)	[redacted]	[redacted]	8,545	4.3%
Subsequent Tx distribution: TA897	[redacted]	[redacted]	11,017	34.5%
Subsequent Tx distribution: TA897	[redacted]	[redacted]	9,013	10.1%

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	Change relative to base-case ICER
Health care resource use: TA897				
Application of subsequent Tx costs: First cycle	[redacted]	[redacted]	14,005	71.0%
Source for % of patients continuing to subsequent Tx Lines: Yong et al. 2016	[redacted]	[redacted]	9,631	17.6%
Equal health state utility for all comparators sourced from DREAMM-7	[redacted]	[redacted]	8,268	1.0%
Health state utility sourced from TA897	[redacted]	[redacted]	8,840	7.9%
Health state utility sourced from TA695	[redacted]	[redacted]	8,564	4.6%
AE disutilities not included	[redacted]	[redacted]	8,183	-0.1%
Source of AE disutilities: TA695	[redacted]	[redacted]	8,189	0.0%

Abbreviations: AE, adverse event; BVd, belamaf plus bortezomib and dexamethasone, DVd, daratumumab plus bortezomib and dexamethasone; HR, hazard ratio; ICER, Incremental Cost-Effectiveness Ratio; IPD, individual patient data; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics

B.3.11.3.2 Scenario results: BVd vs. DVd

The results of the scenario analyses with BVd discounted price for BVd vs. DVd are presented in Table 77.

Table 76. Scenario analyses: ICERs for BVd vs. DVd (BVd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	Change relative to base case ICER
Base case	[redacted]	[redacted]	**3,709**	**0.0%**
30 years	[redacted]	[redacted]	3,464	-6.6%
20 years	[redacted]	[redacted]	2,277	-38.6%
Discount (costs and benefits) 0%	[redacted]	[redacted]	6,575	77.3%
Discount (costs and benefits) 6%	[redacted]	[redacted]	607	-83.6%
BVd PFS extrapolated using a HR applied to DVd baseline	[redacted]	[redacted]	3,091	-16.7%
DVd PFS extrapolated using a HR applied to BVd baseline	[redacted]	[redacted]	3,116	-16.0%

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	Change relative to base case ICER
OS extrapolated using PFS:OS surrogacy (DVd baseline curve)	[redacted]	[redacted]	4,228	14.0%
OS extrapolated using PFS:OS surrogacy (BVd baseline curve)	[redacted]	[redacted]	4,228	14.0%
BVd OS curve: Weibull adjusted for treatment switching	[redacted]	[redacted]	4,808	29.6%
DVd OS curve: Weibull adjusted for treatment switching	[redacted]	[redacted]	3,182	-14.2%
BVd PFS curve: Weibull	[redacted]	[redacted]	2,995	-19.3%
DVd PFS curve: Log-logistic	[redacted]	[redacted]	6,990	88.5%
DVd PFS curve: Lognormal	[redacted]	[redacted]	7,295	96.7%
DVd PFS curve: Generalised Gamma	[redacted]	[redacted]	5,419	46.1%
No wastage costs included	[redacted]	[redacted]	2,117	-42.9%
IPD off-label dosing: Per SmPC dose	[redacted]	[redacted]	3,856	4.0%
Health care resource use sourced from TA897	[redacted]	[redacted]	1,480	-60.1%
Subsequent Tx distribution: clinical expert 1 (Future treatment pathway)	[redacted]	[redacted]	1,276	-65.6%
Subsequent Tx distribution: clinical expert 3 (NICE treatment pathway aligned)	[redacted]	[redacted]	3,576	-3.6%
Subsequent Tx distribution: TA897	[redacted]	[redacted]	Dominant	-
Subsequent Tx distribution: TA897 Health care resource use: TA897	[redacted]	[redacted]	Dominant	-
Application of subsequent Tx costs: First cycle	[redacted]	[redacted]	5,813	56.7%
Source for % of patients continuing to subsequent Tx Lines: Yong et al. 2016	[redacted]	[redacted]	4,133	11.4%
Equal health state utility for all comparators sourced from DREAMM-7	[redacted]	[redacted]	3,784	2.0%
Health state utility sourced from TA897	[redacted]	[redacted]	4,077	9.9%
Health state utility sourced from TA695	[redacted]	[redacted]	3,937	6.2%
AE disutilities not included	[redacted]	[redacted]	3,706	-0.1%
Source of AE disutilities: TA695	[redacted]	[redacted]	3,709	0.0%

Abbreviations: AE, adverse event; BVd, belamaf plus bortezomib and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; HR, hazard ratio; ICER, Incremental Cost-Effectiveness Ratio; IPD, individual patient data; OS, overall survival; PFS, progression-free survival; QALY, Quality-adjusted life year; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics

B.3.11.3.3 Scenario analyses conclusions

Results of the scenario analyses using the discounted price of BVd demonstrate that the CE conclusions remain consistent with the base case despite variations to the

analytical specifications and assumptions. BVd remained dominant and CE under all scenarios versus hKd (Appendix O). The results vs. hKd and vs. SVd were more sensitive to changes in OS extrapolation methodology due to the relatively low efficacy of hKd, and SVd compared to BVd. However, none of the scenarios had an impact on the conclusions of the analysis. Scenarios largely affecting drug acquisition costs were a large driver of the model for the comparison vs. DVd due to the relatively lower cost of staying on treatment. The subsequent treatment distribution assumptions could have a large impact on the ICER however, the distribution of the ICER from these scenarios shows the base case is cost-effective under more conservative assumptions.

B.3.12 Subgroup analysis

Not applicable.

B.3.13 Benefits not captured in the QALY calculation

As described in Section B.1.3.2, the main benefit not captured in the QALY calculation is that the patient mix entering 2L RRMM will change in a predictable fashion over the next few years. In patients who are ineligible for transplant, the new SoC is DRd (197). Therefore, most patients entering 2L today will be eligible for daratumumab, but over the next few years the proportion of patients who are refractory to daratumumab will grow. As described in Section B.3.10 the cost-effectiveness of BVd will always be the same or superior in the daratumumab-refractory subpopulation since this population differs only by the fact daratumumab is no longer an eligible comparator for them. Therefore, the ICER for 2L BVd will gradually drop over time, meaning an ICER slightly greater than £30,000 / QALY could be considered for this submission as – over the course of the entire lifetime of the drug's usage in the NHS – the true ICER will likely drop.

An indirect benefit of offering BVd to patients with RRMM who have received one prior LoT is the potential to increase therapeutic options for subsequent lines of therapy. In discussion with the EAG they confirmed there is no standard method of quantifying the 'option value' of a new MoA, but GSK proposes some possible reference classes:

- An arbitrary inflator could be applied to the clinical results of the newer treatment by the Committee to represent the ability of clinicians to select the most appropriate medicine for patients if multiple treatments are approved.
- The probability that the treatment later ends up as part of a combination treatment with higher cost-effectiveness could be estimated by the Committee and this value added (at an appropriate discount rate) to the QALY benefit of the newer treatment to represent the ability of clinicians to more freely investigate combinations of therapies (either simultaneously or sequentially) if multiple treatments are approved.

Even if these benefits cannot be precisely quantified, they represent the asymmetrical potential for upside; new MOAs are always valuable and it will never be detrimental to have option value in the treatment armamentarium in a disease like MM. These arguments collectively suggest that it might be appropriate to raise the decision ICER threshold by a modest amount above £30,000 / QALY to account for indirect benefits of approving the treatment.

B.3.14 Validation

B.3.14.1 Model technical quality control

An internal validity check was performed by the model developers using a quality control process. The internal validity check was conducted systematically by completing the TECH-VER checklist (198, 199). This involved testing the selection and results of different modelling options, calculation spot checks, validation against source data and extreme value testing to assess whether the model responded logically to the tests.

The quality check explored the following general aspects of the model:

- Top-down tests, involving systematic variation of the model input parameters to establish whether changes in inputs results in expected changes in the model outputs.
- Model internal functionality involving testing all key model parameters, and extreme value testing in key sections of the model.
- Accuracy of input data involving a cross-checking of the model inputs in Excel against the corresponding data sources.

Overall, the validation identified no issues with the computational accuracy of the model. A completed version of the checklist is attached in Appendix O, Section 7.

B.3.14.2 External validation of cost-effectiveness analysis

Model inputs and assumptions were validated during a two-staged interview with three practicing UK based haematologists completed in April 2024 (Section B.2.3.3 Appendix M). The clinical experts confirmed that the model structure captures well the patient pathway for 2L MM patients with one previous LoT. The clinical experts also validated key inputs including extrapolation assumptions of clinical outcomes, healthcare resource utilisation, and subsequent treatment related parameters. More details of the clinical expert validation are provided in Appendix M.

B.3.15 Interpretation and conclusions of economic evidence

Cost-effectiveness modelling in MM is challenging as patients are faced with a complex treatment pathway with room for clinical judgement on the order and rationale

for particular treatment sequences. Unlike at the 1L, where a well-defined SoC has emerged, patient entering the 2L are faced with limited options and limited scope for a long PFS. This challenge is exacerbated in patients for whom lenalidomide is an unsuitable treatment (which is likely to be most patients in NHS clinical practice). For these patients, treatment options are even more restricted. Therefore, optimal use of NHS resources at 2L involves achieving the longest initial PFS, balanced with the need to conserve treatment options for subsequent lines of therapy. A key goal for patients, clinicians and NHS budget holders alike is accessing new and effective MoAs to increase the ability of the patient and their clinician to find an optimal pathway through the stages of the disease. In this sense, interpretation of the economic evidence should include consideration of rewarding innovative new MoAs like belamaf.

A strength of the cost-effectiveness analysis is that the clinical evidence base is driven by head-to-head efficacy data taken from the DREAMM-7 phase III trial for the comparison of BVd to DVd. DVd is the clear SoC in 2L MM in England and Wales, meaning the strong clinical signal should easily generalise into NHS practice. Findings from the trial were consistent across all endpoints and subgroups, demonstrating that BVd was associated with greater depth and durability of response. For non-trial comparators, an NMA was conducted using DSU gold standard methodologies previously accept in recent MM NICE HTAs and driven by a recently performed SLR. External clinical advice was sought to drive the comparators to be included and reinforce key assumptions (Appendix M). All relevant comparators, costs and outcomes required to assess the cost-effectiveness of BVd were present in the economic analysis.

Where there are uncertainties in the analysis, the base-case choice of the model identifies conservative assumptions across the efficacy data used (ITT), the choice of trial data extrapolations and included costs. These were driven by previous methods and clinical expertise in order to minimize the risk to BVd cost-effectiveness. Uncertainty in extrapolation of the immature DREAMM-7 OS data was managed through clinician validation, statistical analysis, methodologies leveraging mature trial data (informative prior using CASTOR (19, 121, 122)) and comparison with a scenario of OS surrogacy with PFS; identified through a rigorous MM-specific analysis.

A challenge of the economic analysis is modelling the rapidly evolving MM treatment paradigm. Various scenarios were conducted to investigate cost impact on the subsequent treatment pathway, with all scenarios demonstrating the strength of BVd cost-effectiveness. An IPCW analysis to adjust the DREAMM-7 OS data for subsequent treatments further strengthened BVd OS outcomes compared to DVd (Appendix O).

Belamaf is a novel MoA with a manageable safety profile broadly comparable to current treatment practice. For eye-related side-effects, which is distinctive of belamaf treatment, the economic analysis appropriately accounts for both the increased resource use associated with ophthalmologist visits and AEs, and management of eye-related side-effects through dose delays and reduction with the IPD methodology

of dosage. The extrapolation of this analysis is conservative, assuming dosage trends do not continue on a downwards gradient where data is limited.

The base-case cost-effectiveness model indicates that BVd PAS extendedly dominates DVd, meaning a mix of BVd and SVd is both cheaper and more effective than DVd. The cost effectiveness estimate (BVd PAS vs other list) was £8,190/ QALY versus SVd. For the hKd comparison, the comparator dominated in the analysis, meaning either BVd was both cheaper and more effective than the alternative by itself. Over time, it is likely most patients will enter 2L refractory to daratumumab, owing to the widespread use of DRd at 1L. This will make DVd an entirely inappropriate option for those patients in the future. Hence, analyses were considered separately for two subpopulations, which differ only by their relevant comparators, i.e., patients eligible for daratumumab and patients ineligible for daratumumab-based regimens. Both analyses indicated that BVd is a cost-effective treatment option for these two subpopulations.

Sensitivity and scenario analysis reassures that these findings are highly likely to be seen in RW settings. These analyses show that BVd raises mean overall survival by an expected ~4.5 years, time spent progression-free by at least 2 years, and the net budget impact of BVd does not exceed the budget impact test of £20 million per year in the first 3 years of its use in the NHS.

The DREAMM-7 trial efficacy results are a ‘step change’ for patients with RRMM. Section B.2 describes how BVd achieves nearly three times greater PFS than any NHS-approved comparator, and Section B.3 demonstrates that the anticipated near doubling of life years and QALYs can be delivered in a cost-efficient manner, representing the best possible use of resources in 2L MM. The economic analysis presented provides robust evidence of the cost-effectiveness of BVd inclusion to tackle the high unmet need found in 2L for patients refractory to or for patients who are unsuitable to lenalidomide against all comparators BVd is likely to displace. There is also a likely whole-system benefit of the introduction of a new MoA by increasing treatment availability in subsequent treatment lines which is difficult to capture in the analysis. Taken together, the broad efficacy benefit observed in this appraisal, manageable safety profile, cost and utility associated with belamaf as an off-the-shelf, outpatient BCMA therapy, offer strong support for BVd as a treatment option at 2L for patients for whom lenalidomide is unsuitable. Should BVd be approved for routine commissioning for this group, it has the potential to redefine the NICE treatment paradigm and fundamentally change the prognosis of 2L patients, bringing hope to patients and their families.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Summary of Information for Patients (SIP)

May 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6212 Belantamab mafodotin with bortezomib and dexamethasone Summary of Information for Patients v1.0 21May2024.docx	**V1.0**	**No**	**21 May, 2024**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response:
Belantamab mafodotin (which is abbreviated in this submission to 'belamaf') is sold under the brand name Blenrep®.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
The main population being appraised by NICE in this submission is adult patients diagnosed with multiple myeloma (MM) that is relapsed (reappearance of signs and symptoms of a disease after a period of improvement) or resistant to the first therapy tried (when you can no longer have a certain treatment it is said that you are 'refractory' or 'resistant' to that treatment, meaning it will not be offered to you because it is very unlikely to work) in the second line (2L). This means that patients have received one prior therapy and discovered that their disease is no longer affected by this therapy. For the context of this submission, belantamab mafodotin ('belamaf') is the medicine which is being assessed. However, it is given as a combination with two existing treatments, namely bortezomib and dexamethasone. This is a common approach which is taken in the treatment of myeloma. The combination treatment will be referred to as BVd throughout.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:

BVd does not yet have a license for use in the population in this submission. The regulatory submission for DREAMM-7 is due to be made halfway through 2024.

1d) 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:

Response:

Myeloma UK have engaged with GlaxoSmithKline (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 Health Technology Assessment (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 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

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. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

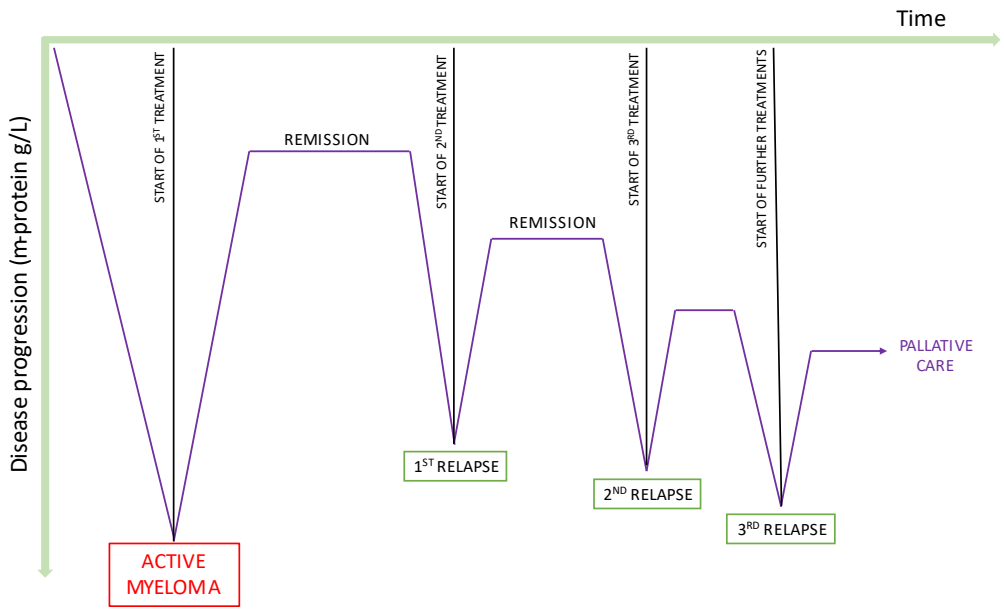
Multiple myeloma (MM) is a rare and debilitating condition caused by an abnormality in the cells of the bone marrow, called plasma cells (abnormal plasma cells are myeloma cells) [1]. These are a type of white blood cell which are normally involved in fighting infection, but in the case of MM instead grow uncontrollably and cause great harm to the patient [1].Nobody knows why plasma cells sometimes become myeloma cells [2].

MM 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 [3].

The impact of myeloma is mostly from the build-up of cancerous cells in the bone marrow [4]. The number and severity of symptoms that patients with myeloma experience can affect their quality of life. Major symptoms include:

- **Fatigue:** Patients are at risk of 'anaemia', which tends to cause extreme tiredness, weakness, and breathlessness. This is because patients don't have enough red blood cells, which carry oxygen around the body. This is due to the fact that too many myeloma cells can cause crowding in the bone marrow meaning that other types of cells cannot be made.
- **Persistent infection:** Myeloma patients are very likely to experience more infections than usual, and for these infections to last longer. This is owing to the fact of limited non-cancerous white blood cells, which ordinarily fight infection. Myeloma cell crowding in the bone marrow means that these types of cells cannot be made either.
- **Myeloma bone disease:** The pressure of the myeloma cells can cause physical changes to the bones. The most common of these changes is 'myeloma bone disease', which is where little cracks or weak spots appear in your bones. This can make the bones more fragile, and broken bones are a common symptom of myeloma. A secondary symptom is that if the myeloma is in the spine, it can compress the spinal bones onto the nerves which send information from the hands and feet to the brain. This can result in damage to the nerve, which is often just tingling in the hands and feet but can be more serious than this. Unfortunately, all of these symptoms can be extremely painful.
- **Kidney damage:** The weakening of the bones can cause changes in the blood chemistry. Bones are made up of a chemical called calcium, and your body needs a certain amount of calcium to remain healthy. However, when little pieces of bone flake off into the blood stream because of myeloma bone disease, the body has far too much calcium and this can be very harmful. Usually, calcium is processed in the kidneys and so a secondary effect of too much calcium in the body can be overworking the kidneys, which is a very dangerous (especially because some of the drugs used to treat myeloma are also processed in the kidneys, which taxes them even more).

Unfortunately, there is no cure for MM. There are multiple effective treatment options, but the cancerous cells will inevitably mutate and change to become resistant to these treatments over time [4]. The patient journey of the disease typically includes period of treatment and remission (where there is a decrease in or disappearance of symptoms) followed by relapses. Management of MM is concentrated around managing 'relapse', which is the period between the disease mutating and a new effective treatment being found [2]. Each treatment usually ends in a 'relapse' once the disease has become 'refractory' (unmanageable/resistant) to that treatment. The diagram below might help to understand the patient journey.



Adjusted figure from Hajek R. et al [5].

Treatment for MM is therefore very complicated, with the options available to patients depending on the treatments they have already tried and relapsed on. In this submission, BVd is expected to be used by patients at second line (2L) with relapsed or resistant multiple myeloma (RRMM). It is likely to be especially relevant in patients for whom lenalidomide is an unsuitable treatment option. This means that these patients have already received one line of treatment and are unsuitable to be treated with any therapy that contains lenalidomide after this as either their myeloma has become resistant to lenalidomide or their clinician believes lenalidomide is a poor choice for some other reason (for example, because they are pregnant). There are limited options for this group of patients and data suggests that the corresponding outcomes are poor (see section 2c for more information). For these patients with poor outcomes, BVd offers a new treatment which has the chance of working so is potentially of high importance.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

Diagnosing myeloma can be tricky, as it is so rare that GPs will not always have had much experience (an average GP will see one new case every 8-10 years [6]) with it and the symptoms are vague so can easily be confused with a few other diseases.

In general, when myeloma is suspected, a blood or urine test can be used to identify it. This is because the myeloma cells produce a large amount of a certain type of non-functioning protein (commonly called a 'paraprotein' or 'M protein') [1]. Therefore, finding paraprotein in the blood or urine is a good sign that there are myeloma cells in the body.

This is not always perfectly accurate, since there are benign (non-cancerous) conditions which cause paraprotein to be produced, such as Monoclonal Gammopathy of Undetermined Significance (MGUS) [7]. MGUS can turn into MM, but this is quite rare [7]. Therefore, often doctors

will order another test to determine whether the paraprotein is caused by myeloma (and needs treatment) or a benign condition like MGUS (which doesn't need 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 you may be offered, and in addition to diagnosing myeloma you may be offered tests to identify what the most appropriate treatment for you would be.

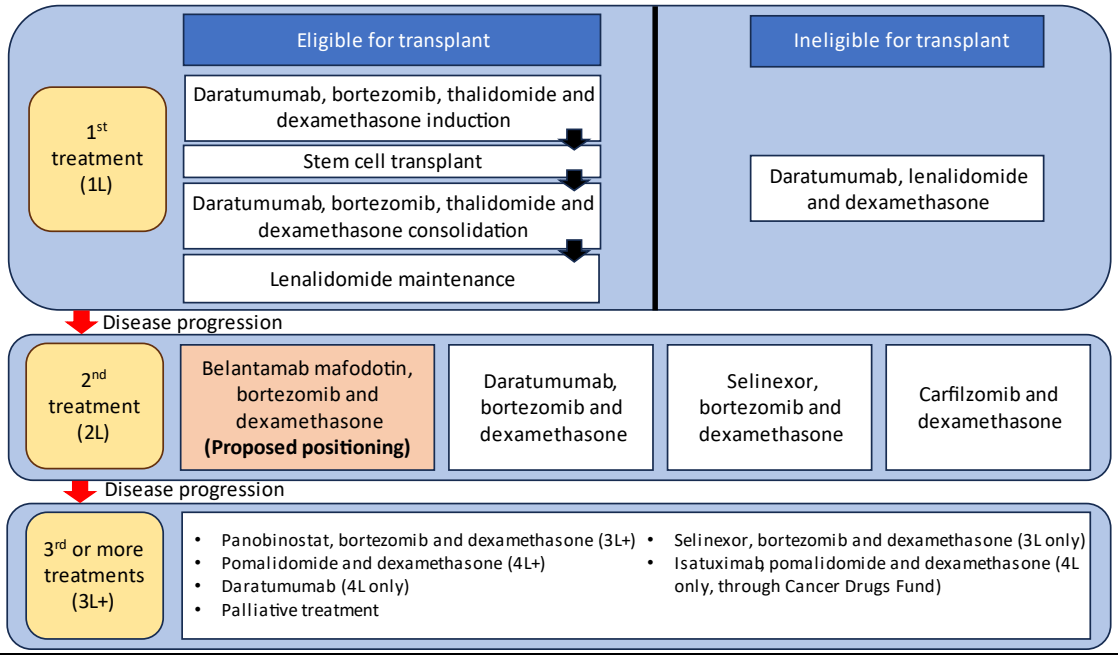
2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

Treatment for MM is extremely complicated, and your clinician will explain the options which are suitable for your individual circumstances in more detail as they become relevant. The summary diagram below might help to show how a typical patient might move through the treatment options, including the proposed positioning of BVd in the 2L (second line, where patients have received one prior therapy). Please note that this diagram does not show the full list of treatment options, but those that most patients are likely to receive. Other treatments are available for those who are not suitable for the options shown.



Source: GSK internal materials

This treatment pathway is described over a number of NICE technology appraisals; however, it is likely that this pathway will change over time as new treatments are introduced.

A summary can be seen below of the journey a patient may go through:

- When initially diagnosed, a discussion will take place between the patient and doctor about whether beginning treatment is right for that patient. Sometimes it is appropriate to monitor the myeloma without directly treating it, and sometimes the patient would prefer not to be treated for a variety of reasons.
- If it is decided that a treatment would be the best option, some patients will be suitable for a bone marrow transplant, which may help control the myeloma by replacing the cancerous bone marrow cells with new healthy cells. Patients undergoing this route will often have a course of therapy called induction treatment to try and kill the bulk of the myeloma cells (often daratumumab, bortezomib, thalidomide and dexamethasone [8]), following the transplant some patients may have another drug therapy for a short time to enhance the transplant's effectiveness and then a course of drug treatment to reduce the risk of myeloma coming back after the transplant (lenalidomide maintenance) [9]. If a patient is not suitable for a bone marrow transplant, they will often receive lenalidomide plus dexamethasone (Rd) or the recently approved daratumumab with lenalidomide and dexamethasone (DRd). As a result of these treatments, a lot of patients have been exposed to lenalidomide meaning lenalidomide may be unsuitable for further treatment as the patient's myeloma may have become resistant to it.
- If the disease comes back despite the first line of treatment, patients will usually then receive more treatment called the second line (triplet regimens are usually recommended (patients receive three drugs), although some patients who are too frail may receive doublet therapies (patients receive two drugs)).
- NICE currently recommends 6 regimens for 2L RRMM patients, of which only three are triplets. Those who didn't receive a lenalidomide based therapy for frontline treatment may benefit from carfilzomib plus lenalidomide and dexamethasone (KRd) or Rd in this 2L. However, in the patient population considered in this submission, lenalidomide-based regimens can be ruled out due to the extensive use of lenalidomide in the frontline making most patients lenalidomide-resistant. Currently, regimens without lenalidomide that are available in the UK in 2L include carfilzomib plus dexamethasone (Kd) [10], daratumumab plus bortezomib and dexamethasone (DVd) [11], selinexor plus bortezomib and dexamethasone (SVd)[12] and bortezomib monotherapy (but this is rarely used in clinical practice in the UK). This leaving Kd, DVd and SVd as treatment options for these patients at 2L however they have limited outcomes in the lenalidomide-resistant population.
- If the disease come back again after subsequent relapses then a variety of different treatments will be used, depending on the treatments that have already been tried by patients. Therefore, when patients reach the time point for later course of treatment they will most likely be resistant to lenalidomide.

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 also include carer burden and outputs from patient

preference studies, when conducted in order to show what matters most to patients and carers 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 that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

MM is a very severe disease, which has a significant impact on the lives of those it affects. Compared to people without myeloma, patients report that having the disease significantly impacts physical functioning and social activities [13]. As myeloma is progressive, patients also report that symptoms get worse over time [14]. This highlights the need for treatments which preserve patient experience of life while treating the myeloma itself. Patients also describe how there is a mental health impact to having myeloma on top of the physical symptoms. For example, difficulty in processing the news that the myeloma has relapsed can lead to a decline in mental health well-being [15]. The symptoms of myeloma can negatively impact a person's ability to work [15] resulting in financial worry about needing to discontinue employment or reduce their earning capabilities [16].

In addition to patients themselves, their caregivers are also 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 [17]. The burden of caring for someone with myeloma may restrict the caregiver's daily activities, leading to isolation and a lack of social support [18].

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

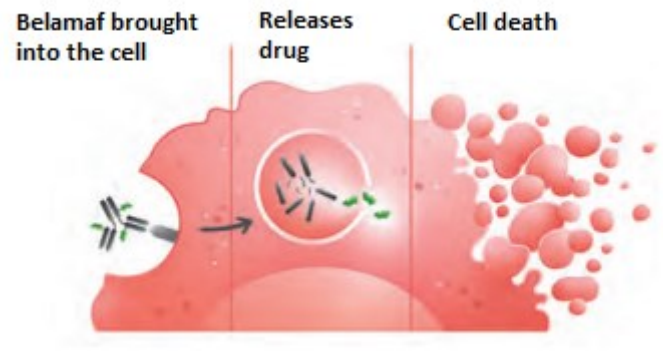
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Belamaf is an 'antibody drug conjugate', meaning it is a combination of an antibody and a drug. Antibodies are designed to find and attach to a specific protein found on the surface of cancer cells. In this case, the antibody is specifically designed to attach to proteins produced by myeloma cells on its surface, called B-cell maturation antigen (BCMA). Once the antibody attaches to the cancer cell, the drug part of the medicine enters the cell. It either destroys the cell or helps the body's natural defences destroy it.

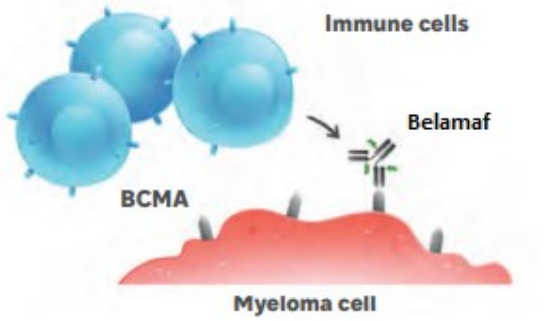
Belamaf therefore works in two ways:

1. It can identify cancerous cells by the fact that they are creating lots of the B-cell maturation antigen, enter those cells and then kill them.



Source: GSK internal materials

2. It can act as a signal to the body's regular immune system that there is something unusual about a myeloma cell and rely on the body's immune system to kill those cells.



Source: GSK internal materials

Belamaf is innovative as it is the first antibody-drug conjugate that targets BCMA for patients with RRMM. Other treatments target MM differently, and that means that when the disease mutates to become resistant to other treatments it may still respond to belamaf. Its novel mechanism of action addresses the unmet need arising in RRMM patients at 2L, who have previously received lenalidomide and may have limited outcomes. Belamaf would provide a valuable treatment option for RRMM patients, including those patients that are resistant to lenalidomide at first relapse.

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 treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

Yes

Belamaf is intended to be used in combination with bortezomib, and dexamethasone. In relapsed/resistant multiple myeloma, the combination of active agents with bortezomib/dexamethasone can provide improved patient outcomes [19]. There is high value placed on having combination therapies available that have differing but complementary mechanisms of action as patients progress and become resistant to different treatments [19].

Bortezomib, also known as Velcade®, is a proteasome inhibitor drug used in the treatment of myeloma. It works by blocking the actions of proteasomes [20]. Proteasomes are large molecules found in all cells of the body, and they are involved in the breakdown of damaged or unwanted proteins. Bortezomib temporarily blocks their function, stopping them from breaking down unwanted proteins. This causes proteins to build up to toxic levels, killing the cell. Myeloma cells rely more heavily on proteasomes, as they produce more proteins than normal healthy cells. They are therefore much more sensitive to bortezomib.

Bortezomib is usually given as an injection under the skin (subcutaneous) but can also be given intravenously (into the vein) [20].

Dexamethasone is a steroid drug used in the treatment of myeloma [21]. It belongs to a class of steroids called glucocorticoids. Dexamethasone mimics the action of a naturally occurring hormone produced in the body. It is effective at killing myeloma cells and can make other anti-myeloma drugs work better. Dexamethasone can also prevent inflammation which can help to reduce pain associated with myeloma bone disease.

Please see section 3g for information relating to possible side effects with belamaf in combination with bortezomib and dexamethasone.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment 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?

Response:

Belamaf is given as a drip infusion taking thirty minutes as long as there is no infusion related adverse reactions (side effects). When belamaf is given plus bortezomib and dexamethasone, the recommended dose for belamaf is 2.5mg/kg every 3 weeks.

Typically, belamaf will be given until the myeloma cells start to grow again and becomes resistant to this treatment. However, some patients will experience side effects that will mean they stop before this and try a different treatment. Patients who experience side-effects can often have these effects managed by reducing the dose or prolonging the dosing interval.

As part of the BVd treatment combination, 1.3mg/m^2 bortezomib is given subcutaneously (injection under the skin) on days 1, 4, 8 and 11 of every 21-day (3 week) cycle. Dexamethasone 20mg is administered on the day of and the day after bortezomib treatment either orally or intravenously (into the vein). Both bortezomib and dexamethasone are only given through the completion of the first 8 doses of belamaf.

Existing treatment combinations that patients may be offered in the 2L have different ways they are given which are summarised below:

- DVd: when given in combination with bortezomib (V) and dexamethasone (d), daratumumab (D) is given as either as an injection into the vein (intravenous) or under the skin (subcutaneous) which is most commonly used in the UK [11].
- Kd: in this treatment combination, carfilzomib is given as an injection into the vein (intravenous)[10].
- SVd: in this treatment combination, selinexor is taken as a tablet orally (by mouth) [12].

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

DREAMM-7

DREAMM-7 (NCT04246047) is an ongoing Phase 3 clinical trial providing a reliable data source on the efficacy and safety of belamaf in combination with bortezomib and dexamethasone (BVd). This trial compared the treatment combination of BVd with that of daratumumab, bortezomib and dexamethasone (DVd).

A total of 494 patients participated in the trial, with 243 receiving BVd and 251 receiving DVd. It was conducted in 151 MM specialty centres in 20 countries, including 7 centres in the UK.

The key inclusion and exclusion criteria of the trial is as follows:

Key inclusion criteria (patients who are considered to be suitable for the trial)	Key exclusion criteria (patients who are not considered to be suitable for the trial)
• Aged 18 or older. • Confirmed diagnosis of MM as defined according to the International Myeloma Working Group (IMWG) criteria. • ECOG performance status of 0-2 (ECOG is a scale from 0-5 which is used to assess how a patient's disease is progressing and affecting the patient's daily life) • Previously treated with at least 1 prior line of MM therapy	• Prior BCMA targeted therapy • Intolerance to daratumumab and bortezomib • Resistance to either daratumumab or any-CD38 therapy or bortezomib • Systemic anti-myeloma therapy received within 14 days or less or five half-lives (half-life of a drug is an estimate of the time it takes for amount in the body of that drug to be reduced by one-half), whichever is shorter • Patients with any serious and/or unstable pre-existing medical condition that could interfere with their safety. • Patients who have received major surgery within the last four weeks

The first patient was given a dose on the 21 May 2020. Primary analysis was completed on 02 October 2023. Additional data from the DREAMM-7 trial will be released in the future.

Details are available at Evaluation of Efficacy and Safety of Belantamab Mafodotin, Bortezomib and Dexamethasone Versus Daratumumab, Bortezomib and Dexamethasone in Participants With Relapsed/Refractory Multiple Myeloma - Full Text View - ClinicalTrials.gov

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

Blenrep® ('belamaf') in combination with Bortezomib and Dexamethasone (BVd) has been shown to be an effective triplet regimen with positive primary analysis results from the DREAMM-7 clinical trial.

BVd was compared against DVd, which is the current best available treatment on the NHS (standard of care for patients at 2L). The trial was designed to test whether BVd was better than DVd, and hence support a case that BVd should become the new best available treatment on the NHS. To prove this, a number of different outcomes were explored. Some key outcomes are summarised below [22] [23]:

- **Progression free survival (PFS):** defined as the length of time during or after cancer treatment that a patient lives with the disease, but it does not get worse. PFS is used to measure how long a patient's condition remains stable or improves without their disease progressing. In the trial, patients treated with BVd had, on average, 23 months longer PFS before their cancer progressed compared to those treated with DVd. This PFS benefit of BVd was also seen in lenalidomide-resistant patients with a 63% reduced risk of cancer progression.
- **Overall survival (OS):** At the time when the data was analysed the OS results showed a trend favouring the patients receiving BVd. OS represents the duration a patient lives from the start of treatment until their death, regardless of whether the cause of death is related to the disease being treated or not. OS is an important outcome measure to assess the effectiveness of treatments and evaluate the impact on patients' survival rates. Additional OS follow-up is ongoing.
- **Duration of response (DOR):** Patients spent longer on treatment in the BVd arm (35.6 months) compared with the DVd arm (17.8 months).
- **Overall response rate (ORR):** A greater proportion of patients responded to the BVd treatment than the DVd treatment (82.7% vs 71.3%)

These results suggest that BVd can potentially be a new standard of care in patients at 2L for whom lenalidomide is an unsuitable treatment owing to the robust efficacy, manageable safety, and ease of administration.

3f) 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? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

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 willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

As part of the DREAMM-7 clinical trial, patient reported outcomes (PROs) were reported in health-related quality of life questionnaires. Patients in the trial were asked to complete questionnaires about their quality of life called the EQ-5D-3L (which isn't specific to any disease), the EORTC-QLQ-C30 (which assesses the quality of life of cancer patients) and the EORTC-QLQ-MY20 (which is a myeloma-specific survey). For example, within the EQ-5D-3L questionnaire patients are asked to score their health state for mobility, self-care, usual activities, pain/discomfort and anxiety/depression [24]. These questionnaires vary slightly but can quantify the patient's perspective on their own health, providing valuable insights into their well-being or any changes in their condition over time [24].

Within the DREAMM-7 trial, no difference in quality of life between the BVd and DVd arms was observed over time. This is despite the higher frequency of eye-related side effects seen in the BVd arm.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment 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 treatment and include details of a benefit/risk assessment where possible. This will support patient 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 compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

The safety and tolerability of BVd in DREAMM-7 was consistent with those already described for belamaf in spite of patients staying on treatment for longer compared to the DREAMM-2 and DREAMM-3 trials. All patients in the DREAMM-7 trial experienced one or more side effects (any health problem that occurs after a treatment is considered an adverse event (AE)).

AEs are graded on a scale of 1 to 5 based on their severity with grade 3 or 4 being deemed 'severe or medically significant'. Serious AEs are usually associated with events that pose a threat to a patient's life or ability to function. When comparing the BVd and DVd treatment arms, there was higher rates of grade 3 or 4 AEs (95% vs 76%) and serious AEs (50% vs 37%). Due to the average time patients are on treatment being greater in the BVd arm compared to the DVd arm, a method is used that adjusts AE rates based on total exposure to treatment. This adjustment helps provide a fair comparison of AE rates when the length of time patients are on treatment differs between treatment groups. In the BVd and DVd arms, when taking this adjustment into consideration, rates (per 100 person-year) of grade 3 or 4 AEs were 68.8 and 62.4 and rates of serious AEs were 36.3 and 30.0. In total, 64 patients (26%) in the BVd arm vs 36 (15%) in the DVd arm discontinued treatment due to AEs. Deaths from serious AEs were reported in 23 patients (10%) in the BVd arm

and 19 (8%) in the DVd arm. Of these deaths, 7 (3%) in the BVd and 2 (less than 1%) in the DVd were considered treatment related. The rates of infections, a known risk with BCMA-targeting agents, was similar between treatment arms in the DREAMM-7 trial (70% in BVd arm vs 67% in DVd arm).

Eye-related side effects, which are a known risk with belamaf, were manageable and resolved with dose modifications (including delays and reductions). These side effects were reported in 79% of patients in the BVd arm and 29% in the DVd arm, suggesting there are some eye-related issues already in the general MM population. Eye-related side effects resulted in a low rate of overall discontinuations (9%), but a significantly higher rate of dose delays (44%) and reductions (78%) in the BVd arm. Supportive care for belamaf is preservative free artificial tears (eye drops) taken four times a day until completion of therapy. Despite the higher frequency of eye-related side effects in the BVd arm, overall health-related quality of life did not differ between arms over time.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

The key benefits of belamaf plus bortezomib and dexamethasone can be summarised as:

- **Clinical benefit:** Within the DREAMM-7 trial the treatment has represented significant clinical benefit in comparison to DVd, the current standard of care at second line. With this in mind, the BVd treatment may offer a new standard of care for RRMM patients for whom lenalidomide is unsuitable in the 2L.
- **Novel mechanism of action:** BVd is a triplet combination treatment including the first antibody-drug conjugate that targets BCMA for patients with RRMM. To improve outcomes, patients require new treatment options that can affect their myeloma in a different way. Therefore, belamaf's novel mechanism of action addresses this key unmet need for patients and would provide a valuable alternate treatment option for RRMM patients for whom lenalidomide is unsuitable at first relapse.
- **Method of administration:** We expect that patients and carers may benefit from the method of administering belamaf. As described above, belamaf can be given over a thirty-minute infusion as long as there are no infusion-related side-effects, which should help prevent patients becoming 'medicalised' (or living their lives exclusively defined by their disease). Belamaf is an off-the-shelf, outpatient therapy which means it has a broad deliverability.
- **Infection profile:** The rate of infections, including opportunistic infections, a known risk with other BCMA options, was similar between treatment arms in the DREAMM-7 trial.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

Whilst BVd aims to improve quality of life and prolong survival, the treatment may not be effective for every patient.

Like all medications, BVd may be associated with side effects. Namely, patient may experience eye-related side effects. However, these are manageable and reversible with dose modifications (see section 3g for more information on safety of the medicine and side effects). There may be logistical challenges associated with the management of these side effects, although these may be overcome by referral to community-based optometrists.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. 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 treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE 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 health outcomes, 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 side effects 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)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

NICE request that manufacturers support their submissions with an economic model, trying to calculate whether the benefits of the drug to patients are worth the costs to the NHS. Benefits are expressed in 'quality adjusted life years' (QALYs) which are a unit of measurement equivalent to one year of life lived in perfect health (so for example two years of life lived at 50% of perfect health is equivalent to one QALY). A key concept in cost-effectiveness analysis is the 'incremental cost-effectiveness ratio threshold', which is a number NICE publish whereby if a treatment can generate a QALY for less than this value then it should be made available in the NHS.

When evaluating the cost effectiveness of belamaf, it's important to look beyond the duration of the DREAMM-7 clinical trial and consider its long-term impact. In this NICE submission a 'partition survival model' was used. Partitioned survival models help researchers estimate how long patients

are likely to survive with the treatment, their quality of life and associated costs over an extended period of time.

This model considers different factors like how the disease progresses, how patients respond to treatment, how patients' quality of life may change as the disease progresses, and how likely patients are to pass away. By taking all these factors into account, the model simulates how the disease will likely progress and how it will affect patients' outcomes.

As outlined in section 3e, belamaf (BVd) has shown to improve the length of time that second line RRMM patients are progression free (meaning they spend longer in the progression free health state) when compared to those receiving standard of care DVd. Although belamaf is associated with higher costs, these have been show using the company's economic model to be cost-effective for the increase in quality adjusted life years that belamaf provides.

Key outcomes from the trial (for example the overall survival of patients, length of time patients are progression free and the time until treatment was discontinued) feed into the model for 28.2 months which is the average time patients were followed up for. After this point, longer-term outcomes have been estimated out into the future using standard statistical tests creating some uncertainty. We expect the methods used for this long-term estimation to be discussed with NICE.

Due to the regularity of dose delays and dose reductions of belamaf, the individual patient-level data was used in the model and extrapolated to give realistic estimations of how treatment with belamaf in the BVd combination is used in practice. This information is used by researchers to estimate the overall costs and benefits of the treatment.

All these considerations impact the decision on whether belamaf represents good value for money and a good use of NHS resources. Based on the evidence available and the company's economic analysis, belamaf plus bortezomib and dexamethasone would be considered as offering a good use of NHS resources, as a new treatment for patients with relapsed/resistant multiple myeloma in the 2L.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Belamaf in combination with bortezomib and dexamethasone offers a 'step change' in the treatment of RRMM patients in 2L for whom lenalidomide is unsuitable. Currently, this patient population experiences limited efficacy outcomes.

The combination of belamaf with bortezomib and dexamethasone has the following innovative characteristics, which are meaningful to both patients and the NHS:

- Belamaf is innovative as it is the first antibody-drug conjugate that targets BCMA for patients with RRMM (as described in section 3a). Its novel mechanism of action addresses the unmet need arising in RRMM patients, who have had one line of treatment. Belamaf

would provide a valuable treatment option for RRMM at second line, including those patients for whom lenalidomide is unsuitable at first relapse.

- BVd has showed a strong clinical response in the body when compared to the current standard of care at 2L DVd in the DREAMM-7 trial. The treatment combination has demonstrated it extends the length of time patients spend disease free (36.6 months with BVd vs 13.4 months with DVd). Therefore, BVd could offer a new standard of care in the second line treatment of RRMM.

3l) Equalities

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

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

Response:

There are several risk factors which are seen with MM, including age, gender, family history, and ethnicity. MM particularly disadvantages black people who are 2-3 times more likely to be affected than white people and tend to be diagnosed with myeloma at a younger age [25]. Exact reasons behind this are not clear but ongoing research suggests certain genetic abnormalities associated with the development of MGUS and/or myeloma are more common against black people than white people. Improving the treatment in 2L MM would therefore improve overall health outcomes being more equal.

It is not expected that this evaluation will exclude any people protected by equality legislation or lead to recommendations that will have an adverse impact on people with a particular disability or disabilities.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients 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 NICE 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.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

The following websites may provide useful information on multiple myeloma and belamaf:

- Myeloma UK: Homepage – Myeloma UK
- Cancer Research UK: Myeloma: Myeloma | Cancer Research UK
- Macmillan Cancer Support: Myeloma: What is myeloma? | Macmillan Cancer Support
- The DREAMM-7 study is registered on clinicaltrials.gov: Evaluation of Efficacy and Safety of Belantamab Mafodotin, Bortezomib and Dexamethasone Versus Daratumumab,

Bortezomib and Dexamethasone in Participants With Relapsed/Refractory Multiple Myeloma – Full Text View – ClinicalTrials.gov

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: 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

Response:

- RRMM: relapsed/refractory (or 'resistant') multiple myeloma
- MM: multiple myeloma
- 2L: second line
- MHRA: Medicines and Healthcare Regulatory Agency
- EMA: European Medicines Agency
- BVd: belantamab mafodotin plus bortezomib and dexamethasone
- DVd: daratumumab plus bortezomib and dexamethasone
- MGUS: monoclonal gammopathy of undetermined insignificance
- BCMA: B-cell maturation antigen

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:

Response:

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22. Maria-Victoria Mateos PR, Marek Hus, Zhongjun Xia, Vera Zherebtsova, Christopher Ward, P. Joy Ho, Roman Hajek, Kihyun Kim, Meletios A. Dimopoulos, Claudio Cerchione, Antonio Riccio, Astrid McKeown, Rachel Rogers, Hena Baig, Lydia Eccersley, Sumita Roy-Ghanta, Joanna

Opalinska, Vania Hungria. Results from the randomized phase III DREAMM-7 study of belantamab mafodotin (belamaf) + bortezomib, and dexamethasone (BVd) vs daratumumab, bortezomib, and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM). American Society Of Clinical Oncology 2024.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Clarification questions

June 2024

File name	Version	Contains confidential information	Date
ID6212 belantamab mafodotin with bortezomib and dexamethasone clarification response v1.0	1.0	Yes	28 June 2024

List of Tables

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Section A: Clarification on effectiveness data

Literature searches

A1. The documentation of the clinical evidence searches in Appendix D do not include the search strategies for the conference proceedings. Similarly, the documentation of the cost-effectiveness searches, health-related quality of life searches, and cost and healthcare resource searches in Appendix G do not include the search strategies for the grey literature or website searches. Please can the company provide these missing search strategies.

Response:

Conference proceedings were searched for key terms using centralized searches of the conference websites where available or directly in the conference proceedings where necessary. Given differences across the conferences, each approach was unique. Conference materials were searched for instances of (relapse* OR refract*) AND myeloma. From there, studies of preliminary interest were searched to ensure they had outcomes of interest as per the PICOS (assuming they already qualified for population of interest).

Similarly, for the economic SLR the search strategy for the grey literature and/or website searches included ‘myeloma’ or ‘multiple myeloma’ only due to the limited number of articles reported, and due to limitations with the search tools available on HTA/conference websites.

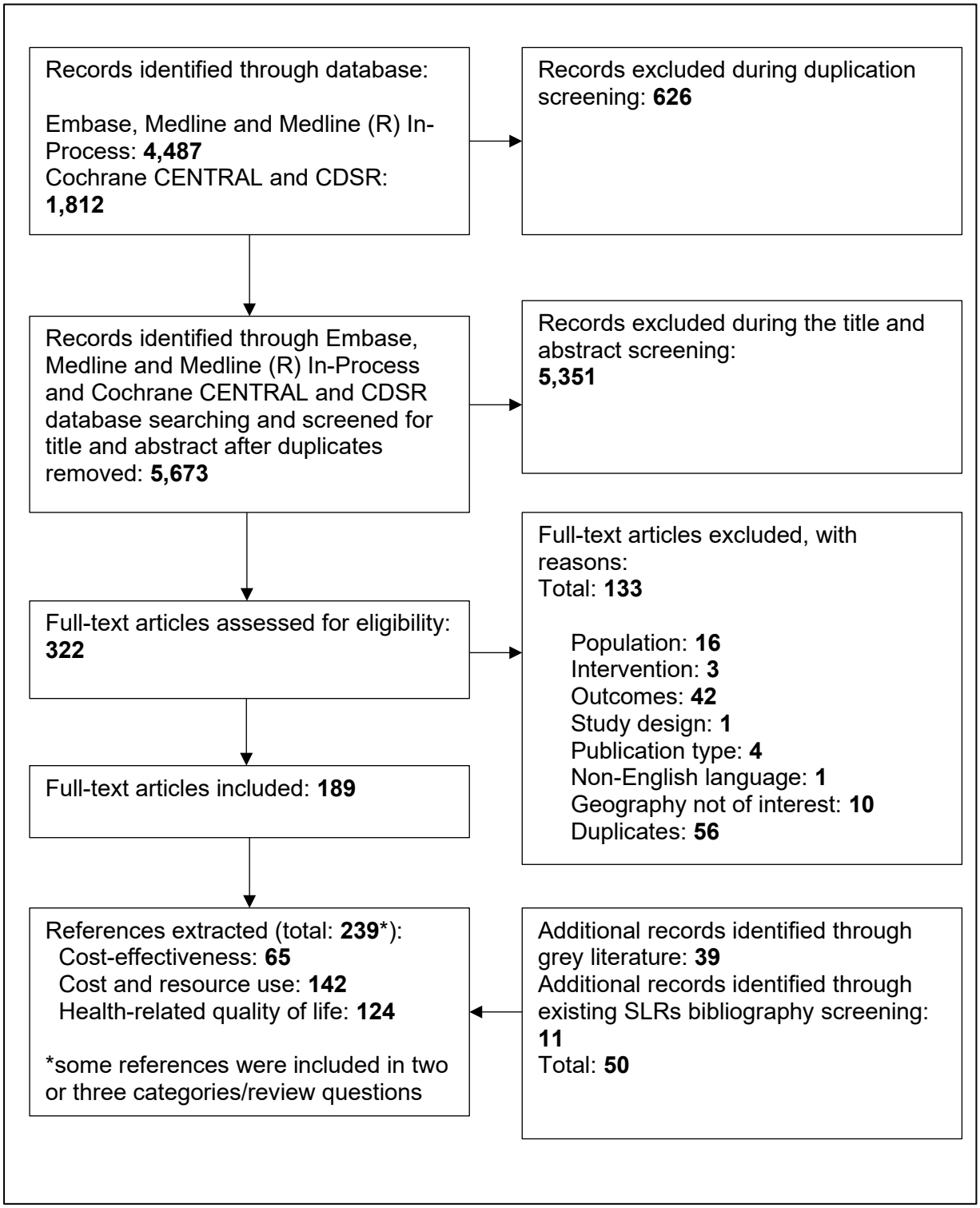
A2. In the clinical evidence searches in Appendix D, there were many differences between what the results of each database list (or add up to) and what the various PRISMA diagrams state. Moreover, the figures reported in the text of D.1.4.1 do not always match the PRISMA diagrams. There are too many errors to list. Similarly, for the cost-effectiveness searches, health-related quality of life searches, and cost and healthcare resource searches in Appendix G, the PRISMA diagrams do not tally with the results of the database searches. Please can the company provide updates to any incorrect figures.

Response:

An updated version of Appendix D has been uploaded as an additional file. The updated Appendix D includes updated PRISMA diagrams, search tables, and text to ensure the correct numbers and information are presented consistently throughout.

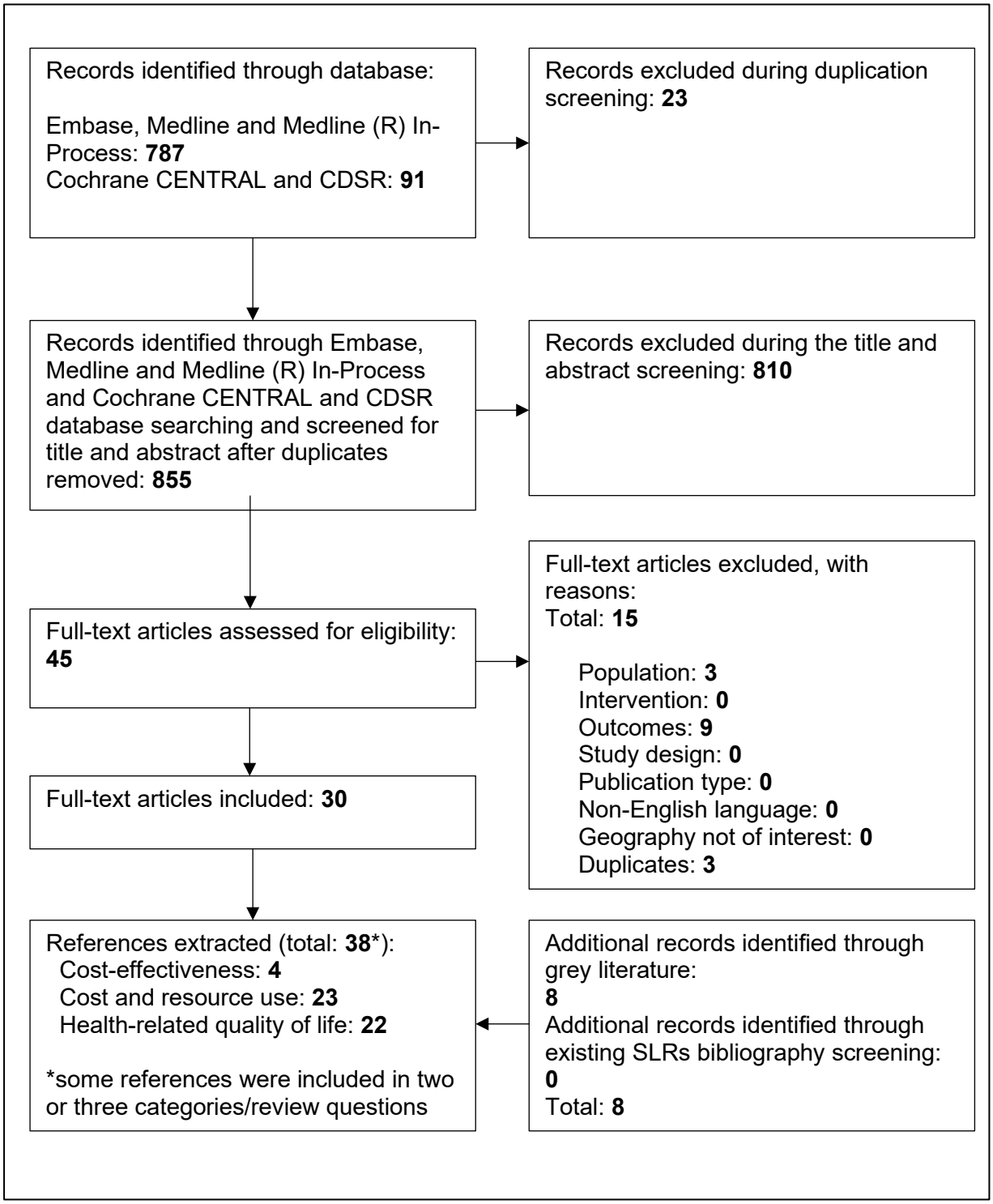
Thank you for the opportunity to clarify the figures reported in the text of Appendix G and the PRISMA diagrams (Figure 1 and Figure 2 in Appendix G). GSK have now improved the PRISMA diagrams' clarity by including the initial records identified from each database as detailed in Figure 1 and Figure 2 below. Additionally, GSK would like to correct a discrepancy in Cochrane CENTRAL and CDSR search results presented in Table 6 in Appendix G. The final number of records identified in this search conducted during the first update in January 2024 should be 91 instead of 84. After removal of duplicates from two databases (Embase and Cochrane), 855 records were included in the title and abstract screening. These numbers were corrected in Figure 2 below.

Figure 1. Updated PRISMA diagram – January 2023 search



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials

Figure 2. Updated PRISMA diagram – January 2024 search



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials

A3. For all searches in Appendices D and G, it is not always clear how many records were found through each source, either due to vague PRISMA diagrams (as in Appendix G), or due to the PRISMA representing the source yields in a way that cannot be determined from the yields reported in the search strategies

(as in Appendix D). Please can the company make sure all PRISMA diagrams represent sources searched clearly and that the yields from search strategies can be understood in the context of the PRISMA diagrams?

Response:

We have updated the PRISMA diagrams in Appendix D, search tables, and corresponding text so that the information is consistent with the searches as executed. Please note Appendix D has been uploaded as an additional file in response to question A2 and the PRISMA diagrams for Appendix G have been updated in the response to question A2.

A4. In the clinical evidence searches in Appendix D; and the cost-effectiveness searches, health-related quality of life searches, and cost and healthcare resource searches in Appendix G, for all sources searched, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. For instance, on Embase alone, there are several missing subject headings to represent treatment failure, recurrent disease, etc, and there are many more synonyms that could also have been searched as free-text terms for this concept. Please can the company clarify whether any relevant studies were missed due to excluding these additional search terms?

Response:

<u>Clinical SLR (Appendix D)</u>

The search strategies adopted across each of the SLRs utilised a wide range of terms with the aim to capture all relevant studies for the population of interest. A broad selection of search terms were included to capture data for patients with recurrent disease or treatment failure, including terms which made reference to line of therapy or history of prior treatment. The search strategy was then validated by comparing the adopted approach with a similar systematic literature review that was conducted by another manufacturer and reported at 2023 ISPOR Europe and our search and selection captured all of the same studies where selection criteria overlapped (1). We therefore believe the search strategy adopted was sufficient, reproducible, and transparent.

Economic SLR (Appendix G)

We believe all relevant papers have been captured with the search strategy employed by the company. The economic SLR search strategy was based on the clinical SLR and SLRs conducted for previous Belamaf submissions in MM (for example, for NICE ID2701), suggesting that NICE Committee would agree the strategy is appropriate. The search strategy is broad; 239 papers in the original SLR and 38 papers in the update were identified and extracted. There are a variety of search terms used for 2L+ MM included in the search strategy, including 'recurrent' and treatment lines to represent failure of previous lines of treatment.

The following search terms were included: relaps*:ti,ab OR refract*:ti,ab OR recurren*:ti,ab OR 'resistant':ti,ab OR 'prior treatment':ti,ab OR 'prior treatments':ti,ab OR 'prior therapy':ti,ab OR 'prior therapies':ti,ab OR 'previously treated':ti,ab OR 'second line':ti,ab OR 'third line':ti,ab OR '2nd line':ti,ab OR '3rd line':ti,ab OR 'fourth line':ti,ab OR '4th line':ti,ab OR 'fifth line':ti,ab OR '5th line':ti,ab

Decision problem

A5. PRIORITY: The proposed positioning of BVd in the treatment pathway for RRMM is as a second line treatment (2L-only), which is a more restrictive population than the [redacted] NICE scope that includes adults who have had at least one prior therapy, i.e., includes second and subsequent lines of treatment (2L+).

a) ***Please justify why the evidence informing the cost-effectiveness of BVd is informed by the ITT population of DREAMM-7 (2L+) rather than the subgroup specific evidence for the 2L-only population in line with the decision problem defined by the company.***

Response:

We believe using ITT data to inform the cost-effectiveness analysis is the best possible approach for modelling the proposed population for the rationale outlined below.

The proposed population is eligible 2L patients for whom lenalidomide is unsuitable, due to the high unmet need identified in this patient subgroup. Given the most common

reason a patient is unsuitable for lenalidomide is due to lenalidomide refractoriness, the most plausible subgroup to inform cost-effectiveness would be 2L-only patients who are lenalidomide refractory. However, this poses a challenge, since this patient group is small (n=22 in the BVd arm and n=27 in the DVd arm). Using this population in the economic model would present too high a degree of uncertainty, especially in any extrapolation of the trial data.

While the 2L only subgroup concerns 125 patients in the BVd arm and 125 patients in the DVd arm of DREAMM-7, as stated in the previous paragraph only a small number of these are lenalidomide refractory. As stated in Document B, and consistent with clinical expert feedback, almost all patients at 2L in the UK are lenalidomide refractory and therefore the clinical relevance of the 2L only subgroup is low.

If the ITT population is considered by the EAG to be unsuitable, the next best population to explore cost-effectiveness would be the lenalidomide refractory subgroup, where the conclusions of cost-effectiveness results are broadly in line with ITT. Although we are happy to present 2L, GSK do not believe the 2L subgroup to be generalisable to 2L patients receiving treatment in the NHS given only 20% of patients overall are lenalidomide refractory in the 2L-only subgroup.

The evidence from the DREAMM-7 trial in B.2.7.2 and Appendix E for the lenalidomide-refractory subgroup (all LoT) shows the comparative efficacy benefit for BVd versus DVd [PFS HR=0.31 (95% CI: 0.19, 0.48; [redacted] and for the 2L-only subgroup [redacted] Prior lines of therapy and refractory status are well established prognostic variables in MM (2, 3).

In addition, the ITT dataset has the strongest evidence base due to the large sample size across both arms (494 relapsed/refractory multiple myeloma (RRMM) participants randomised to either BVd or DVd (4)) and availability for further methodologies to test the robustness of the cost-effectiveness results. These additional methodologies available for the ITT population only include; use of RWE evidence to support OS extrapolations (informative prior analysis), external expert validation, the most robust

and complete NMA data (with both PFS and OS available), adjustment of OS for NHS aligned subsequent treatment and use of the PFS:OS surrogacy relationships identified in other RRMM trials.

b) ***Please justify why the submission has not presented separate subgroup cost-effectiveness analyses for BVd at 3L-only and 3L+, in light of the company's concerns about equity, i.e.,*** [redacted]

Response: The DREAMM-7 trial is a head-to-head phase III randomised, open-label trial evaluating the clinical efficacy and safety of BVd compared with DVd for the treatment of adult RRMM patients with at least one prior line of therapy. From work with UK clinicians, the strongest clinical case is in 2L since the DREAMM-7 trial is a head-to-head with the current 2L standard of care, DVd and that positioning BVd at 2L results is the most cost-effective use of NHS resources compared to other possible positionings.

DREAMM-7 Trial

A6. For the CONSORT diagram (Figure 4, Appendix D) please:

i. ***Clarify the number of DVd participants in the safety population (n=262 is higher than the n=251 in the ITT population).***

Response: This is a typographical error. The correct number of DVd participants in the safety population is 246 (please see Table 11 in the CSR).

ii. Provide a breakdown of the reasons (with numbers) for patients having treatment discontinued due to "physician decision" and explain why there is an imbalance between the treatment arms.

Response: Discontinuations of belamaf and daratumumab for physician's decision occurred in 33 versus 10 participants. Where further explanation was given, the commonest reasons for physician decision in the BVd arm were clinical progression (not meeting IMWG criteria), ocular reasons and other adverse events. In the DVd arm, the commonest reason was clinical progression. "Physician decision" can only be selected if the subject discontinues treatment at the investigator's discretion and none of the other reasons apply, the other reasons being progressive disease (IMWG criteria), protocol deviation, subject reached protocol-defined stopping criteria, withdrawal by subject, or site/study terminated by sponsor. Full breakdown of the reasons for patients having treatment discontinued due to "physician decision" can be found in '[CON]_A6 response Physician Decision'.

iii. Clarify whether daratumumab discontinuations cover the combination and monotherapy phases, as is foot-noted for the belamaf discontinuations. If not, please provide a new CONSORT diagram with consistent reporting across groups.

Response: Daratumumab discontinuations cover both the combination and monotherapy phases. Therefore, a new CONSORT diagram is not required.

A7. Please provide results tables for the EQ-5D-3L data presented in Figures 9 and 10 of Document B and explain how missing baseline data and missing follow up data were handled in the analyses.

Response: Figure 9 in Document B shows the mean (95%CI) of EQ-5D-3L utility scores by visits, using the UK value set, separately for BVd, DVd, and pooled analysis. There are [redacted] measurements for EQ-5D presented in the figure. Similarly, Figure 10 in Document B shows the mean (95% CI) change in EQ-5D-3L utility scores from baseline by visits recorded before progression by visits, using the UK value set, separately for BVd, DVd, and pooled analysis. This figure also presented [redacted] measurements for EQ-5D. As requested, GSK provided the output of all those [redacted] analyses, including n, mean, 95% CI, and have uploaded these files separately for

Figure 9 and Figure 10 (folder ‘Response A7’), to avoid convoluting the current document, as very long tables would be required otherwise (5, 6).

Missing data was not handled separately in the utility analysis, as the number of responders was considered adequate to obtain robust estimates for utility scores. In particular, a total of [redacted] patients completed EQ-5D at baseline, [redacted] at week [redacted], and [redacted] at the last follow-up.

A8. For the subgroup analyses presented in Figure 11 of Document B, please provide test for interaction results for each of the analyses.

Response: The test for the interaction results for each of the subgroup analyses for the ITT population are provided below (Table 1).

Table 1. Summary of Progression-Free Survival subgroup analysis interaction results based on Independent Reviewer - Assessed Response

Subgroup	Treatment*Subgroup *p*-value
Number of Prior Lines of Therapy (1 vs 2/3 vs >=4)	[redacted]
Number of Prior Lines of Therapy (1 vs >1)	[redacted]
Prior Bortezomib (yes vs no)	[redacted]
Prior Lenalidomide (yes vs no)	[redacted]
Refractory to Lenalidomide (yes vs no)	[redacted]
Revised ISS Staging at Screening (I vs II/III)	[redacted]
Age (<65 vs 65-<75 vs >=75)	[redacted]
Gender (Female vs Male)	[redacted]
Time to Relapse after completion of 1L treatment (<=12 months vs >12 months)	[redacted]
Cytogenetic Risk (High Risk vs Standard Risk vs Missing or Not Evaluable)	[redacted]
Extramedullary Disease at Baseline (yes vs no)	[redacted]

Abbreviations:1L, first line; ISS, International Staging System, vs, versus

A9. Please provide a copy of Table 51 of the CSR (p120) populated only for grade 3 or 4 ocular adverse events.

Response: GSK provide below a copy of Table 51 of the CSR (p120) populated only for grade 3 or 4 ocular adverse events, as requested (Table 2).

Table 2. Onset, Duration, and Outcome of ≥3 Ocular Adverse Events (CTCAE) (Safety Population)

Ocular AESIs (by CTCAE) Characteristics, n (%)	BVd (N=242)	DVd (N=246)
Outcome of first occurrence, n[a]	[redacted]	[redacted]
Resolved prior to the end of treatment exposure	[redacted]	[redacted]
Resolved post end of treatment exposure	[redacted]	[redacted]
Not Resolved	[redacted]	[redacted]
Number of occurrences (% based on participants with an event), n	[redacted]	[redacted]
One	[redacted]	[redacted]
Two	[redacted]	[redacted]
Three or more	[redacted]	[redacted]
Outcome of ongoing event at the end of treatment exposure, or with event onset post treatment exposure, n[b]	[redacted]	[redacted]
Resolved	[redacted]	[redacted]
Not resolved, follow-up ongoing	[redacted]	[redacted]
Not resolved, follow-up ended	[redacted]	[redacted]
Outcome of last event, n	[redacted]	[redacted]
Resolved	[redacted]	[redacted]
Not resolved, not discontinued	[redacted]	[redacted]
Not resolved, follow-up ongoing	[redacted]	[redacted]
Not resolved, follow-up ended	[redacted]	[redacted]
Duration of occurrence for participants who recovered from last event (days)	[redacted]	[redacted]
n	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Outcome of last event in participants who discontinued from study treatment, n	[redacted]	[redacted]
Resolved	[redacted]	[redacted]
Not resolved, follow-up ongoing	[redacted]	[redacted]
Not resolved, died	[redacted]	[redacted]
Not resolved, withdrawn from study	[redacted]	[redacted]
Not resolved, lost to follow-up[c]	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; CTCAE, common terminology criteria for adverse events; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone

a. Duration is the time from onset of any ocular AE to the first time the participant is free of any such event. It requires at least 1 day gap between resolution of all events from first occurrence to the onset of second occurrence.
b. The end of treatment exposure is defined as last study treatment dose date +20 days.
c. Lost to follow-up refers to those who were under survival follow-up but confirmed they were not coming back to site for further examination.

Note 1: Ocular AEs are based on a hybrid of terms identified in the eCRF, and a list of terms identified by GSK internal review. For the complete list of PTs used to analyze ocular AEs (CTCAE grade), refer to DREAMM-7 CSR.
Note 2: Events are counted as the number of distinct ocular AEs reported in the database for a participant.
Note 3: Occurrences are counted by grouping overlapping ocular AEs. To count as a new occurrence, at least a 1-day gap is required, where a participant will have no ongoing ocular AEs in order to count as a new occurrence.
Source: Table 3.0029

A10. For the quality assessment (Document B, p49) please clarify the response to the question about allocation concealment (question 2, Table 11). The response seems to relate to blinding during the study, whereas the question is about methods to ensure that investigators could not manipulate which trial interventions patients were randomised to.

Response: DREAMM-7 is an open-label study; therefore, no blinding of treatment identity is needed for either Treatment Arm A (belamaf in combination with bortezomib, and dexamethasone; BVd) or Treatment Arm B (daratumumab in combination with bortezomib, and dexamethasone; DVd). However, to ensure trial integrity, steps were taken to restrict access to key information while the study was ongoing and prevent data aggregation except for where specified in the protocol.

All participants were centrally randomised using a central Interactive Response Technology (IRT) system, RAMOS NG, by the investigator or authorised site staff. RAMOS NG allows study sites to register and randomise participants, and also records stratification information.

Randomisation list was done centrally using a randomisation schedule generated by the GSK Clinical Statistics Department in RandALL NG, which assigned participants in a 1:1 ratio to Treatment Arm A (BVd) or Treatment Arm B (DVd). Separate randomisation lists were generated for any extension cohorts required.

Stratification factors used for the stratified analyses were number of prior lines of therapy (1 vs 2 or 3 vs ≥4), prior bortezomib (yes vs no) and International Staging System (R-ISS I vs II/III).

No more than 50% of participants with 2 or more prior lines of treatment were enrolled. No cross-over was allowed.

A11. Please provide separate baseline characteristics tables (the same as Table 8, Document B) for the 2L-only subpopulation, 3L- only subpopulation and the 3L+ subpopulation.

Response: Table 3 below shows the baseline characteristics tables for the 2L-only subpopulation. The trial results for 3L-only or 3L+ analyses are not provided due to the company's positioning BVd in 2L (see response to question A5b). As noted in the response to A5b, the strongest clinical case is in 2L since the DREAMM-7 trial is a head-to-head with the current 2L SoC DVd and that positioning BVd at 2L results is the most cost-effective use of NHS resources compared to other possible positionings.

Table 3. Baseline demographics, clinical characteristics, and prior therapies (2L-only intention to treat population)

Characteristics	**BVd (N=125)**	**DVd (N=125)**
Age, median (range), years	[redacted]	[redacted]
Age category, n (%)		
18 to <65 years	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race, n (%)		
White European	[redacted]	[redacted]
White Arabic/North African	[redacted]	[redacted]
Black	[redacted]	[redacted]
East Asian	[redacted]	[redacted]
Japanese	[redacted]	[redacted]
Southeast Asian	[redacted]	[redacted]
Central/South Asian	[redacted]	[redacted]
R-ISS stage at screening, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

Characteristics	BVd (N=125)	DVd (N=125)
Cytogenetic risk, n (%)		
Standard†	[redacted]	[redacted]
High‡	[redacted]	[redacted]
t(4;14)	[redacted]	[redacted]
t(14;16)	[redacted]	[redacted]
17p13del	[redacted]	[redacted]
Missing or nonevaluable	[redacted]	[redacted]
Other cytogenetic abnormalities, n (%)		
del 13	[redacted]	[redacted]
del 1p	[redacted]	[redacted]
Hyperdiploidy	[redacted]	[redacted]
t(11;14)	[redacted]	[redacted]
t(14;20)	[redacted]	[redacted]
1q21+	[redacted]	[redacted]
Other	[redacted]	[redacted]
Extramedullary disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Myeloma immunoglobulin, n (%)		
IgG	[redacted]	[redacted]
Time to relapse on latest prior line of therapy, n (%)§		
<18 months	[redacted]	[redacted]
≥18 months	[redacted]	[redacted]
Prior proteasome inhibitor, n (%)		
Any	[redacted]	[redacted]
Prior immunomodulatory drugs, n (%)		
Any	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]
Chemotherapy, n (%)	[redacted]	[redacted]
Steroids, n (%)	[redacted]	[redacted]
Positive refractory status by agent, n (%)		
Lenalidomide	[redacted]	[redacted]

Notes: † Standard risk cytogenetics was defined as having negative results for all high-risk abnormalities: t(4;14), t(14;16), or del(17p13).
‡ High-risk cytogenetics was defined as the presence of ≥1 of the following: t(4;14), t(14;16), or del(17p13).
§ Patients could be included in more than 1 category.

¶Time to relapse was defined as the time between start date of 1L of therapy to PD date on 1L treatment. If no PD date was available, start date of second line of treatment was used. If no PD date on start date of second line treatment was available, date of randomisation in the trial was used.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; IgG, immunoglobulin; PD, progressive disease; R-ISS, Revised International Staging System.

NCRAS study

A12. Please clarify the company's view of the implications of the results of the NCRAS study (p16 and p65-6, Document B) – is it to demonstrate that lenalidomide refractory subgroup effects exist in patients receiving DVd? Please also clarify what is meant by the 'overall 2L only cohort' (p17, document B) in terms of the treatments received at 2L.

Response: The NCRAS study is relevant as it supports the case that lenalidomide refractoriness is of very high prognostic relevance in 2L treatment in the UK. The NCRAS study cohort was broadly aligned to the eligibility criteria of the ongoing DREAMM-7 clinical trial. The DREAMM-7 like cohort (overall 2L-only cohort) included 10,720 patients as noted on page 16 of Document B. The overall 2L-only cohort represents the 2L treatment patterns for RRMM patients. The results of the NCRAS study demonstrate a marked decline in clinical outcomes for DVd from the overall 2L-only cohort (median OS was 43.0 months) to a lenalidomide refractory subgroup (median OS was 23.0 months) highlighting the high unmet need at 2L for lenalidomide refractory patients. Additionally, the time to next treatment or death (TTNTD) (used a proxy for PFS), were available for DVd. The median TTNTD (10.3 months; 95% CI: 7.4, 13.9) was markedly lower than the overall PFS reported by the multicentre analysis, suggesting poorer outcomes in lenalidomide-refractory patients and further demonstrating the high unmet need. The NCRAS cohort TTNTD value for lenalidomide-refractory patients (10.3 months) and the DVd arm of the DREAMM-7 study for lenalidomide-refractory patients (8.6 months) shows consistent results with the CASTOR study, where the median PFS for the lenalidomide-refractory subgroup in CASTOR was substantially lower than that for the 2L subgroup (7.8 months versus 27 months) (7-13).

Indirect treatment comparisons

A13. Please provide complete data tables, similar to Table 48 in Appendix D, for all NMAs conducted for PFS, ORR, OS, and TTD that were part of Document B

as well as additional analyses requested in questions A15. For each included trial, please provide references to the specific publication where data were extracted from.

Please also explain why Table 48 in Appendix D is entirely marked confidential when presumably data for comparators are in the public domain.

Response:

We have provided the entirety of the PowerPoint summary file for the NMA results in the documents shared with GSK's response ('A13 Response_DREAMM-7 NMA for Belamaf' file). This includes all the information requested, including subgroup analysis undertaken in the NMA.

The file contains all the data required to replicate these tables for OS for the populations that were considered for the NMA (inclusive of HRs, patient numbers and CIs). The file also contains event numbers for all binary outcomes for NMAs conducted by GSK.

The latest data tracker has also been shared with GSK's response to A14 ('A14 Response_NMA data and code' folder) which contains a consolidated list of all inputs used in the NMA, inclusive of ORs for all binary outcomes conducted by GSK.

GSK did not consider any NMAs for TTD and as these were not considered within the feasibility assessment, data cannot be provided. Please also note, that ORR and OS data is only available for the populations for which NMAs were conducted and not all subgroups reported in Table 48 (Appendix D).

In addition, the data reported in the provided PowerPoint and the data tracker will have some minor differences in comparison to the data which was used for the NMA results shared in the original submission. Therefore, if the EAG re-runs the networks, some results and the networks may vary slightly. The differences in the NMA results shared in this response and those included in the NICE submission are as follows:

- Inclusion of GEM_KyCyDex study to ITT networks (where feasible).
- OS data from IKEMA identified from SLR update which was not included in initial run due to time constraints.

- Minor corrections made to data inputs for the NMA.

These updates have been provided for the ITT population, however at this time these are not available for the lenalidomide refractory or 2L-only subgroups. The impact, however, is assumed to be minor.

Regarding Table 48 in Appendix D, GSK agree with the EAG that this data does not need to be marked up, as all data in Table 48 is publicly available. The confidential marking has been removed from Table 48 in the updated version of Appendix D which has been uploaded as an additional file.

A14. PRIORITY: Please provide details of the 'multinma' code used to run all network meta-analyses (NMAs), including data inputs, and wrap-around functions used to produce all results presented in the submission, so that the NMA models can be re-run and checked by the EAG. Please ensure the code and input files are ready to use and suitable for loading into R, and that the versions of any packages used are clearly noted.

Please also ensure equivalent code is provided for all other NMAs requested in question A15.

Response:

GSK have provided the code and data tracker used to run the NMAs, for the EAG to check for quality assurance ('A14 Response_NMA data and code' folder). This includes the most up to date data GSK have available for the ITT, 2L only and lenalidomide refractory networks in addition to the included code for the TTE and binary outcomes. The code can be used for all populations and outcomes (for which we have provided data) using the correct filters within the code.

Please note that the same improvements to the networks described in A13 apply here. The NMA results in the original document submitted to NICE will not align exactly to the results the EAG will generate using the data inputs, given the corrections that were made to the networks, however all updated NMA results will be available by Q4 2024. Additionally, the latest version of the code (in line with the results file included as a response to A13, present in the appendix of the slides)

includes code for outputs which were run on all networks subsequent to submitting to NICE.

The cost-effectiveness model is aligned to the previous NMA results shared in the original submission; however, all HRs for the included comparators based on the updated NMA results are very closely aligned with 0.01 difference.

A15. PRIORITY: For each of the outcomes of PFS, OS, TTD, and ORR (ORR outcome is not a priority), please conduct separate NMAs and provide the results for the following subgroups stratified by number of prior lines of therapy (which were considered in NICE TA974):

- **2L-only (i.e., after one prior line of therapy)**
- **3-L only (i.e., after two prior lines of therapy)**
- **3L+ (i.e., after two or more prior lines of therapy)**

For each analysis, please provide data tables and code as requested in questions A13 and A14.

Response:

As detailed in the response to priority question A5, GSK have proposed that the population for BVd reimbursement is as a second line treatment for patients unsuitable for lenalidomide is appropriately modelled through the ITT population. For the 2L-only population and lenalidomide refractory population, an NMA has been conducted for the PFS endpoint and results for this are available in response to question A13. No other analyses have been planned or explored for alternative endpoints or for alternative populations.

The NMA results for 3L only and 3L+ are not provided due to the company's positioning BVd in 2L (see response to question A5b).

A16. The rankograms presented in Figures 11, 13, 19, 23, 26, 31 and 33, Appendix D, appear to contradict the results presented in the corresponding forest plots which show BVd to be superior, hence should be ranked 1 (using the convention that being ranked 1st is better than being ranked last). Please check the options

used to generate these figures specify that higher response is the desired outcome (as opposed to lower mortality), and provide corrected figures, if appropriate.

Response: For the ORR Rankograms the order of ranking for binary outcomes was inverted with 12th as the highest ranking. This is due to the 'posterior_rank_probs' function using "TRUE" as the default for the 'lower_better' argument in the NMA code and just applies to the ORR rankograms (all other rankograms and forest plots are correct). We appreciate that this will have caused some confusion for the EAG and apologise for this. Unfortunately, due to time constraints we are not able to re-draw all the rankograms with ordering reversed.

Section B: Clarification on cost-effectiveness data

Comparators in the DVd eligible population

B1. Given that SVd is only approved by NICE in the 2L population for patient's refractory to both daratumumab and lenalidomide, please clarify why SVd is included as a comparator in the DVd eligible population, i.e., SVd cannot be included in the 2L population where DVd is included as a relevant comparator.

i. Please provide a revised version of the model with sufficient flexibility to allow fully incremental cost-effectiveness analyses in the separate DVd eligible and ineligible subpopulations. Please signpost the changes made to the model.

Response:

In alignment with the treatment pathway described in B.1 question above, the economic model has been adapted to provide fully incremental cost-effectiveness analyses separately for DVd eligible and ineligible subpopulations. In this updated analysis, SVd is not included as a comparator in the DVd eligible population.

Separate tables presenting the fully incremental analyses for the DVd eligible and DVd ineligible subpopulations are now reported in the model in the "Results" tab (cells C19:K24), and the "PSA" tab (cells W7:AE13). In the updated base case (deterministic) analysis, BVd remains a cost-effective treatment option for the DVd

eligible subpopulation (Table 4), while results remain the same for the DVd ineligible subpopulation (Table 5). Please note that results of Table 4 and Table 5 are slightly different to the base case results presented in Section B.3.10.1 of NICE Document B, due to CEM updates in the application of ocular AE costs for BVd in response to the clarification question B10.

Table 4. Updated fully incremental cost-effectiveness results for DVd eligible subpopulation (SVd is not a relevant comparator)

Treatment	Total Costs (£)	Total QALYs	ICER (£ / QALY)
DVd	[redacted]	[redacted]	-
BVd	[redacted]	[redacted]	3,757

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: dominated treatment strategies are excluded from the fully incremental results tables

Table 5. Updated fully incremental cost-effectiveness results for DVd ineligible subpopulation

Treatment	Total Costs (£)	Total QALYs	ICER (£ / QALY)
SVd	[redacted]	[redacted]	-
BVd	[redacted]	[redacted]	8,231

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: dominated treatment strategies are excluded from the fully incremental results tables

Subgroup analyses stratified by treatment line

B2. PRIORITY: The proposed population is 2L-only but the data informing the model is based on the overall ITT population (2L+) from DREAMM-7.

a) Please provide 2L-only subgroup cost-effectiveness analysis for the 2L-only population (i.e., in patients who have received only one prior line of therapy). For each treatment comparison, please provide the following:

i. Kaplan-Meier curves of PFS from DREAMM-7 (2L-only subgroup) for BVd and DVd, with 2L-only subgroup comparative data from the NMA for SVd and hKd, and parametric goodness of fit measures and corresponding extrapolation curves.

Response:

We understand from this question that the EAG would like us to present subpopulation data closer to the 2L population for patients unsuitable to lenalidomide which we describe as being the best positioning for BVd in clinical practice, despite the issues with uncertainty this subgrouping could create. On this basis, we have provided the lenalidomide refractory subgroup. As described in A5, the lenalidomide refractory subgroup describes the UK 2L patient population better than data from the 2L only subgroup.

For many reasons, GSK advises the use [redacted]

To assist the EAG and NICE Committee, we have also interpreted their question literally and provided the 2L only data everywhere we provide the lenalidomide refractory data. The 2L only data has the same issues of robustness that the lenalidomide refractory data do, but also adds serious issues of generalisability as the 2L trial population is not representative of the 2L UK population.

Detailed results are provided are provided as a separate Appendix document.

ii. Kaplan-Meier curves of OS from DREAMM-7 (2L-only subgroup) for BVd and DVd, with 2L-only subgroup comparative data from the NMA for SVd and hKd, and parametric goodness of fit measures and corresponding extrapolation curves. If providing 2L- only subgroup OS is not feasible, please provide the 2L-only subgroup surrogacy relationship for PFS and OS, as requested in question B4.e, and apply it to the 2L-only subgroup PFS curve to derive the corresponding 2L-only subgroup OS curve.

Response: Please refer to appendix for clarification responses (provided as a separate document).

iii. ***Kaplan-Meier curves of TTD from DREAMM-7 (2L-only subgroup) for BVd and DVd, with alternative assumptions for 2L-only subgroup comparative data for SVd and hKd, and parametric goodness of fit measures and corresponding extrapolation curves.***

Response: Please refer to appendix for clarification responses (provided as a separate document).

iv. ***Please provide a revised version of the model incorporating the data from i)-iii), with sufficient flexibility to examine cost-effectiveness analyses in the 2L-only subgroup and allows a switch between alternative sources of data/analyses. Please signpost the changes made to the model.***

Response: [redacted]

B3. Linked to your response to question A5b, please consider providing subgroup cost-effectiveness analysis for the 3L-only population and/or 3L+

population, where evidence from separate subgroup NMAs are available in response to question A15. For each treatment comparison, please provide the same information as requested in B2a parts i)-iv) for the 3L-only and/or 3L+ subgroups.

Response: The DREAMM-7 trial is a head-to-head phase III randomised, open-label trial evaluating the clinical efficacy and safety of BVd compared with the current SoC at 2L, DVd for the treatment of adult RRMM patients with at least one prior line of therapy. The trial results for 3L-only or 3L+ analyses are not provided due to the company's positioning BVd in 2L (see response to question A5b). As noted in the response to A5.b, the strongest clinical case is in 2L for patients unsuitable for lenalidomide due to the rationale outlined in the submitted dossier.

Surrogacy relationship between PFS and OS

B4. PRIORITY: Given the immaturity of the OS data from DREAMM-7 and the potential confounding effects of subsequent therapy use on OS, the scenario analyses based on extrapolating OS from a surrogacy relationship between PFS and OS outcomes appear important.

a) ***Please provide details on how the hazard ratio for the surrogacy relationship based on the median PFS to median OS used in the scenario analyses was derived (Table 5 of Appendix O). If this was based on a simple weighted average of the absolute median PFS:OS ratio from across the included studies, please explain why the effect was not estimated from the models of weighted least squares regression, univariate meta-regression, or bivariate Bayesian meta-analysis, which are included in reference 5 of Appendix O (file GSK 2023 [Con]).***

   Response: In the model, an absolute median OS:median PFS ratio of 3.4 was used. It was calculated as a simple weighted average of the absolute median PFS:OS ratio from across the included studies. Since it was considered for the scenario analysis only, a simplified approach was taken from the OS surrogacy study (14).

The methodology used is outlined below:

1. Median PFS was calculated based on the model settings
2. Median OS was estimated for each treatment as median PFS multiplied by median OS:PFS ratio
3. HRs (applied separately for each intervention) that need to be applied to the PFS curve in order to obtain an OS curve with the corresponding median OS estimated previously was calculated.
4. This HR was applied to PFS curve to get the OS curve

GSK acknowledges the EAGs comments that other approaches are available in the OS surrogacy study which should be incorporated in the model. The results from the regression analyses have now been included into the updated model and are outlined in the response to question B4.c.

b) Please explain how uncertainty in the absolute median PFS:OS surrogacy ratio was incorporated into the scenario analyses.

Response: Uncertainty was not incorporated into the PFS:OS surrogacy relationship since this was only considered for the scenario analysis. This has been incorporated for the additional functionality included in the updated model (details are provided in the response to B4.c.ii).

c) Please provide additional scenario analyses based on the surrogacy relationship of PFS:OS derived from the alternative models included in reference 5 of Appendix O (i.e., weighted least squares regression, univariate meta-regression, and bivariate Bayesian meta-analysis).

i. Please specify clearly the values (and measure of uncertainty) of the hazard ratio for the surrogacy relationship derived using the alternative models included in reference 5 of Appendix O.

Response: Additional functionality has been included in the updated CEM to align to the models present in the OS surrogacy report (14).

A recent update to this study has been performed and the report has been included in the response. The model has been adapted to incorporate the most recent report. This report contains an update to a Relapsed or Refractory Multiple Myeloma

surrogacy analysis previously performed in June 2023. The analysis used the same methodology as the previous analysis and updated the results based on systematic literature reviews conducted in October 2023 and February 2024, which included an additional 14 trials for the analysis. Results were broadly consistent with previous findings. The model has been adapted to incorporate the most recent report.

The three additional models are based on the PFS:OS absolute medians, aligning with current functionality in the model to extrapolate the OS curve. The R^2 value among WLS models was highest for the absolute median PFS – OS case in the OS surrogacy study, with 84% of variation in OS medians across studies attributable to variation in PFS medians. The included models are based on the following results from the OS surrogacy report; WLS regression, univariate meta-regression (fixed effects) and univariate meta-regression (random effects). The results of the three models are summarised in the Table **6** and Table **7** below:

Table 6. Summary of WLS regression by inverse-variance method based on sample sizes

Characteristic	Beta	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]
median_pfs	[redacted]	[redacted]	[redacted]
Nunber of observations	[redacted]	-	-
R^2	[redacted]	-	-
Adjusted R^2	[redacted]	-	-
Statistic	[redacted]	-	-
p-value	[redacted]	-	-

Abbreviations: CI, Confidence Interval; R^2, coefficient of regression

Table 7. Summary of meta-regression – fixed and random effect models

Characteristic	Fixed effect			Random effect		
	Beta	95% CI	p-value	Beta	95% CI	p-value
intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
median_pfs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
i.squared	[redacted]	-	-	[redacted]	-	-
h.squared	[redacted]	-	-	[redacted]	-	-
tau.squared	[redacted]	-	-	[redacted]	-	-
tau.squared.se		-	-	[redacted]	-	-
cochran.qe	[redacted]	-	-	[redacted]	-	-
p.value.cochran.qe	[redacted]	-	-	[redacted]	-	-

cochran.qm	[redacted]	-	-	[redacted]	-	-
p.value.cochran.qm	[redacted]	-	-	[redacted]	-	-
Residual df	[redacted]	-	-	[redacted]	-	-
Log-likelihood	[redacted]	-	-	[redacted]	-	-
Deviance	[redacted]	-	-	[redacted]	-	-
AIC	[redacted]	-	-	[redacted]	-	-
BIC	[redacted]	-	-	[redacted]	-	-
AICc	[redacted]	-	-	[redacted]	-	-
Number of observations	[redacted]	-	-	[redacted]	-	-

Abbreviations: AIC, Akaike's information criterion; AICc, AIC corrected for small sample sizes; BIC, Bayesian information criterion; CI, Confidence Interval

In the updated model, uncertainty has been captured to vary the intercept and median_pfs coefficients to the 95% CIs.

ii. Please provide a revised version of the model incorporating the alternative estimates for the surrogacy relationship, and with sufficient flexibility to switch between alternative sources of data. Please signpost the changes made to the model.

Response: A revised version of the model has been provided with the additional OS surrogacy models. In the 'Clinical Inputs' tab, an additional switch has been added to choose between the included regression models.

To investigate sensitivity in the included sources of data, a switch in the 'Data Store' sheet for the additional analyses (cells R28:R29) has been included to separately vary the intercept and median_pfs coefficient. Since the macro in 'clinical inputs' is required to calculate the appropriate HR to apply to the PFS curve to match the calculated median OS for each comparator, this sensitivity analysis cannot be incorporated into the OWSA and has to be run manually.

d) Please comment on how the surrogacy relationship estimated from the weighted least squares regression reported in reference 5 of Appendix O differs from that derived in the recent study by Dimopoulos et al., (2024) (15), which used a similar weighted least squares regression by arm-level

to estimate the effect of median PFS on median OS in RRMM, and explain the reasons for the difference.

Response: Thank you for making us aware of this recent publication. Because it was published less than one month before our company submission was sent to NICE, its findings were not considered in the TLR which informed the surrogacy relationship. Due to the short time for responding to all the clarification questions, we have not had the time to undertake a comprehensive comparison between our chosen approach and that undertaken by Dimopoulos et al., (2024). Based on a topline review, we agree with the EAG that the authors of this study appear to have applied a similar weighted least squares regression approach, and this has resulted in very similar results (see clarification response B4c). We believe that this is helpful external validation of the robustness of the methodology applied for our quantification of the surrogacy relationship.

e) ***Please provide estimates of the surrogacy relationship stratified by number of prior lines of therapy; specifically, the relationship in the 2L-only subpopulation and/or 3L-only, 3L+ subpopulations (conditional on your response to question B3) for each of the alternative models considered in reference 5 of Appendix O. If this is not feasible, please comment on the validity of assuming the same surrogacy relationship across treatment lines in RRMM.***

Response: Estimates of the OS surrogacy relationship stratified by number of prior lines are not available. In addition, due to the NMA being unfeasible for the subgroups (lenalidomide refractory, 2L-only) the likelihood is this would also be reflected in the feasibility for the OS surrogacy analysis. In addition, reducing the number of available data points from published materials is likely to increase the uncertainty in the analysis and the confidence in the identified relationship.

The validity of assuming the same surrogacy relationship across treatment lines in RRMM would require validation with clinical experts, which given the time frame for GSK's response is unfeasible.

f) ***Please provide a revised version of the model incorporating the alternative estimates for the surrogacy relationship by treatment line from***

e), and with sufficient flexibility to switch between subpopulations. Please signpost the changes made to the model clearly.

Response: Please see response to B4.e.

Baseline survival used in model

B5. Baseline survival is informed by the DVd curves from DREAMM-7, which is modelled independently from the BVd arm.

a) ***Please comment on how the survival curves (PFS, OS and TTD) for DVd from DREAMM-7 differ from the CASTOR study (see, for example, Sonneveld et al., 2023(8)), and explain the reasons for any significant differences. Please provide the corresponding Kaplan-Meier curves from both studies on the same figure for comparison, and separately for each outcome.***

Response: The values below for DVd correspond to the intention to treat populations of the DREAMM-7 and CASTOR trials.

PFS:

The median PFS (mPFS) survival of 13.4 months (95% CI, 11.1 to 17.5) in the DVd group (in the DREAMM-7 study; median follow up of 28.2 months) is consistent with that seen in the CASTOR trial (16.7 months; 95% CI, 13.1 to 19.4; median follow up of 19.4 months) (4, 8).

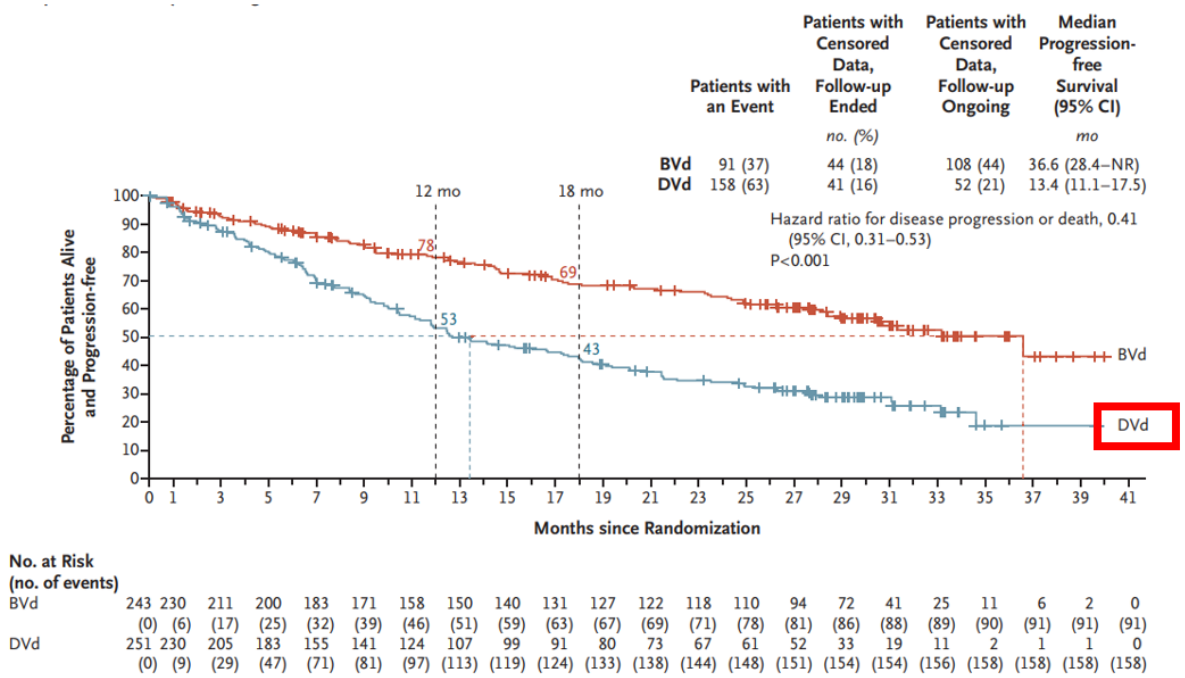
A summary table (Table ***8***) and corresponding Kaplan-Meier curves (Figure ***3*** to Figure ***5***) are presented below.

Table 8. Summary of results for mPFS

Study	N	Median follow up (months)	mPFS for DVd (months)
DREAMM-7	251	28.2	13.4
CASTOR	251	19.4	16.7

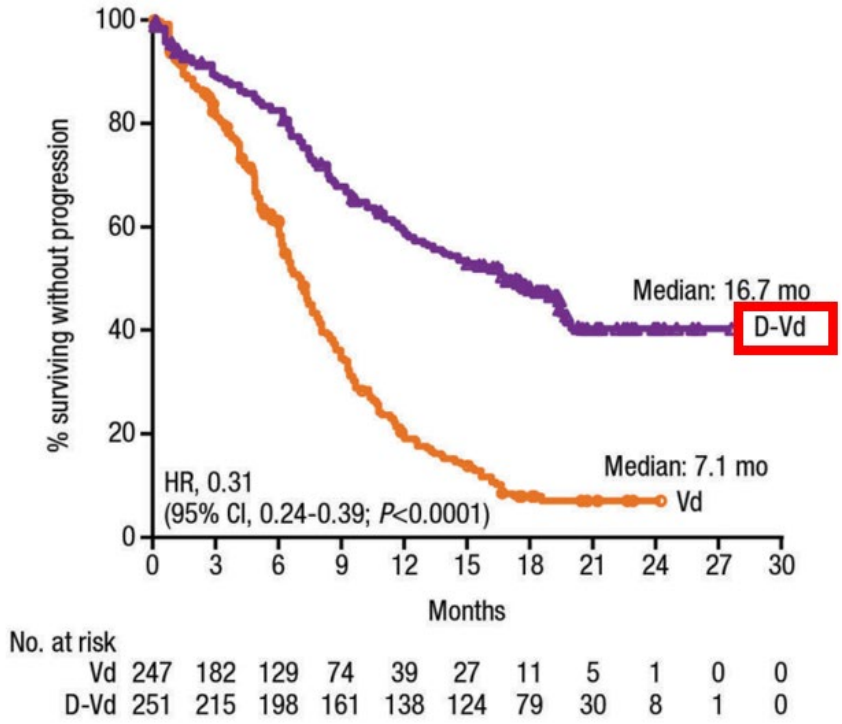
Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; mPFS, median progression-free survival; N, total number of patients

Figure 3. DREAMM-7; PFS Kaplan-Meier curve for DVd



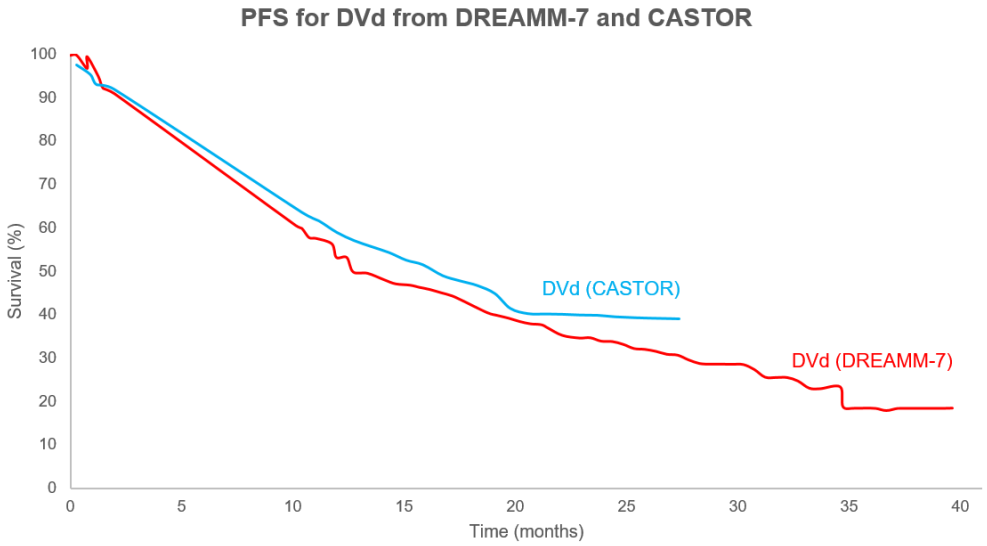
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone
Source: Dimopoulos et al (4)

Figure 4. CASTOR; PFS Kaplan-Meier curve for DVd



Abbreviations: CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; HR, hazard ratio; PFS, progression-free survival; Vd, bortezomib and dexamethasone
Source: Spencer et al (9)

Figure 5. Digitization and overlay; PFS Kaplan-Meier curves for DVd



Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; PFS, progression-free survival

OS:

At the time of the latest data cutoff of DREAMM-7 (median follow up 28.2 months), 87 patient (35%) in the DVd group had died; median OS (mOS) not reached. Overall survival at 18 months was 73% in the DVd group. The 25th percentile of the distribution of overall survival was 15.2 months (95% CI, 12.3 to 21.1) in the DVd group. Follow-up for overall survival for DVd within DREAMM-7 is ongoing (4). At a median follow-up of 72.6 months in CASTOR, mOS was 49.6 months with DVd (8).

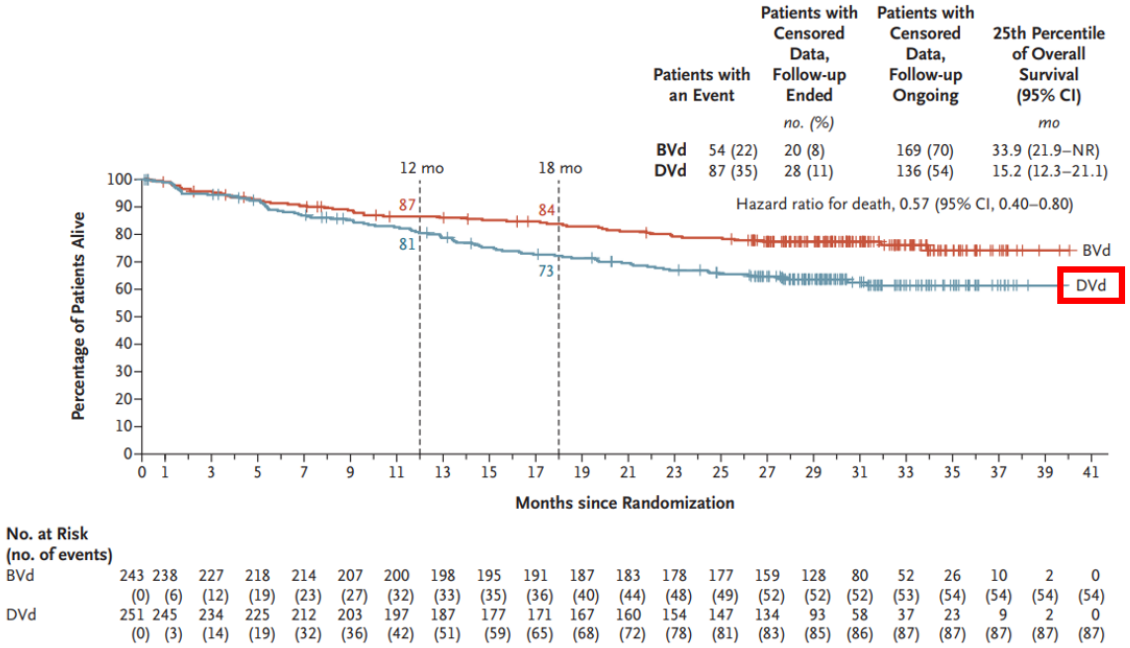
A summary table (Table ***9***) and corresponding Kaplan-Meier curves (Figure ***6*** to Figure ***8***) are presented below.

Table 9. Summary of results for mOS

Study	N	Median follow up (months)	mOS for DVd (months)
DREAMM-7	251	28.2	Not reached; Events, n (%) = 87 (35)
CASTOR	251	72.6	49.6

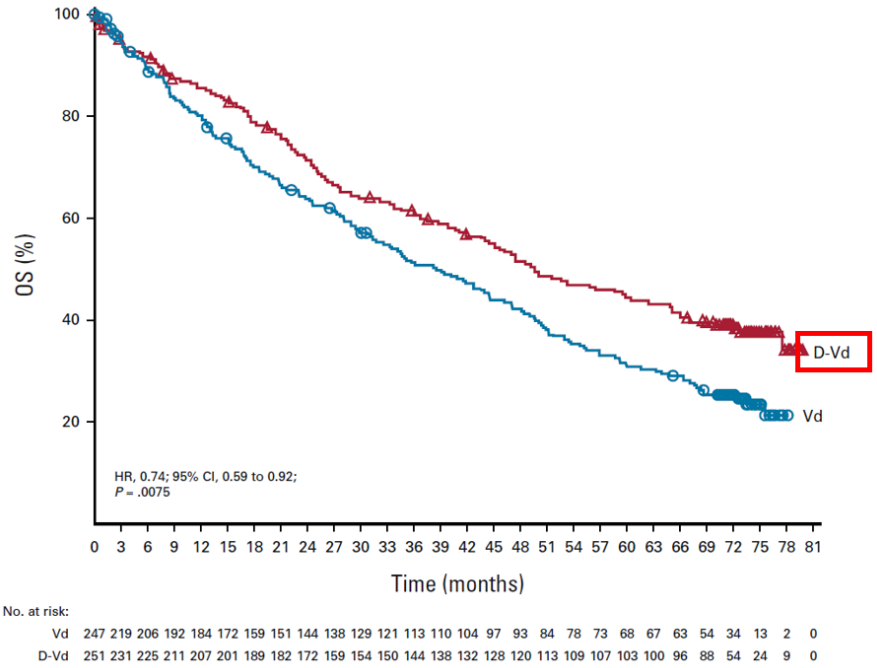
Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; mOS, median overall survival; N, total number of patients

Figure 6. DREAMM-7; OS Kaplan-Meier curve for DVd



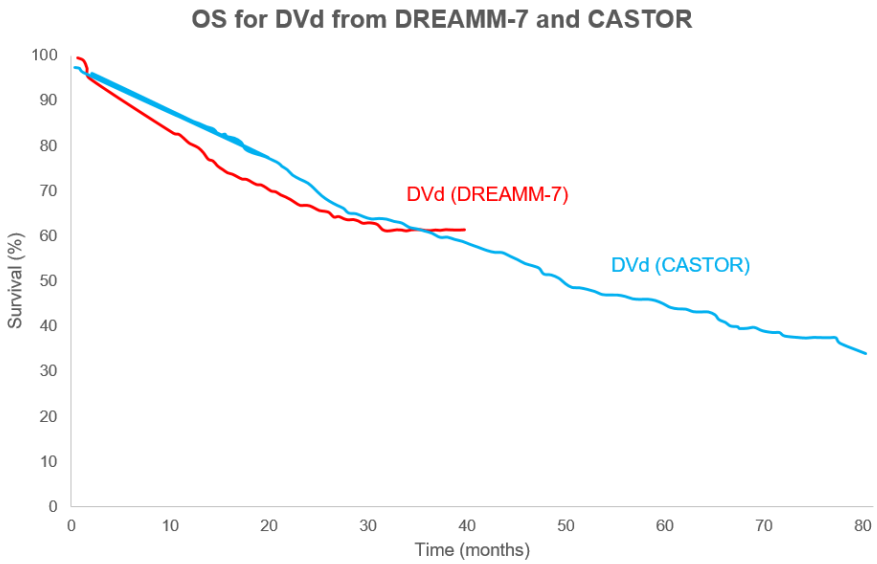
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; OS, overall survival
Source: Dimopoulos et al (4)

Figure 7. CASTOR; OS Kaplan-Meier curve for DVd



Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; OS, overall survival; Vd, bortezomib and dexamethasone
Source: Sonneveld et al (8)

Figure 8. Digitization and overlay; OS Kaplan-Meier curves for DVd



Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; OS, overall survival

TTD:

At the time of the latest data cutoff of DREAMM-7 (median follow up 28.2 months), median TTD (mTTD) in the DVd group was [redacted] (95% CI, [redacted]; safety population) (Section B.2.6.1.6 of NICE Document B). Corresponding data for DVd in CASTOR has not been reported, nor has it been reported for any subgroups.

A summary table (Table ***10***) and corresponding Kaplan-Meier curves (Figure ***9***) are presented below.

Table 10. Summary of results for mTTD

Study	N	Median follow up (months)	mTTD for DVd (months)
DREAMM-7	251	28.2	[redacted]
CASTOR	251	Not reported	Not reported

Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; mTTD, median time to treatment discontinuation, N, total number of patients

Figure 9. DREAMM-7 Kaplan Meier curves of time to treatment discontinuation (safety population)

B6. Please comment on what is the most appropriate source for baseline survival and whether any consideration was given to the use of National Cancer Registration and Analysis Service (NCRAS) data as an alternative source. In response, please provide details about distribution of treatments received at second- and third-line in NCRAS and the survival outcomes available from NCRAS. If considered appropriate, please consider providing a scenario analysis that uses NCRAS data to provide a baseline for DVd in the model for PFS, OS and TTD (where data permits).

Response: The most appropriate source for baseline survival in this appraisal is the DREAMM-7 trial, as this is a pivotal registrational phase 3 study directly comparing BVd to DVd. DVd is the current standard of care at 2L in the NICE pathway for patients who are unsuitable for lenalidomide, and it is therefore the most relevant comparator for this appraisal. The DREAMM-7 study also allows for a network meta-analysis versus other comparators of interest in GSK's proposed positioning (Kd and SVd) using Vd as an anchor. Considering the presence of this gold standard baseline survival data source, little consideration was given to the use of NCRAS data as an alternative source as NCRAS is a descriptive, retrospective, non-interventional study.

GSK do not consider a scenario analysis that uses NCRAS data to provide a baseline for DVd in the model for PFS, OS and TTD to be appropriate considering availability of the DREAMM-7 data, and the limitations of the NCRAS study which can be found in GSK's NCRAS study draft manuscript (11). NCRAS data was only considered in this appraisal in the context of unmet needs for lenalidomide refractory patients at first relapse in England, with a focus on those treated with DVd.

Details about the distributions of treatments received at second- and third-line in the NCRAS study can be found in GSK's NCRAS study draft manuscript (11).

OS extrapolation with informative priors

B7. Please provide full details on how the informative prior distribution from the CASTOR study was informed, and how it was combined with data from DREAMM-7, to provide an adjusted-informative-prior OS curve for DVd in the company's base case analysis. Please compare the approach used to the approach suggested by Soikkeli et al. (2019)(16) where the parametric distributions for DVd and BVd would be fitted jointly in a Bayesian survival analysis.

Response: A Bayesian survival analysis approach was undertaken to allow the incorporation of external information from the CASTOR study in addition to the observed DREAMM-7 data. This was conducted due to the immature OS data for DVd in DREAMM-7, which results in significant uncertainty in long-term extrapolation when using standard parametric survival models.

The approach that was used requires that the shape parameter of the OS distribution for DVd arm is exchangeable between the two studies. The appropriateness of using CASTOR as a historic data to define an informative a-priori distribution for the shape of OS for the DVd arm of DREAMM-7 was investigated in a feasibility assessment (available in previously shared reference pack), which concluded that CASTOR had similar trial design features, treatment dose and schedule, eligibility criteria and OS outcome definition as DREAMM-7, and therefore, the assumption that the shape parameter of OS is exchangeable between studies is expected to hold. Importantly, CASTOR has a longer follow-up period (59% OS events over a maximum follow-up of 79.8 months) compared with DREAMM-7 (35% OS events over a maximum follow-up

of 40.2-months). Individual patient data (IPD) were not available from the CASTOR trial. However, the OS Kaplan-Meier (KM) curves from the CASTOR trial were digitized and along with the reported number of patients at risk at each time interval these data were used to obtain reconstructed IPD (RIPD) for OS following the method by Guyot et al. (17)

The approach used to extrapolate overall survival for DVd in DREAMM-7 using an informative prior from the CASTOR study included two steps outlined below:

1) Standard parametric survival models were fitted to the OS RIPD for DVd in the CASTOR study using the *flexsurv* package in R. Six parametric distributions were explored: Weibull, Gompertz, log-normal, log-logistic, Gamma and generalised Gamma. As the exponential model does not have a shape parameter, it could not be considered within this analysis. Additionally, the Gompertz was excluded due to clinically infeasible long-term projections resulting from a negative shape parameter. The Weibull model provided the lowest AIC and BIC values, indicating the best statistical fit to the CASTOR OS data.

2) Bayesian parametric survival models were fitted to the OS IPD for DVd in the DREAMM-7 trial using informative priors for the shape parameter(s) that were defined based on the results of the fitted models in Step 1. The Bayesian informative prior analyses were conducted in R using survHE package. The package assumes that the shape parameter of the Weibull, log-logistic, Gamma and generalised Gamma distribution follows a Gamma distribution with parameters a and b; $Gamma(a,b)$, whereas the shape of the log-normal distribution is assumed to follow a uniform distribution with parameters a and b; $Uniform(a,b)$. The package allows to specify parameters a and b so that the mean and variance of the $Gamma(a,b)$ or $Uniform(a,b)$ distribution that is used as a prior, matches the mean $(\mu)$and variance (σ^2) of the shape parameter that was estimated using standard parametric survival analysis in the CASTOR study in Step 1. Table ***11*** shows estimates for ancillary parameters of different distributions on the natural scale.

Table 11. Estimates for ancillary parameters of different distributions on the natural scale

Parametric Distribution for OS	Estimated Ancillary Parameter using Standard Parametric Survival Analysis			Informative Prior		
	Ancillary Parameter	Mean	SE	Assumed Distribution for Ancillary Parameter	a	b
Weibull PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal						
Log-logistic						
Gamma						
Generalized Gamma						

Abbreviations: OS, overall survival; PH, proportional hazard; SE, standard error

E.g., for gamma distribution with parameters *a* and *b*

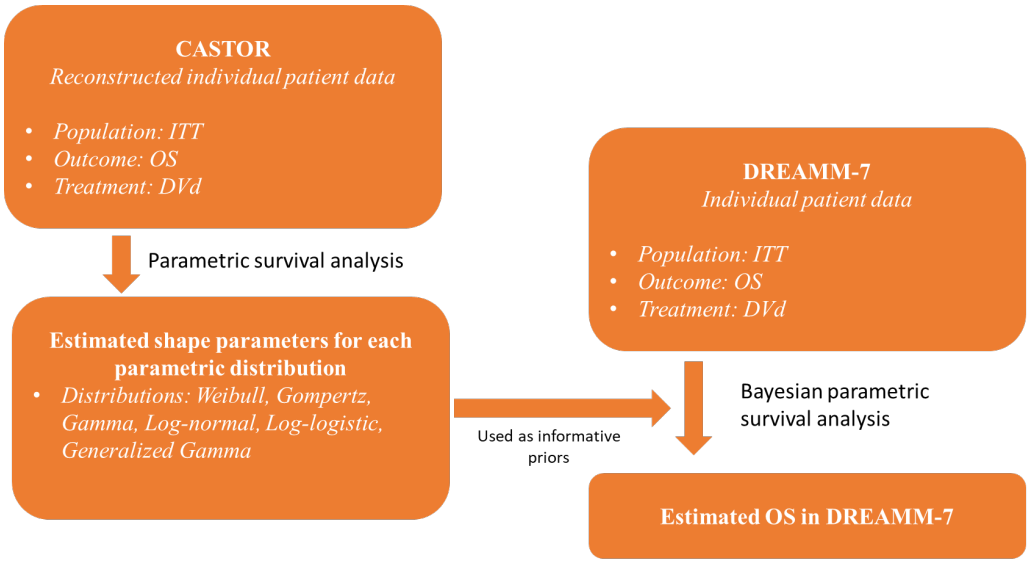
$mean(\mu) = \frac{a}{b}$; $standard\ error\ (\sigma) = \sqrt{a}/b$ giving, $a = \mu \times b$, $and\ b = \frac{\mu}{\sigma^2}$

Non-informative priors were assumed for the scale parameters, by assuming that they are distributed as N(0,100).

The log-normal distribution provided the best fitting curve based on AIC and BIC, however, all AIC and BIC values are within three points of each other, and can therefore be considered comparable with regards to statistical fit. While all models showed a similar short-term fit, log-term survival showed differences. Experts considered that on average approximately 5-10% of patients would be alive at 15 years, with Weibull distribution reflecting these estimates. Therefore, based on long-term assessment and expert opinion, the Weibull distribution was selected for DVd OS extrapolation.

Figure ***10*** provides a schematic representation of the statistical approach that was used to extrapolate overall survival for DVd in DREAMM-7 using an informative prior from the CASTOR study.

Figure 10. Schematic Representation of Statistical Approach for OS Estimation using Informative Priors



- Parametric survival analysis with RIPD from CASTOR to estimate shape parameters for a range of distributions
- Bayesian parametric survival analysis with IPD from DREAMM-7, using the shape parameters estimated above as informative priors

Abbreviations: DVd, daratumumab in combination with bortezomib, and dexamethasone; IPD, individual patient data; ITT, intent to treat; OS, overall survival; RIPD, reconstructed individual patient data

The approach used to extrapolate overall survival for DVd in DREAMM-7 using an informative prior from the CASTOR study was very similar to the method used by Soikkeli et al (2019) (16). Specifically, in Soikkeli et al., mature historical trial data with the same comparator as in the pivotal trial were incorporated in 2 stages: First, the parametric distribution selection was based on historical trial data from a study by Shustik et al. with 8 years of follow-up (18). Second, the shape parameter estimate of the CASTOR trial was used to define an informative a-priori distribution for the shape of the 30-month pivotal VISTA trial data (18). The difference between Soikelli et al and our approach was that Soikelli et al. used the best fitting distribution in Step 1 as the only distribution for which they conducted Bayesian analyses with informative priors. In our analyses, we considered informative priors for all feasible distributions and used clinical expert opinion to select the most appropriate distribution for the base case analysis. It is worth mentioning that clinical expert opinion indicated that the Weibull distribution provided the most clinically meaningful extrapolations, which is the distribution that also provided the best statistical fit to the CASTOR data. Therefore, the Soikelli et al. approach would have provided identical results.

B8. Please provide the adjusted-informative-prior OS curve and unadjusted-non-informative prior OS curve for the 2L-only subgroup for DVd from the DREAMM-7 trial. Please provide both curves on the same figure for comparison and comment on any significant differences between curves.

Response: GSK do not have the informative prior OS analyses available for the 2L only subgroup. It was not prioritised as the 2L only subgroup is not reflective of UK clinical practice that is better represented by the ITT population (or subsequently the lenalidomide refractory population). GSK have, however, provided the subgroup data for the unadjusted OS curve for the DVd arm in the response to question B2 and in the updated economic model.

Health-related quality of life utility values

B9. PRIORITY: Health-related quality of life data from DREAMM-7.

a) ***Please provide details on numbers of patients providing EQ-5D-3L data at each assessment time point in DREAMM-7 to inform the utility values associated with the progression-free (PF) and progressive disease (PD) health states in the model. Please report the numbers separately for the PF and PD states and by treatment arm.***

   Response: The summary table for these data is provide in Table 4.0010 which is contained in the file shared in our response named: B9_Response_t1_m_ru_stat_hs_uk.rtf.

b) ***Please clarify whether missing EQ-5D-3L data were imputed and, if appropriate, please provide details on the methods used.***

   Response: Missing EQ-5D-3L data were not imputed in the analyses. All analyses were carried out based on available data without any imputations for missing data.

c) ***Please provide comprehensive details on how the utility values sourced from DREAMM-7 in Table 45 of Document B were derived. Specifically, please provide details on how to interpret the fitted two- and three-state regression models, with and without a treatment arm covariate, in Tables 42-44 of the Document B, and explain how the regression output is used***

to derive the utility values reported in Table 45. Please provide the corresponding output from the regression models and demonstrate how it is used to derive the modelled utility values in the electronic version of the model, signposting the changes made to the model.

Response: The value set for EQ-5D-3L index score used for the U.K. analysis was based on the model provided in the following published paper by Dolan et al (19). The EQ-5D-3L data obtained for each subject at each visit were converted to utility score using the model provided in this article.

Utility analyses including the progression-free and progressed health states showed that utility decreases significantly after progression. Table 42 presents the results obtained from the fitted two-state model for EQ-5D-3L scores including progression-free and progressed health states. The results indicate that when compared to progression-free state, utility decreases significantly after progression [redacted]

Table 43 shows the results obtained from the two-state utility model when the health states ("progression-free" and "progressed") and treatment arms (BVd and DVd) are included as covariates in the model together with baseline utility score. The results indicate decrease in utility from progression-free state to progression [redacted] when adjusted for treatment effect and baseline utility score. In addition, utility values are higher for the BVd arm when compared to the DVd arm [redacted]

[redacted]

Table 44 shows summary results obtained from the mixed-effect model when three-health states (1: progression-free, in response, 2: progression-free, no response, and 3: progressed) were included as covariates as well as treatment arms and baseline utility score. [redacted]

The mean utility value obtained for the BVd and DVd treatment arms from the two-and three-state model are used in Table 45. Please see the full utility tables with exponential estimates available in the shared file 'B9 Response_health state utilities'.

d) Please provide the effects on utility of an additional interaction term for treatment by number of prior lines of therapy (2L-only, 3L-only, and 3L+ subpopulations) if available.

Response: We did not perform analysis separately assessing the effects of interaction term for treatment by number of prior lines of therapy on utility. Given the time frame of the required response, GSK do not have the time to complete the requested analysis.

e) Please clarify how uncertainty was captured in the estimates of utility values used in the model. If not already included, please consider

incorporating uncertainty in the regression outputs through the variance-covariance matrices.

Response: GSK agree with the EAG's question that incorporating uncertainty would be more robust using the utility analysis outputs. In the updated model, the values derived from the 95% CIs available. This is a more appropriate methodology to test the robustness of the health state utility values in analysis and can be run through the OWSA functionality.

f) Please justify the use of treatment-specific utility values by health state, based on limited comparative data from one trial. Please discuss the reasons for the higher utility value for BVd compared to DVd for the same PF health state, and comment on whether this is double counting the effects of BVd on PFS.

Response: Similar to the results obtained for the two-state model, the utility values for the BVd arm from the three-state model are significantly higher than those obtained for the DVd arm [redacted]. The gain in utility for the BVd arm may be explained by infrequent dosing (see response to question B11) of belamaf for patients who remain on treatment, and patients discontinuing belamaf but remaining progression-free.

The treatment specific utility states were chosen to reflect the conclusions of the utility analysis. Varying the utility between treatment arms does not double count the utility benefit, as long as the utility used is representative of the findings in the data.

g) Please explain the reasons for a higher utility value for the PD health state ([redacted]) compared to the PF health state for the comparators of DVd, SVd and hKd ([redacted]).

Response: The values used in the model are directly elicited from the DREAMM-7 utility analysis. While the PFS health state allowed for varying

health state utilities between treatments, an assumption was made that utilities for progressive disease (PD) are equal ([redacted]) between arms.

There is insufficient granularity in the available utility analyses to comment on the rationale for the higher PD utility value. However, [redacted] (PD – all arms) and [redacted] (PFS – DVd) are closely aligned for any difference to likely be considered statistically insignificant.

h) Please comment on how the magnitude of the decrement in utility for progressive disease, relative to PF, for BVd from DREAMM-7 ([redacted]) compares to the corresponding decrement associated with the PD health state from different external sources (e.g., that used in previous NICE TAs, including TA974, and the meta-regression by Hatswell et al., 2019) (20), and explain the reasons for the difference.

Response: The utilities that were used to populate the health states in the economic model were derived from DREAMM-7 trial, an approach aligned with previous NICE TAs, including TA974 in which utilities were derived from the BOSTON trial. An overview of the approach taken for health state utilities in previous TAs is provided in Table 30 in Document B (page 106), and in general the preferred approach was to use utilities from the clinical trials when available, as it better reflects the health-related quality of life of the modelled population. Furthermore, in TA974 the difference in utilities between progressed disease and progression free survival was relatively small (i.e., 0.037 for the pooled utilities from the BOSTON study arms), which appears to be aligned with the findings from the utility analysis performed in DREAMM-7 that informed the economic model. In TA974, the justification provided for the small difference in utility between the different health states was that utilities for the progressed health state are based on an assessment at one timepoint shortly after disease progression, whereas the EQ-5D-3L was collected at 3, 6 and 12 months during OS follow up in DREAMM-7 (CSR, Schedule of Activities (SoA); page 6958).

The meta-regression by Hatswell et al., 2019 showed from the systematic literature review the mean 1L utility was 0.627, the mean 2L 0.636, the mean 3L 0.610, and the mean 4L 0.486 (Hatswell et al., 2019). It is noted here that the mean 2L utility in Hatswell et al. is the closest value to the one derived from

the DREAMM-7 trial utility analysis. The decrement found in DREAMM-7 analysis for progressed disease and progression free survival is, in general, smaller compared to the difference in utilities found between LoT in Hatswell et al., 2019 meta-regression. This difference is expected to lead to a conservative estimate of the incremental QALYs between BVd and DVd, since patients in BVd remain progression free for longer compared to DVd.

Overall, GSK is confident that approach to use utilities derived from DREAMM-7 trial is the most robust approach, which is also largely aligned with previous TAs.

i) ***Please comment on whether the EQ-5D-3L data from DREAMM-7 was sufficient to capture the impact of treatment-related adverse events of Grade 2 and below. More specifically, please comment on whether the PF health state utility value used in the model for BVd is sufficient to capture ocular adverse events of Grade 2 and below.***

Response: The rationale of incorporating Grade 3+ events only is that adverse events of Grade 2 or less are unlikely to have significant impact to cost-effectiveness results and therefore influence decision making. This approach aligns with previous MM TAs (21, 22).

It is difficult to capture acute adverse events in the EQ-5D-3L questionnaires elicited in the trial, and such the appropriate modelling approach is to account for these separately as utility decrements (applied in the base-case as one-off at the start of the model time horizon).

Management of eye-related adverse events with dosage modifications is clinical practice for treatments with a belamaf component, and eye-related adverse events are common (as outlined in B.2.10.3). Given the regularity of eye-related side effects, and the regularity of the EQ-5D-3L questionnaire scheduling the DREAMM-7 trial (CSR, Schedule of Activities (SoA); page 6958) the impact on QoL is likely to be captured (including Grade 2 events) and accounted for in the EQ-5D utility analysis applied to health states in the model.

Costs of ocular adverse events

B10. The unit cost of managing a keratopathy adverse event (AE) episode (£29.18) for BVd appears to be calculated based on the unit cost and resource use associated with ophthalmologist visits and artificial tear eye drops. The electronic version of the model suggests that this calculation reflects different levels of resource use across severity levels (mild, moderate and severe), which seems to be in line with a previous NICE technology appraisal of belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies [ID2701]; however, the details are not clear in Document B.

a) ***Please provide details on the assumptions and evidence used to inform the calculation of the unit cost of a keratopathy AE in cells S270:X273 of the 'Data store' worksheet in the economic version of the model.***

   Response: Please see the response to the identified error and the method on how this has been rectified in response to B10.b.

b) ***The unit cost of a keratopathy AE is considerably lower than the unit cost applied for this AE in the previous NICE appraisal of belamaf [ID2701] (£397.18), despite similar unit costs per category of resource use (ophthalmologist visits and artificial tear eye drops). Please explain the different assumptions used to estimate unit costs between the two appraisals and comment on the appropriateness of the unit cost applied in the current appraisal.***

   Response: GSK thank the EAG for identifying an error in the model. The current calculations apply the cost of keratopathy proportional to weekly costs (proportional to 1 year) where these costs should be presented as overall resource use from keratopathy events. This has no material impact on calculated ICERs.

   GSK have adapted these costs in the updated model to correct this error using the below methods:

   - Frequency for resource use has been adapted for the following costs for both ophthalmologist visits and artificial tear usage: Mild: 1,

Moderate: 1, Severe: 5. This is based on the below rationale identified from belamaf [ID2701] (23):

- "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)."

- The average cost of moderate and severe cost was used to approximate Grade 3+ events (£505.87), closely aligning with the cost indicated in the EAG's question (£397.18)

- This cost was applied as a one-off cost for grade 3+ events occurring for keratopathy, blurred vision and dry eyes (£156.82)

In addition, the original model provided in this submission included resource use of ophthalmologist directly, once per cycle for the first 4 treatment cycles (BVd arm only – patients on treatment) to account for the recommendation in the SmPC.(24) the model therefore accounts for both initial ophthalmologist visit costs and the cost of keratopathy from the safety data. There is likely some degree of double counting between these two estimates, as some of these events are expected to be resolved in the per cycle ophthalmologist visits. The combined costs are therefore likely to be lower in clinical practice.

Drug acquisition costs

B11. PRIORITY: Dose delays and reductions associated with BVd.

a) ***Please provide details on how belamaf dosing in BVd was calculated from the IPD from DREAMM-7. Specifically, please show how Figure 34 in Document B was derived from the IPD included in the worksheet 'Dosing data' from the electronic version of the model.***

Response: In the DREAMM-7 trial, clinicians modified the dose of belamaf in accordance with the trial protocol (both dose delays and dose reductions).

Consequently, in order to model the acquisition costs of belamaf accurately, both within and beyond the observed trial period, it is important to model dosing in granular detail. Consequently, an individual patient-level based dosing method was applied in the base-case.

In this analysis, the proportion of on-treatment patients receiving a dose of [redacted] increments in each week of the trial was estimated. Patients receiving higher doses than [redacted] were assumed to have received the closest dose-band [redacted] this adjustment was only applied in the few occurrences of these doses ([redacted] total doses throughout the available trial data). The use of these dose-bands enabled the evolution of dose within the trial to be modelled accurately. Furthermore, it enabled wastage to be estimated accurately using a methods of moment (MoM) approach. Dosing was analysed on a weekly basis to enable accurate modelling of the schedule changes observed in the trial and applied to the extrapolated TTD curve.

Figure 34 illustrates the dose intensity by [redacted] interval for patients remaining on treatment. The plot shows the average dose intensity calculated as cumulative dose over each time period (without taking into account if the time between the last dose and the end of a time interval is [redacted]) divided by [redacted] If a subject drops out within each time window, the equation used to calculate cumulative dose is not adjusted. This is different from the computation used by GSK statisticians in order to calculate mean and median RDI (present in the dossier and model) which incorporates the totality of the dosing data. This analysis cannot be replicated from the IPD data from the model which does not track individual patients and serves only as a visual of the changing average dose intensity over time, for patients remaining on treatment.

i. ***Please illustrate graphically how the average dose intensity changes over time in DREAMM-7, including how this is extrapolated over time in the company's base case analysis. Please state any assumptions used for the extrapolation.***

Response: An overview of the IPD DREAMM-7 data which was incorporated into the model is provided below for three main areas:

1. A summary of the different doses administered over time (Figure 11) in DREAMM-7
2. A summary of the changes to dosing schedule over time for patients remaining on treatment (Figure 12)
3. Average dose administered over time for patients on treatment and average extrapolated dose (Figure 13)

Each of the supporting figures are available in the updated economic model for reference.

Figure 11 below illustrates the cumulative doses received for all patient included in the ITT population of the DREAMM-7 trial. Dose quantities administered less than 50 times are excluded from this figure [redacted].

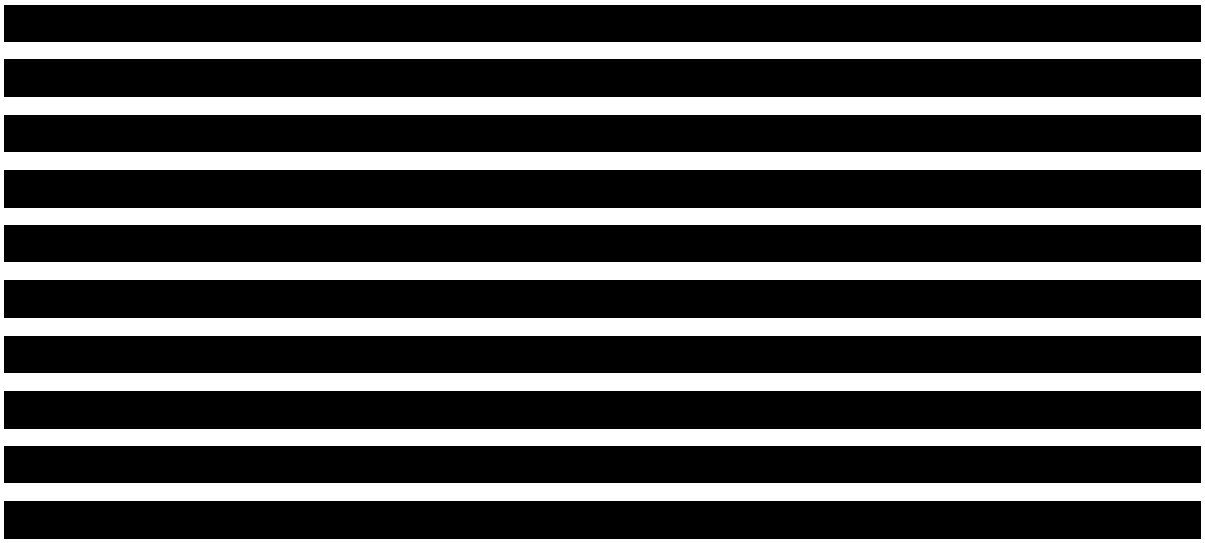
[redacted]

Figure 11.

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone.

While the above figure summarises the relationship between time and doses quantities administered to patients, in DREAMM-7 patients dosing schedule also diverges from the originally planned schedule with the majority of patients receiving a delayed dose administration.

Figure ***12*** below summarises the total patients on treatment (continuing to receive belamaf without discontinuation) and the sum of administered doses within the originally planned Q3W dosing schedule.



[redacted]

Figure 12. [redacted]

[redacted]

.

The two identified trends are patients remaining on treatment receive lower doses over time, and most patients receive doses with a delayed schedule. The overall average dose (summarised within a Q3W time frame to allow comparison to original schedule) incorporating both these trends is summarised in Figure ***13*** below.

Figure 13. [redacted]

In order to extrapolate the trial data, an arbitrary point of extrapolation of 50 patients remaining on treatment was used and summarises the proportion of all remaining doses received after this time point [redacted]. The extrapolated doses remain fixed for the remaining treatment time frame in the model. As seen in Figure ***13***, this is a conservative estimate to address the uncertainty in the reduced number of patients [redacted] given the likely downwards trend of the average dose over time.

ii. Please provide the median and mean relative dose intensity (RDI) for belamaf, based on the IPD from DREAMM-7, used in the company's base case analysis and contrast the RDI estimates derived from the model with the corresponding estimates reported in Table 27 of Document B.

Response: Median and mean RDI based on the IPD data are the values available in the dossier (Section B.2.10.4; median RDI: 51% [redacted]). Table 27 summarises the cumulative median RDI estimates

(overall, over the first 6 months [months 1-6] and over the first 12 months [months 1-12]).

Mean RDI accounts for patients still on treatment. It is therefore not simply a function of the dose in each cycle, it is weighted by the number of people in each cycle. Consequently, mean RDI skews towards the earlier points in follow-up where more patients are yet to have stopped belamaf treatment. As both the dose and schedule of belamaf reduces over time (outlined in response B.11.a.i), application of a mean RDI across the whole follow-up period is inappropriate, as this: (1) doesn't account for the long terms trends which impact extrapolation beyond the trial period and (2) treats mean RDI as if it were an average over time, rather than reflecting dosage for patients remaining on belamaf treatment over a longer period.

In a typical constant RDI scenario where originally planned dose is followed closely, point (1) or point (2) are of little importance. In the case with belamaf, since dosage commonly diverges from the initially planned dose and schedule, dosing based on mean RDI in the CEM is incorrect both within and beyond the trial period.

The mean RDI and IPD dosage methodologies are summarised in Figure ***14*** below (modelled for 242 patients to align with the available dose data, prior to incorporating wastage), which shows cumulative milligrams of belamaf administered in the model. These are compared to the total dose of belamaf (in mg) administered to ITT patients in the DREAMM-7 trial from the IPD dose data. The SmPC planned dose (2.5mg/kg Q3W) is included for reference. The figure explicitly shows the modelled IPD dose methodology incorporated in the base case to closely align with the total administered dose from the trial, with the mean RDI method quickly overestimating belamaf administered dose.

It is therefore sensible to use the time varying analysis available from the IPD dosage data in order to capture the true impact of dose reductions and dose schedule delays as seen in clinical practice.

Figure 14. [redacted]

Abbreviations: IPD, individual patient data; ITT, intent to treat; mg, milligram; RDI, relative dose intensity; SmPC, summary of product characteristics

iii. Please provide the median and mean relative dose intensity (RDI) for belamaf, based on the SmPC recommendations, used in the company's scenario analysis.

Response: As per the draft of the SmPC, the dosage of belamaf should be individualised for each patient (e.g. recommended modifications to manage adverse reactions are provided in Table 3 of the SmPC). For this reason, the median and mean relative dose intensity (RDI) for belamaf in DREAMM-7 is exactly the same as the dose intensity recommended in the draft of the SmPC.

b) Please comment on whether the dose reductions for belamaf in DREAMM-7 are likely to be reflected in NHS clinical practice.

Response: In DREAMM-7, eye-related side effects, which are a known risk with belamaf, were managed with dose modifications, including delays and reductions. The efficacy of BVd was maintained even with delays and reductions of the belamaf dose, which resulted in the lower relative dose intensity (RDI) reported for belamaf (versus daratumumab). The median RDI of belamaf was 51% for the full duration of treatment

and this is likely to be reflected in NHS clinical practice considering: 1) RDI from the UK [redacted] dataset; and 2) UK clinical expert advice.

1) **RDI from the UK [redacted] dataset**

[redacted] This study is a retrospective national analysis of the [redacted], and is independent of GSK (i.e. GSK have not been involved in its design or management). This study has been published in poster form at British Society Haematology 2023 (26) and International Myeloma Society 2023 (27). The project lead of this study shared raw data with GSK in Jan 2023, and has provided their consent for GSK to use this data.

The RDI from the [redacted] dataset is based on dose delays. For dose reduction, the number of patients with a dose reduction is recorded within the [redacted] dataset, but when patients received the reduction and how much the dose was reduced by was not recorded.

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. 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], and when including dose reductions, the RDI in NHS clinical practice is likely to be lower than this value. These values demonstrate that the RDI for belamaf in DREAMM-7 is likely to be reflected in NHS clinical practice.

2) **UK clinical expert advice**

GSK conducted six 1:1 Advice Seeking Consultancy Meetings with 3 UK Multiple Myeloma clinical experts prior to submission. Clinical experts were selected based on: 1) Their experience of belamaf via the DREAMM clinical trial program and/or GSK's [redacted]; 2) Their experience of NICE technology assessments in myeloma; and 3) Their extensive experience in managing myeloma patients in the UK (Appendix M).

Feedback from these Meetings suggests that in NHS clinical practice BVd will be aligned to the posology of DVd, i.e., utilisation of a 28-day cycle rather than the 21-day cycle employed in DREAMM-7. Clinical experts suggested that administration could start with belamaf once every 4 weeks, and then when a patient achieves a partial response, the dose interval would be extended to once every 8 weeks, and then once every 12 weeks. Clinical experts stated that the first dose of belamaf would be administered at 2.5 mg/kg and then HCPs would dose reduce to 1.9 mg/kg. Clinical experts also highlighted that the BVd treatment effect is expected to be maintained for at least 12 weeks, but that this could be longer.

Based on the BVd arm in DREAMM-7 study, 82.7% of patients achieved a partial response or better and the median time to partial response or better was 1.4 months (range: 0.7-8.4 months) (28), so overall this feedback indicates that partial responders or better will quickly switch to a schedule of 1.9 mg/kg once every 8 weeks after the first cycle of belamaf. This observation demonstrates that the RDI for belamaf in DREAMM-7 (median: 51%) is likely to be reflected in NHS clinical practice.

B12. In Table 10 of Appendix F, it is reported that 15% of belamaf doses in DREAMM-7 were missed because of COVID interruptions. Please provide an additional scenario with an adjustment factor that inflates the doses to take account of those missed specifically as a result of COVID interruptions.

Response: Table 10 in Appendix F outlines the adverse events leading to dose interruptions/delays. It is unknown to the extent these AEs individually interrupt the doses of the treatments in each arm of DREAMM-7 with currently available data. In addition, dose interruptions due to adverse events are also reflected in the efficacy data included to inform the cost-effectiveness analysis.

B13. Please clarify how the RDI was calculated for the drugs listed in Table 50 of Document B.

Response: The RDI for high-dose carfilzomib, Isatuximab, and Pomalidomide were sourced from the literature from sources specified in the Company Evidence Submission, Document B, Table 50.

For Belamaf, Bortezomib, Dexamethasone, and Daratumumab the corresponding RDIs were estimated based on DREAMM-7. In short, for these treatments the RDI is calculated by using each patient's Overall Dose Intensity from DREAMM-7, dividing it by the Planned Dose Intensity, and multiplying by 100 to express it as a percentage.

The overall dose intensity reflects the cumulative actual dose divided by the duration of exposure (expressed in mg/kg/cycle) and was calculated as described below:

- Dose intensity (units/3 weeks) = cumulative actual dose divided by duration of exposure in 3 weeks (duration of exposure in days /21); was used for belantamab mafodotin (all cycles), and daratumumab, bortezomib, dexamethasone (cycles 1-8).

- Dose intensity (units/3 weeks) = cumulative actual dose divided by duration of exposure in 3 weeks (duration of exposure in days /21); was used for daratumumab (cycles 9+).

- Duration of exposure in days used for the dose intensity calculation was defined as: *end date of the cycle – first date + 1 day*.

    - The end date of the cycle is defined as the cycle start date +2 - days for belantamab mafodotin (all cycles), and daratumumab, bortezomib, dexamethasone (cycles 1-8).

    - The end date of the cycle is defined as the cycle start date +27 days for daratumumab (cycles 9+).

        - The end date of the last cycle is calculated as the earliest of: the calculated end date of the last cycle, treatment discontinuation date, or the death date, if the participant discontinues study or dies before the expected end of the last cycle.

The RDI was summarized for belantamab mafodotin, bortezomib, and dexamethasone separately. For daratumumab, RDI was calculated for cycles 1-4, 4-8, and 9+. RDI was calculated as a percent and was defined as 100*(mean overall dose intensity divided by planned dose intensity). Planned dose intensity for each treatment was calculated as:

- Belantamab Mafodotin = 2.5 mg/kg
- Daratumumab = Cycles 1-3: 48 mg/kg; Cycles 4-8 and 9+: 16 mg/kg
- Bortezomib = 5.2 mg/m2
- Dexamethasone = 160 mg for participants with a first dose of 20mg, and 80mg for participants with a first dose of 10mg.

The mean RDI was used in the scenario analysis for belamaf and in the base case for all other treatments in the submitted CEM.

Model Implementation

B14. PRIORITY: Flexibility in model to select between alternative sources of evidence and approaches

a) Please ensure that the electronic model is sufficiently flexible to allow the user to select between all alternative options for methodological choice (e.g., direct extrapolation, surrogacy, IPCW approaches) for each of the outcomes of PFS, TTD, and OS, including accessibility to select alternative parametric distribution choices for parameters that are provided in other worksheets but not currently selectable (e.g. 'Survival coefficients' worksheet).

Response: The model allows the user to select between all alternative sources of evidence and approaches implemented to support the model development.

- Direct extrapolation: this approach is applicable to the PFS, TTD, and OS outcomes with the accessibility to select all standard parametric

distributions (i.e., exponential, Weibull, Gompertz, log-logistic, log normal, generalized gamma).

- IPCW approach: As described in Appendix O, this approach was used to adjust survival estimates and curves for the effect from patients switching to therapies which are not available in the NHS. This approach is applicable to the OS outcome only, as the primary outcome for the adjusted analysis is OS and the analysis is geared towards estimating an effect of randomization on OS "purified" by the intermediary effect of follow-up anticancer treatment on OS. The application of this analysis in the model is accessible via the "Clinical Inputs" tab (cells D38, D44) by selecting "Adjusted" as the OS source of data. The model user can select between all standard parametric distributions (i.e., exponential, Weibull, Gompertz, log-logistic, log normal, generalized gamma).

- Surrogacy: this approach is applicable to OS only, and can be selected via the "Clinical Inputs" tab (cells D31) by selecting "mPFS:mOS surrogacy" as the Method for OS survival analysis. The model user can then select between all standard parametric distributions (i.e., exponential, Weibull, Gompertz, log-logistic, log normal, generalized gamma) from the PFS section of the "Clinical Inputs" tab (cells D15, D19). Noting the OS surrogacy analysis applied is aligned to RRMM data (which is broadly similar to the ITT population).

b) Please ensure that in the "Clinical Inputs" tab (cells D43-45), all alternative sources of OS data (both informative and non-informative priors) and all parametric distributions (Exponential, Weibull, Gompertz, Log-logistic, Lognormal, and Generalized Gamma) for extrapolation of DVd are accessible and usable in the model.

Response: GSK apologise as these switches were fixed due to an error in the data validation functionality in these cells. As requested, minor updates were made to the model regarding the data validation of lists included in cells D43-45 of the "Clinical Inputs" tab. The user can now select the informative prior approach for DVd via the "Clinical Inputs" tab (cell D44) by selecting "Informative prior" as the OS source of data. The informative prior approach is

not applicable for the BVd OS outcome, as mature OS data were available only for DVd (59% events over a maximum follow-up of 79.8 months) from the CASTOR study, hence an informative prior was estimated only for the control arm (i.e., DVd) in DREAMM-7.

The parameter estimates for different distributions using Bayesian informative prior analysis can be found in the “Survival coefficients” tab (cells BO77:CA91). Accessibility is provided to the CEM user to select between a subset of standard parametric distributions (i.e., Weibull, Log-logistic, Log-normal, Generalized Gamma). The exponential model was not considered in the Bayesian informative prior analysis as it does not have a shape parameter, while the Gompertz model was excluded due to clinically infeasible long-term projections resulting from a negative shape parameter which is not supported by the survHE package used for the analysis.

Section C: Textual clarification and additional points

C1. The abbreviation “PFS-2” is used. Please clearly define its meaning.

Response: As per the DREAMM-7 protocol, PFS2 is defined as the time from randomisation to disease progression after initiation of new anti-cancer 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 anti-cancer therapy, or death from any cause, whichever is earlier.

C2. Appendix D, Figure 2 “PRISMA flow diagram of identified publications (Update 1)”: please explain the ‘’ in the “Qualifying studies” box.**

Response: The ‘**’ provides more information on study screening and data extraction. In particular, ‘**’ in the “Qualifying studies” box indicate that in the first review update, the screening and selection studies was conducted as per the protocol. However, not all qualifying studies were extracted, but instead the focus was on extracting studies that were deemed to be most relevant. A list of qualifying studies that were not extracted are given in Appendix D. Most qualifying studies that were not included for extraction were Phase 1 or Phase 1/2 studies that were not randomized or were single-arm.

C3. Please provide a document or URL for reference 25 (from Document B) which relates to the NCRAS study.

Response: The document (e-poster presentation) for this reference can be found in GSK's reference pack for clarification questions (29). The URL for the corresponding abstract is: EHA Library - The official digital education library of European Hematology Association (EHA) (ehaweb.org).

C4. The landmark survival estimates from 1 to 20 years for the BVd TTD extrapolation with a generalised gamma distribution presented in Table 39 of Document B do not appear to match the corresponding estimates in the electronic version of the model ('Survival analysis' sheet, cells U62:U2401).

a. ***Please check the source of this inconsistency and provide correction to table in Document B and/or the electronic version of the model accordingly.***

Response: GSK apologies for this inaccuracy. The figures presented in Table 39 of Document B for the generalised gamma extrapolation were inaccurate. Updated figures which align with the model are presented in Table **12** below.

Table 12. TTD – BVd goodness of fit statistics for parametric distributions

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	-	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan-Meier; TTD, time to treatment discontinuation.
Note: Weibull is in bold as this represents the choice of parametric curve selected for the base case.

C5. The first sentence is section B.2.9.5 states that "Findings of the conducted NMA are consistent with the efficacy results of the DREAMM-7 study, indicating the robustness and generalisability[…]". Given that the DREAMM-7 study is the only evidence on the BVd vs DVd comparison, and there are no loops in the network, NMA results must agree with the DREAMM-7 study. Please explain why this should be considered to indicate "robustness and generalisability of the results to UK clinical practice[…]".

Response: The comment added in section B.2.9.5 regarding the alignment in the results of the comparison of BVd vs DVd in DREAMM-7 trial and in the NMA regarded the validity of the NMA results. In particular, the consistency of the findings reduces any potential uncertainty that may be associated with the interpretation of the NMA. This is indeed because the DREAMM-7 study serves as the most robust source of evidence for the BVd vs DVd comparison, and overall the general trend of the results for the NMA validate the findings from the DREAMM-7 trial. GSK is confident that the NMA was conducted appropriately, and thus its findings are supportive of the direct evidence from the pivotal trial.

C6. In the clinical evidence searches in Appendix D, the date limits applied within the searches of MEDLINE and Embase via ProQuest were not shown, so the EAG could not appraise how these had been applied. The same issue applies to the documentation of the second update of the Cochrane library databases and the update searches for INAHTA, clinicaltrials.gov, and WHO ICTRP. Please can the company provide these lines?

Response: We have updated this information in the 'C6 Response_Clinical SLR - Search strategy' document (included in response) in the tables / notes for: MEDLINE and EMBASE (per ProQuest), Cochrane (dates for update 1 were already included and we have added dates for update 2), INAHTA, CT.Gov, and ICTRP.

C7. In the clinical evidence searches in Appendix D; and the cost-effectiveness searches, health-related quality of life searches, and cost and healthcare

resource searches in Appendix G, please can the company provide the dates that all sources were indexed to and from?

Response: The time horizons over which the databases have been searched have already been presented for each SLR in the relevant appendices.

C8. In the clinical evidence searches in Appendix D, search line 2 of the Cochrane database strategies was missing. Please can the company provide this line?

Response: This has been provided in the updated version of Appendix D.

References

1. Mastikhina L, Cope S, Marshall T, Maciel D, Mojebi A, Karampampa K, et al. CO91 Association Between Progression-Free Survival (PFS) and Overall Survival (OS) in Patients with Relapsed/Refractory (RR) Multiple Myeloma (MM). Value in Health. 2023;26(12):S30-S1.

2. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. British journal of haematology. 2016;175(2):252-64.

3. Cornell R, Hari P, Tang S, Biran N, Callander N, Chari A, et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH. American journal of hematology. 2021;96(1):E5-E8.

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10. Sally Moore LC, Christina-Jane Crossman-Barnes, Sophie Jose, Zeyad Khalaf, Kwee Yong, Megan Soutar, Philip WOODS. REAL-WORLD CHARACTERISTICS AND OUTCOMES FOR LENALIDOMIDE-REFRACTORY PATIENTS WITH MULTIPLE MYELOMA RECEIVINGDARATUMUMAB–BORTEZOMIB–DEXAMETHASONE AS SECOND-LINETREATMENT IN ENGLAND. European Hematology Association (EHA) 20242024.

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Single Technology Appraisal

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

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.

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About you

1.Your name	[redacted]
2. Name of organisation	Myeloma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myeloma UK is the only organisation in the UK dealing exclusively with myeloma and related conditions. We represent 24,000 people living with myeloma in the UK. 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.
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.**	We have received funding from the manufacturer of the technology (GlaxoSmithKline UK Limited) in the last 12 months. In 2023, 6% of Myeloma UK's income came from pharmaceutical companies. The table below shows the 2023 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, and gifts, honoraria, or sponsorship.

	Core grant	Research / Project	Donation	Consultancy/ Honoraria	Events	Total
AbbVie Ltd	-	10,000	-	870	-	10,870
Alexion Pharma UK Ltd	-	7,500	-	-	-	7,500
Amgen Ltd	-	20,000	-	-	-	20,000
The Binding Site Ltd	20,000	-	-	437	-	20,437
Bristol-Myers Squibb Pharmaceuticals Ltd	15,000	-	-	-	-	15,000
GlaxoSmithKline UK Limited	-	20,026	-	-	-	20,026
ITECHO Health Ltd	-	6,600	-	-	-	6,600
Janssen-Cilag Ltd	-	15,907	-	260	9,093	25,260
Menarini Stemline UK Limited	-	7,000	-	-	-	7,000
Pfizer Limited	-	-	-	73,448	-	73,448
Stemline Therapeutics Switzerland GmbH	-	-	-	1,451	-	1,451
Sanofi	-	-	-	-	27,990	27,990
Takeda UK	30,000	-	-	-	29,681	59,681
	65,000	**87,033**	**-**	**76,466**	**66,764**	295,263

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information included in this submission came from the myeloma patients and carers we engage with through our research, services and advocacy programmes, including: - Semi-structured interviews in April and May 2024 with relapsed/refractory myeloma patients. These interviews provide valuable experience and insight data from patients who have either had belantamab mafodotin via clinical trials or who have relapsed and view this technology as a potential next step in their treatment pathway. - A Myeloma UK-funded, multi-criteria decision analysis study of 560 myeloma patients run by the European Medicines Agency (EMA) and the University of Groningen. The study explored patient preferences for different benefit and risk outcomes in myeloma treatment. - Analysis of the experiences and views of patients, family members and carers gathered via our Myeloma Infoline, Patient and Family Myeloma Infodays, posts to our online Discussion Forum and insights gathered for earlier appraisals.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myeloma is a complex and heterogenous cancer that originates from abnormal plasma cells in the bone marrow. It is incurable but treatments can halt its progress and improve quality of life. The complications of myeloma can be devastating, debilitating and painful; they include severe bone pain, kidney damage, fatigue and a depleted immune system that can lead to increased infections. ***"I had severe back pain and couldn't get up from bed at times. I've lost nearly six inches in height. I was a very active person and now I can't do any of my hobbies."*** ***"I'm just really tired. It's like when you go to sleep but wake up just as tired as when you went to sleep. You never feel as if you're not tired."*** Each complication severely impacts quality of life in its own way. Patients can experience a dramatic loss in height, serious fatigue, reduced appetite, breathing problems, reduced mobility and independence, and poorer mental health. In a survey of 1324 patients and carers, 72% of respondents said that their myeloma and a high or moderate impact on their quality of life.[1] ***"Myeloma has closed my world. I no longer have the freedom to do what I was doing before."*** ***"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health. Some of the simplest tasks become impossible to undertake such as going to the bathroom or making a cup of tea… things we take for granted."*** It is an incurable, relapsing and remitting cancer. The constant possibility of relapse completely disrupts the lives of patients and their families and has a huge psychological impact. Throughout their myeloma journey, patients must switch treatments and adjust to different side effects and new routines for hospital visits and treatment administration. They also face the uncertainty of whether the new treatment will be effective and tolerable and are aware that every time they need to change treatment, their options and life expectancy decrease. ***"It never goes away. When you've got myeloma like me, I'm living with it, but still waiting for it to come back. And then you think "look what they did to me the first time; what if it does come back?" And what if they just ignore it, or what if..."*** ***"There is a constant pressure of wondering what's going to happen to me next because myeloma is like that, it's not curable and it's going to come back, I'm sure every month there's the possibility of relapse and it's hard to ignore that. It's a massive relief every month when I'm told that my paraproteins haven't risen."*** The individual and heterogeneous nature of myeloma means that some patients may respond to or tolerate treatment well, and others may not. How well a patient responds to or tolerates a drug impacts their future treatment options.

	Myeloma also evolves and becomes resistant to treatment. In general, a drug that did not work, stops working or caused serious side effects would not be offered again, even when administered in a different combination. Therefore, it is essential to have a range of treatments with different mechanisms of action at all stages of the myeloma pathway to ensure patients have a treatment available when they need it. ***"The more options the better chance of having one work and be compatible. Two previous ones have failed, or I reacted badly to."*** ***"I have many different treatments and my response to them has been disappointingly average. I have never really had a long remission – not like some patients. That's my hope."*** 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 - 42% of carers were not given enough information at diagnosis about how myeloma may affect them[2] Living with myeloma is therefore often extremely challenging physically and emotionally for patients and their families. ***"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."*** ***"When you have a cancer diagnosis, however long or short that journey is, you drag everyone else along with you. It's a tough journey for everyone. My parents are in their 80's now but despite the fact I'm 58 this year, you are always a son or daughter – they say "we wish we could do anything to take this off your shoulders. We struggle to cope with the fact that you've got it (myeloma) and there's this cloud constantly hanging over you.""***

[1] Myeloma UK (2022) A Life Worth Living The impact of a delayed diagnosis on myeloma patients' quality of life. Available at https://www.myeloma.org.uk/library/a-life-worth-living/ (Accessed May 2024)
[2] 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?	Patients and carers feel fortunate that although myeloma is incurable, it is treatable in most cases. The community appreciate the wider range of effective treatments that are now available for treating relapsed and refractory myeloma, which has delivered significant improvements in survival in myeloma over the past decade. However, myeloma remains a challenging cancer to treat, often particularly so for multiply relapsed patients. Myeloma is a relapsing and remitting cancer which evolves over time and becomes resistant to treatment; a range of treatment options with different mechanisms of action at each stage of the pathway is therefore vital for myeloma patients. ***"Myeloma is currently incurable, so having a variety of available strategies/options gives me and my partner some hope and time."*** Patients know that everyone's experience of a treatment is different and sometimes unpredictable. They know that the level of effectiveness and side effects can differ, either from direct experience of treatments not working or causing unbearable side effects or through discussions with peers. Understandably, this can cause a great deal of worry for myeloma patients and their families. There is uncertainty about the future, whether the next treatment will work and if it will negatively affect their quality of life, and the fear of reaching the 'end' of treatment options for their cancer. ***"You don't know how you're going to react to particular drugs until you've had them. I guess it's a bit of a lottery."*** Patients want a choice of clinical options at each line of their treatment that are the most appropriate for their myeloma disease. Patients are concerned that they have limited options at each line of the pathway, either because they are resistant to the regimen or one of the treatment components or cannot tolerate a treatment. Patients want their clinician to have several options to treat their myeloma using new medicines, including those with new modes of actions which demonstrate good safety and efficacy and provide as long a remission time as possible with the best quality of life. All currently available anti-myeloma treatments have side effects which affect quality of life. The most impactful side effects are the ones which limit daily activities or reduce independence. These include fatigue, peripheral neuropathy, and gastrointestinal disturbances. ***"For me fatigue and peripheral neuropathy had the biggest impact on my daily life."***

8. Is there an unmet need for patients with this condition?	There is a clear need for innovative anti-myeloma treatments which deliver deep, durable responses for relapsed and refractory myeloma patients. There have been significant advancements in the treatment of myeloma. However, myeloma is still incurable, and patients respond differently to currently available myeloma treatments. Patients, following diagnosis, are aware that they will relapse with significant impact on their physical and emotional health. Knowing that there are limited treatment options at each line of treatment is a significant concern for patients. There is a critical need to ensure that the myeloma treatment pathway offers options for each myeloma patient based on their individual health status and their response to previous treatment regimens, including tolerability and co-morbidities. Access to new myeloma treatments offer significant hope and health and wellbeing benefits, and address a major unmet need, the need to increase duration of remission, be able to respond to relapse with a potent and long-lasting new treatment and to maintain and improve quality of life. 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 uses this novel mechanism and therefore it has much potential to fulfil an unmet need for multiply relapsed/refractory myeloma patients. It is also important to note that more than a quarter of myeloma patients have high-risk disease at diagnosis. They either don't respond to existing treatments or relapse shortly after successful treatment. They move through the myeloma treatment pathway and run out of viable treatment options more quickly than standard-risk patients. Treatments with new mechanisms of action are a lifeline for high-risk patients with the potential to deliver significant remission times when other established classes of anti-myeloma drugs have not.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We know from our research that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day-to-day life.[3] The DREAMM-7 clinical trial evaluated the use of belantamab mafodotin in combination with bortezomib and dexamethasone (BVd), and compared it to daratumumab, bortezomib and dexamethasone (DVd), which is the current standard of care. The results from the trial[4] show that patients treated with BVd had a median progression-free survival (PFS) time of 36.6 months, compared to 13.4 months with DVd. This demonstrates a statistically significant PFS benefit of belantamab mafodotin with an mPFS improvement of 23.2 months. The overall response rate (ORR) was 82.7% for patients treated with BVd and 71.3% for DVd. The median duration of response (mDOR) was 35.6 months for patients treated with BVd and 17.8 months for DVd. The trial therefore demonstrates that belantamab mafodotin, bortezomib and dexamethasone led to a greater depth of response and doubling of mDOR for patients, compared to daratumumab, bortezomib and dexamethasone. 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 years. ***"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.*** ***"It was quite quick that the cancer went away. It was within 3 or 4 sessions I think and then my oncologist came to me and said you've done so well and the cancer's gone."*** ***"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."*** 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. 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 that delivers an effective remission cannot be underestimated for myeloma patients. The benefits it delivers are hugely meaningful to patients and 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 while they are in remission from existing or newly approved treatments.

[3] Postmus, D., et. al. (2018). Individual Trade-Offs Between Possible Benefits and Risks of Cancer Treatments: Results from a Stated Preference Study with Patients with Multiple Myeloma. The oncologist, 23(1), 44–51.

[4] Maria-Victoria Mateos et al. (2024) Results from the randomized phase III DREAMM-7 study of belantamab mafodotin (belamaf) + bortezomib, and dexamethasone (BVd) vs daratumumab, bortezomib, and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM). *JCO* **42**, 439572-439572.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We know 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. All patients in the DREAMM-7 trial experienced at least one side effect from treatment. Side effects are graded from 1-4 in terms of severity (1 being mild, 4 being life-threatening). During the trial, Grades 3 and 4 treatment-related side effects were reported in 90% of patients treated with belantamab mafodotin, bortezomib and dexamethasone (BVd) and 67% of patients treated with daratumumab, bortezomib and dexamethasone (DVd). Serious adverse effects were reported in 50% of patients treated with BVd and 37% of patients treated with DVd. Ocular side effects, that affect the eyes and vision, were more frequent in patients treated with BVd than DVd (79%, 29%) and were described as manageable. 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 belantamab mafodotin 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."*** Additional clinical 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 most patients with such side effects (77%) had recovered since their first eye examination.[5] 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 belantamab mafodotin 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 it is made available to allow doctors the flexibility to prescribe this treatment to 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." ***"I hear people in hospitals on their cancer journeys saying, I have my last treatment next week, they tell me that should be it then, I can go back to my life. I'm really happy for them but there's a degree of envy. I wish there was a form of treatment that would just categorically end this cancer, and I could just rebuild the life that I had and go back to that. Unless new treatments are made available, I think that seems very unlikely."***

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.

[5] 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.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None.

Other issues

13. Are there any other issues that you would like the committee to consider?	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."***
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a clear need for innovative anti-myeloma treatments with novel mechanisms of action which will deliver deep, durable responses for relapsed and refractory myeloma patients. • There is currently no treatment with this mechanism of action licensed for routine commissioning at this point in the treatment pathway. If approved, belantamab mafodotin will be the first NHS-commissioned first B cell maturation antigen (BCMA) targeted treatment for myeloma. Therefore, it has much potential to overcome treatment resistance and fulfil an unmet need for multiply relapsed and refractory myeloma patients. • 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 in combination with bortezomib and dexamethasone can deliver benefits which are most important to patients: high response rates and good remission times. • Patients take the view that the frequently reported side effects on the eyes are manageable and do not negate the treatment's overall benefit.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Myeloma Society & Royal College Physicians
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? **Yes** or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	UK Myeloma Society is the only organisation that represents Physicians, Nursing staff, Pharmacists and Healthcare professional who are directly involved with providing clinical care or research for patients with myeloma. Membership is free by application and members of the executive are elected by the membership. It aims to improve the care of myeloma patients through the development and promotion of trials and provides education about myeloma to healthcare professionals.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	UKMS receives unrestricted educational grants from myeloma drug and diagnostic manufacturers to support the biannual educational programmes.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Myeloma is currently incurable. Most people diagnosed with myeloma will die as a result of complications of the disease. Symptoms and signs associated with active myeloma include bone pain, fractures secondary to bone deposits, fatigue, anaemia, recurrent infections, renal failure, high calcium levels and occasionally spinal cord compression. Treatment is primarily aimed at reducing these symptoms by controlling the disease. There is a direct association between how well the myeloma is controlled and the improvement in quality of life. Patients are clinically better if in complete response rather than partial response. Additional aims of treatment are to control the disease (and thereby symptoms) for as long as possible (i.e. lengthen the progression free survival / duration of response), lengthen life associated with the disease (i.e. increase overall survival) and prevent significant morbidity associated with progression of the disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	There are internationally agreed criteria for assessing response (International Myeloma Working Group Kumar et al Lancet Oncol 2016; 17: e328–46) These are based on the proportional reduction of serum paraprotein / serum free light chains (serological markers of myeloma), urine monoclonal protein and the bone marrow proportion of myeloma plasma cells. Generally, a Partial Response (PR) or better is considered clinically significant. Increasingly with more efficacious treatments the aim of the therapy is to achieve Complete Response (CR) or Very Good Partial Response (VGPR) for as many patients as possible. It is apparent in many studies that the greater the depth of response the longer the duration of the response (CR>VGPR>PR). Patients who achieve a CR have a longer survival than those who do not. Achieving minimal residual disease (MRD) is associated with an even longer duration of response and overall survival.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Myeloma is incurable with current therapy for the majority of patients. There is a clear unmet need to provide better treatments to induce a longer and more durable period of remission and limit, or prevent, myeloma associated complications.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There are a range of NICE Technology Appraisals that have been published. The options currently available include: • 2nd line include Carfilzomib Dex, Daratumumab Bortezomib Dex. Carfilzomib Lenalidomide Dex or Lenalidomide Dex can be used when the patient is not refractory to Lenalidomide. Selinexor Bortezomib Dex is available for patients who are refractory to Lenalidomide and Daratumumab • 3rd line include Panobinostat or Selinexor with Bortezomib Dex and Ixazomib Lenalidomide Dex (assuming the patient is not refractory to Lenalidomide). • 4th line includes Pomalidomide Dex, Daratumumab monotherapy, Isatuximab Pomalidomide Dex (CDF). • 4th line and beyond includes Pomalidomide Dex. • 5th line and beyond Selinexor for penta-refractory patients. There are ongoing NICE appraisals looking at new indications.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	No current guidelines. Clinical guidelines for relapsed myeloma management led by BCSH in development.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes the pathway of care is well defined, and treatment options are defined by reimbursed treatment options. There are a range of options (listed above). Treatment decisions will be based on response to prior therapies in the pathway.
9c. What impact would the technology have on the current pathway of care?	Belantamab mafodotin with bortezomib will provide a new treatment modality for myeloma patients. Belantamab provides a novel mechanism of action (BCMA targeted). Belantamab mafodotin bortezomib dex significantly improved progression free compared to standard of care (Daratumumab bortezomib) in the DREAMM7 trial. This translates into a clinically meaningful benefit for patients. The dataset shows early separation of curves for overall survival

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Belantamab mafodotin monotherapy is available on a compassionate for patients with Relapsed Refractory Myeloma (4th line and beyond). This has been widely used in the UK. Belantamab mafodotin would easily fit into the current treatment algorithm and would be easily delivered.
10a. How does healthcare resource use differ between the technology and current care?	Most treatments require patients to attend day units to receive either intravenous or subcutaneous injections. Belantamab is delivered as an intravenous infusion and would replace treatments that are already given on day units. Belantamab (iv infusion) would replace Daratumumab (sc injection) and given together with Bortezomib (sc injection). The treatment schedule would be different for each treatment (according to the DREAMM7 trial).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None regarding delivering Belantamab mafodotin. There would be need for specialist eye monitoring in hospital or in the community.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Belantamab bortezomib significantly improved progression free survival compared to standard of care (Daratumumab bortezomib) in the DREAMM7 trial (Mateos et al, ASCO 2024). This translates into a clinically meaningful benefit for patients.

11a. Do you expect the technology to increase length of life more than current care?	DREAMM7 trial (Mateos et al, ASCO 2024): Belantamab mafodotin bortezomib dex (BVD) demonstrated: • Statistically significant PFS benefit (HR, 0.41; P<.00001) with a median PFS that was 23 months longer than that with DVd (36.6 vs 13.4 months) • PFS benefit was consistent across subgroups. BVD was significantly better in patients with high risk genetic features • OS benefit favoured the BVd arm vs the DVd arm (HR, 0.57; P=.00049) • BVd was associated with deeper responses compared with DVd • Eye-related side effects, a known risk with Belantamab, were generally reversible and manageable with dose modifications.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. This is a well-tolerated regimen with a predictable and manageable side effect profile. There are no additional concerning adverse events reported. Occular side effects are known to occur with Belantamab. No difference was observed between arms over time in global QOL as measured by the EORTC QLQ C30 scale.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	Belantamab mafodotin monotherapy has been widely used in a compassionate use programme (patients with relapsed refractory myeloma). Healthcare professional will have some experience of administration and dealing with potential complications. There will be additional health resource needed to access specialist eye clinics.

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.)	Patients will need to spend time on day units to receive Belantamab.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Response is based on clinical assessment (blood tests/imaging) that are routinely used.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. Quality of life is likely to be improved due to reduced myeloma associated complications.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Belantamab mafodotin targets BCMA through a unique mechanism of action (antibody-drug conjugate). BCMA is novel myeloma target. There are no BCMA targeted treatment currently available (although there are other ongoing NICE TA).

16a. Is the technology a 'step-change' in the management of the condition?	Belantamab mafodotin involves a novel myeloma target (BCMA) using a unique mechanism of action (antibody-drug conjugate).
16b. Does the use of the technology address any particular unmet need of the patient population?	Myeloma remains an incurable cancer. Compared to standard of care at 1st relapse, Belantamab bortezomib dex improves progression free survival (see details of the DREAMM7 trial mentioned in 11a).
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Eye-related side effects, a known risk with Belantamab, are generally reversible, and manageable with dose modification. There was a low treatment discontinuation rate in the DREAMM7 trial.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The comparator arm of the DREAMM7 trial reflects the standard of care at 2nd line (Daratumumab bortezomib).
18a. If not, how could the results be extrapolated to the UK setting?	See above.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Depth of response. sCR, CR and MRD were measured in this trial. Survival has been assessed using PFS and OS. Toxicity and quality of life.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	sCR, CR and MRD were measured in this trial as surrogates for long term survival. There is a wealth of data to support depth of response correlating with long term survival.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No
21. How do data on real-world experience compare with the trial data?	No

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Belantamab bortezomib dex significantly improves outcomes (PFS) compared to standard of care at 2nd line (Daratumumab bortezomib) in the DREAMM7 trial • There is widespread use of Belantamab mafodotin monotherapy in the UK through the compassionate use programme • Novel target (BCMA) and mechanism of action (antibody drug conjugate) • Belantamab mafodotin ocular side effects are manageable, but will require access to specialist eye clinics • There is a low discontinuation rate of patients treated on the DREAMM7 indicating side effects are manageable

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Single Technology Appraisal

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Clinical expert statement

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 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.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **24 September 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating relapsed or refractory multiple myeloma 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	UKMS/ RCP/ RCPath/ BSH
3. Job title or position	Executive Member/ 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? ☒ A specialist in the clinical evidence base for relapsed or refractory multiple myeloma 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?	Relapsed refractory myeloma is challenging disease state to treat. Patients often have had worsening quality of life due to side effects of previous treatment,

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	morbidity of relapse and refractoriness to prior anti myeloma agents. Therefore the aim is to arrest disease progression, induce disease response, with deeper response to induce durable remission whilst maintaining quality of life for patients during therapy.
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)	ORR, VGPR rates and MRD negativity rates
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma?	Patients who are Lenalidomide refractory or intolerant in newly diagnosed setting have a significant unmet need in early relapse. In later relapses patients who are refractory to Daratumumab and Lenalidomide have a significant unmet need.
11. How is relapsed or refractory multiple myeloma 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?	In 1st relapse – DVD is treatment options for patients who enter second line therapy if they have been exposed to lenalidomide or unsuitable for Lenalidomide at second line. KD is available for all patients at second line. KRD is available for patients who are Lenalidomide naïve and had Bortezomib in newly diagnosed setting. In 2nd relapse RD is available for patients who are not lenalidomide and Bortezomib refractory. SVD is available as a treatment option for patients who are Lenalidomide refractory. Velcade dex Panobinstat is also an option although rarely used due to toxicity, and lack of data in patients treated with prior Daratumumab, lenalidomide and Carfilzomib therapies.
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?	Bortezomib and dexamethasone are part of routine care for myeloma patients. Belantamab mafodotin has been previously available on a compassionate use programme and in clinical trials. Patients attend day unit for therapy and have eye appointments prior to first 3 doses of Belantamab mafodotin. Treatment is given in day treatment units in secondary care setting

• 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)	Eye care specialist appointments in hospital or optometrist appointment in high street prior to first 3 doses
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?	Yes the data presented at ASH 2024 showed a significantly improved overall survival. https://ash.confex.com/ash/2024/webprogram/Paper200336.html BVD was compared with DVD which is predominant second line therapy used in England and superiority for both response and survival were noted
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
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)	Eye care specialist appointments prior to first three disease and adhoc if clinically indicated
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This treatment will not invoke any new starting or stopping rules established for relapsed myeloma.

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	QOL data was presented in ASH 2024 and no significant detrimental effects were noted in the BVD arm when compared to DVD (the 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?	Significant step change in targeting BCMA earlier in myeloma disease course. Belantamab mafodotin is the first licensed technology that targets BCMA using a novel immunotherapy approach using an antibody-drug conjugate.
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?	Eye related adverse events require monitoring and patients may require dose reduction and longer dose intervals
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?	Yes DREAMM-7 reflects current UK standard of care VGPR rates, MRD neg rates, PFS and OS Yes MRD negativity predicts long term outcomes in this trial

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA974]?	No
23. How do data on real-world experience compare with the trial data?	No real world experience has been reported
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	No equality issues noted

• 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.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

BVD is compared with current standard of care DVD and shows superiority for tested primary and secondary clinical outcomes

Belantamab mafodotin as monotherapy was used in a compassionate use scheme with a good take up across UK centres

This is an outpatient therapy applicable for all ages of myeloma patients

This is the first BCMA targeted therapy used earlier in disease course

Higher MRD negativity rates with longer OS in comparison with VD makes a compelling case for patients with RRMM

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Single Technology Appraisal

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

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 05 August 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

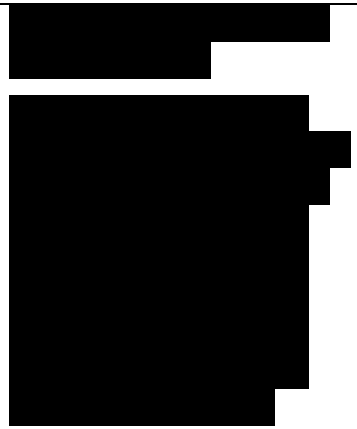
Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

CONTENTS

Issue 1 Correct description of the ID2701-like pricing assumption

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Section 1.2 Overview of key model outcomes. "*The company's cost-effectiveness analyses assume a* [redacted] *Under the currently approved PAS price for belamaf, BVd* [redacted] *in the EAG analyses and the company's fully corrected base-case analysis, for both subpopulations considered*."	"*The company's cost-effectiveness analyses assume a* [redacted] *. The EAG therefore based their analysis on a previous set of prices for belamaf, connected to ID2701. In this analysis BVd* [redacted] *in the EAG analyses and the company's fully corrected base-case analysis, for both subpopulations considered*."	[redacted]	The EAG sought clarification from NICE on which PAS discount to use. The price used by the EAG was at the request of NICE. The EAG have edited the sentence in the report to state, "[redacted] Under this price for belamaf, BVd…"

		[redacted]	
Page 14, Section 1.2 Overview of key model outcomes. "*The company's cost-effectiveness analyses assume a* [redacted] *Under the currently approved PAS price for belamaf, BVd* [redacted] *in the EAG analyses and the company's fully corrected base-case analysis, for both subpopulations considered*."	"*The company's cost-effectiveness analyses assume a* [redacted] *. The EAG therefore based their analysis on a previous set of prices for belamaf, connected to ID2701. In this analysis BVd* [redacted] *in the EAG analyses and the company's fully corrected base-case analysis, for both subpopulations considered*."	[redacted]	Same as above.

Issue 2 **Uncertainty about the extent to which reduced exposure to belantamab mafodotin (belamaf) in the DREAMM-7 trial is representative of NHS clinical practice**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, The clinical effectiveness evidence: summary of the EAG's key issues: On **page 18**, the following summary statement is made: *"Expert opinion or evidence of how belamaf is administered in NHS practice could help inform whether dose reductions in practice are substantially different from the DREAMM-7 trial, and whether expected effectiveness is reduced."*	The company would like to highlight that expert opinion and evidence of how belamaf is administered in NHS practice was provided in the company's responses to clarification questions: please see **page 53** (clarification question: *"B11b) Please comment on whether the dose reductions for belamaf in*	This amendment may help to partially resolve key issue 4 (uncertainty about the extent to which reduced exposure to belamaf in the DREAMM-7 trial is representative of NHS clinical practice).	Not a factual inaccuracy. However, the title of key issue 4 has been reworded for clarity: "Exposure to belantamab mafodotin (belamaf) in NHS clinical

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	DREAMM-7 are likely to be reflected in NHS clinical practice"). The company propose that the statement is modified to reflect the expert opinion and evidence the company provided in response to clarification questions.		practice may be lower than in the DREAMM-7 trial, with an unclear impact on effectiveness." In their response to clarification question B11b, the company presented real-world data from patients receiving belamaf monotherapy in 5L+. This information is not incorporated in the EAG report, as clinical advice to the EAG indicated that the balance of benefits and risks of treatment will be different for earlier versus later lines of therapy, and that

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			clinicians may treat more conservatively earlier on in the pathway. The EAG has added the following sentence to the last paragraph of section 3.2.5. “As part of the response to clarification (question B11b), the company presented additional clinical expert advice, which suggests clinicians would extend the dosing interval from every four weeks to eight weeks.”

Issue 3 Proposals for clarification (which are not factually inaccurate)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3 The decision problem: summary of the EAG's key issues. On **page 15**, the following summary statements are made: "*In the decision problem table the company states that the population of interest is patients "who have had one prior line of therapy", i.e. all 2L patients*." In the response to EAG clarification question A5, the company states that, "*The proposed population is eligible 2L patients for whom lenalidomide is unsuitable", but elsewhere in the clarification response document and in the CS, the company refers to 2L patients in general, without reference to whether these patients are lenalidomide unsuitable or not."* On **page 25**, the following statement is made: *"The EAG recommends that the company clarifies the proposed positioning of BVd, by stating explicitly whether it is to be offered for all 2L patients for whom it may be a suitable treatment, or whether it is to be restricted to lenalidomide-refractory patients only."*	The sentence should read: *"The proposed population is eligible 2L patients for whom lenalidomide is unsuitable."*	The company apologies if the positioning was not clear. While not strictly a factual inaccuracy, the company proposes the included amendment to make the report read as clearly as possible.	Not a factual inaccuracy. The company's terminology in the submission and response to clarification was unclear and this was the EAG's position at the time of writing the report. However, the statement on page 25 has been changed as follows. "The EAG recommends that the company confirms that the proposed position of BVd is eligible 2L patients for whom

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			lenalidomide is unsuitable.”
Page 102, section 4.2.9.7 Subsequent treatment costs, Paragraph 2; *“The EAG also notes that the exact values for the proportion of patients who received 3rd and 4th line subsequent treatments could not be reconciled with the values in the source referenced by the company.”*	The company suggests clarity is included on the calculations for the proportion of subsequent therapies; “The values for the proportion of patients receiving first and second subsequent treatments were calculated by the difference between proportion of patients in 2L from the publications (Raab et al. (1)) and Yong et al. (2)) versus subsequent lines (3L for first subsequent treatment and 4L for second subsequent treatment). For the Raab et al. paper (base-case assumption), the UK patients numbers were	It is factually inaccurate to state that the source referenced by the company cannot be reconciled with the values included. However, for the sake of making the report as clear as possible the company accepts it may have been helpful if they had included more details on how to reconcile these sources and values.	Amended to remove this critique point.

	used for patients on active treatment: • For first subsequent treatment: 64 patients are included at 2L and 52 patients are included at 3L. 52/64 is equal to 82%. • For second subsequent treatment: 64 patients are included at 2L and 22 patients are included at 4L. 22/64 is equal to 34%. For Yong et al. paper (included as a scenario analysis), attrition %'s across lines was used directly. • For first subsequent treatment: 61% reach 2L treatment, while 38% reach 3L. 38%/61% is equal to 62%. For second subsequent treatment: 15% reach 4L		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	therapy. 15%/61% is equal to 25%."		
Page 18, **Section 1.5** The cost-effectiveness evidence: summary of the EAG's key issues. "More mature OS evidence from the ongoing DREAMM-7 trial should reduce the uncertainty of the long-term predictions for the BVd OS."	The company propose the following amendment: "More mature OS evidence from the ongoing DREAMM-7 trial **expected in Q4 2024** should reduce the uncertainty of the long-term predictions for the BVd OS."	While the company accepts the EAG is not factually inaccurate in its analysis here, this amendment may help to resolve key issue 5 (uncertainty in the overall survival predictions for BVd due to immature data from DREAMM-7 and optimistic long-term survival extrapolations.	Not a factual inaccuracy. The company submission does not provide information on when additional mature OS evidence from the ongoing DREAMM-7 trial can be expected. This is new information since the writing of the report.

Issue 4 Factual inaccuracies and typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, The decision problem: summary of the EAG's key issues: On **page 16,** the following summary statement is made: *"Clinical advice to the EAG indicated that, at least in the next 3-5 years, a substantial proportion of 2L patients will be eligible to receive combination therapies containing lenalidomide."* This statement is factually inaccurate considering the corresponding clinical advice on **page 23**: *"The EAG's clinical advisors expect to continue seeing patients for whom lenalidomide is a suitable treatment option for the next three to five years, after which practically all 2L patients will have received lenalidomide previously and many will be refractory."* While this statement is clear that the EAG's clinical	The company propose the word *"substantial"* is removed from the summary statement on **page 16** and propose the following amendment: *"Clinical advice to the EAG indicated that, at least in the next 3-5 years, a proportion of 2L patients will be eligible to receive combination therapies containing lenalidomide."*	The word 'substantial' is highly likely to be misunderstood by readers as meaning 'a large number of patients'. This amendment ensures that the EAG's clinical advice on the proportion of 2L patients who are suitable to receive therapies containing lenalidomide in the next 3-5 years is not misrepresented.	Not a factual inaccuracy. Key issue reworded as follows, for clarity: "Clinical advice to the EAG indicated that, at least in the next 3-5 years, a substantial proportion of 2L patients **(about 30% of transplant eligible and 15% of transplant ineligible patients)** will be eligible to receive combination therapies containing lenalidomide."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
advisors expect to continue seeing patients for whom lenalidomide is a suitable treatment option for the next 3-5 years, it does not quantify the number of patients the clinical advisors will see. Therefore, the claim on **page 16** that a *"substantial proportion"* of 2L patients will be eligible to receive therapies containing lenalidomide is not accurate. Connected to this point, the company would like to highlight contradictory feedback from one of the EAG's clinical advisors which indicates that only 15% of transplant-ineligible and 30% of transplant-eligible patients are not refractory to lenalidomide and therefore these groups may currently be suitable for a lenalidomide based option at 2L (**page 24**, *"One of the EAG's clinical advisors estimates that 70% of transplant-eligible*			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients and 85% of transplant-ineligible patients in 2L are currently refractory to lenalidomide."). Note, transplant-ineligible patients represent the majority of patients in the front-line setting (ca. 66%) (3).			
Page 16, 'Key issue 2' table, Row 2; *"2L patients will be eligible to receive combination thearpies containing lenalidomide."*	The company propose the following amendment: "2L patients will be eligible to receive combination therapies containing lenalidomide."	Typographical error.	Amended.
Page 31, section 3.2.1 Critical appraisal DREAMM-7; *"Randomisation was conducted appropriately; the Clinical Study Report (CSR) reports* [redacted]	The company propose the following amendment: *"Randomisation was conducted appropriately; the Clinical Study Report (CSR) reports* [redacted]	Typographical error. The values stated in the EAG report are incorrect and not aligned to the Primary Analysis CSR.	Amended as follows. ".. reports [redacted] (CSR Table 10).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 33, Paragraph 2; ***"****The EAG notes that, in the DREAMM-7 trial population, 64.6% (166/257) of patients who had previously received lenalidomide were refractory, leaving 35.4% of lenalidomide-experienced patients"*	The company propose the following amendment: "The EAG notes that, in the DREAMM-7 trial population, 64.6% (166/257) of patients who had previously received lenalidomide were refractory, leaving 35.4% of lenalidomide-exposed patients"	Incorrect clinical terminology.	Amended.
Page 33, Paragraph 2; ***"****lenalidomide after receiving it i(CS Table 8, pp. 38-40)."*	The company propose the following amendment: "lenalidomide after receiving it (CS Table 8, pp. 38-40)."	Typographical error.	Amended.
Page 38, Final paragraph; *"Participants in the BVd arm who received lenalidomide previously were less likely to have progressed than those who had not received lenalidomide (35% versus 41%, respectively). Prior lenalidomide was associated with an improved PFS for BVd (HR 0.33, 95% CI 0.23; 0.48) versus*	The company propose the following amendment: "Participants in the BVd arm who received lenalidomide previously were less likely to have progressed than those who had not received lenalidomide (35% versus 41%, respectively). Prior lenalidomide was associated with an improved PFS for BVd versus DVd (HR 0.33, 95% CI 0.23; 0.48) compared to no prior	Reordering of values required for clarity.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
DVd (HR 0.57, 95% CI 0.39; 0.83) compared to no prior lenalidomide (p=0.022).”	lenalidomide (HR 0.57, 95% CI 0.39; 0.83) (p=0.022).”		
Page 48, section 3.4.1 Consistency and similarity of studies included in the company NMA; *“The studies included in the company’s network are consistent with those used in recent STAs conducted in MM, namely TA897[16] (daratumumab in combination with bortezomib) and TA974[37] (selinexor in combination with bortezomib and dexamethasone), with the exception that both these STAs exclude the LEPUS study.”*	The company propose the following amendment: *“The studies included in the company’s network are consistent with those used in recent STAs conducted in MM, namely TA897[16] (daratumumab in combination with bortezomib and dexamethasone) and TA974[37] (selinexor in combination with bortezomib and dexamethasone), with the exception that both these STAs exclude the LEPUS study.”*	Typographical error. Incomplete treatment combination stated for TA897 as dexamethasone has been omitted from the sentence.	Amended.
Page 54, section 3.5 Conclusions of the clinical effectiveness section; *“Data on OS are immature, though median overall survival was higher in the BVd arm*	The company propose the following amendment: *“A strong and clinically meaningful OS benefit favoured the BVd group vs. the DVd group (HR=0.57; 95% CI: 0.40, 0.80; p-value=0.00049). Median OS*	The statement should be corrected as the median OS was NR in either arm.	Corrected as follows. “Data on OS for BVd versus DVD are immature. Median OS was

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
(median 33.9, 95% CI 21.9; -) than in the DVd arm (median 15.2, 95% CI 12.3; 21.1).”	*was not reached in either treatment group.”*		not reached in either treatment group (HR=0.57, 95% CI 0.40; 0.80).”
Page 64, section 4.2.4.2 Points for critique; *“The company’s cost-effectiveness base-case analysis is considered reflective of the belamaf observed dose reductions in DREAMM-7 and allows exploring the impact on costs of applying the SmPC recommended dose for belamaf (see Section xxx).”*	The company propose the amendment includes the missing Section number.	Typographical error. The Section number is missing from the statement.	Amended.
Page 70, section 4.2.6.2 Points for critique, first paragraph; *“Further to the company’s interpretation of the PH assumption assessment, the EAG notes that, although there is crossing between the log*	The company propose the amendment is: “Further to the company’s interpretation of the PH assumption assessment, the EAG notes that, although there is crossing between the log cumulative hazard plots (see Figure 7), this occurs mostly in the	Typographical error. The cross-reference Figure number is incorrect in the statement.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
cumulative hazard plots (see Figure 2), this occurs mostly in the initial time points, with the lines looking parallel for the majority of the follow-up"	initial time points, with the lines looking parallel for the majority of the follow-up"		
Page 71, section 4.2.6.3 Overall survival, second paragraph; *"As highlighted in Section 3.4.4, the observed OS from the DREAMM-7 trial is immature, with median survival not yet observed over the trial follow-up (maximum [redacted] months), and the BVd arm data being less mature (22% events) than the DVd arm (35% events)"*	The company propose the amendment is: "As highlighted in Section 3.2.6, the observed OS from the DREAMM-7 trial is immature, with median survival not yet observed over the trial follow-up (maximum [redacted] months), and the BVd arm data being less mature (22% events) than the DVd arm (35% events)"	Typographical error. The cross-reference Section number is incorrect in the statement.	Amended.
Page 78, First paragraph; *"The median PFS:OS ratios estimated by the company using a regression framework suggested that one month increase in median PFS is*	The company propose the amendment is: "The median PFS:OS ratios estimated by the company using a regression framework suggested that one month increase in median PFS is associated	Typographical error and additional context around 95% CI.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
associated with [redacted] [redacted] increase in median OS"	with 1.8 months (95% CI; [redacted] [redacted] increase in median OS"		
Section 4.2.6.4, Page 84-85, third and fifth paragraphs; *"TTD data was not available for the non-trial comparators. The HRs for hKd and SVd derived from the company's PFS NMA were used as proxies and applied to the extrapolated DVd TTD curve to extrapolate TDD for hKd and SVd. In a scenario analysis, the company applies the assumption that TTD is equal to PFS for all treatments under comparison."* *"The EAG shows in Figure 19 the company's base-case TTD extrapolated curves for each treatment comparison alongside the respective PFS and OS curves. For all treatments except BVd, the TTD curve is almost overlaps the corresponding PFS curve,*	The company propose deletion of these paragraphs.	Duplication of text from previous paragraphs.	Amended, duplication of text removed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
which suggests that individuals will spend little time in the PF-off treatment health state before transitioning to PD. In contrast, the BVd TTD curve is considerably lower than the corresponding PFS curve, so individuals who are initially treated with BVd spend a considerable proportion of their time on PFS in the PF-off-treatment health state. Table 22 shows the QALY's accrued in the model in the PF health states."			
Page 88, Section 4.2.7 Adverse Events; *"The AEs included in the model have associated cost and HRQoL decrements, which are reported in Sections 4.2.9.6and 0respectively."*	The company propose the following amendment: *"The AEs included in the model have associated cost and HRQoL decrements, which are reported in Sections 4.2.9.6 and 4.2.8.3 respectively."*	Typographical error. The cross-reference section numbers are incorrect in the statement.	Amended.
Page 88, Section 4.2.7 Points for critique, first paragraph;	The company propose the amendment is:	Typographical error. The cross-reference to the Table number	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"However, in the company's model the probability of experiencing a keratopathy event is just [redacted], blurred vision [redacted], and dry eyes [redacted], all of which were applied only in the first model cycle (Appendix F, table 9)"	"However, in the company's model the probability of experiencing a keratopathy event is just [redacted], blurred vision [redacted], and dry eyes [redacted], all of which were applied only in the first model cycle (Table 63 of the CS)"	in the CS is incorrect in the statement.	
Page 96, Section 4.2.9.2 Summary of company's submission, second paragraph; "Table 69 in the CS provides more detailed information"	The company propose the amendment is: "Table 68 in the CS provides more detailed information"	Typographical error. The cross-reference to the Table number in the CS is incorrect in the statement.	Amended.
Page 97, Section 4.2.9.4 Drug acquisition and administration costs "These prices were discounted in the model according to the company's proposed PAS [redacted] discount resulting in unit costs of [redacted] and [redacted] respectively."	The company propose the amendment for the company's proposed PAS is corrected: "These prices were discounted in the model according to the company's proposed PAS [redacted] discount resulting in unit costs of [redacted] and [redacted] respectively."	Typographical error. The company's proposed PAS was not completely accurate.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 98, First paragraph; [redacted]	The company propose the amendment is: [redacted]	Correction to align to the text from the company within the clarification questions.	Amended.
Page 98, Section 4.2.9.4 Drug acquisition and administration costs; "*Administration costs in the base case areapplied for belamaf based on the proportion of patients on treatment who receive a belamaf dose*."	The company propose the following amendment which includes a space between 'are' and 'applied': "*Administration costs in the base case are applied for belamaf based on the proportion of patients on treatment who receive a belamaf dose*."	Typographical error.	Amended.
Page 99, section 4.2.9.5 Health state costs; *"The resource use, unit costs and overall health state costs are summarized in table 60 if the CS."*	The company propose the following amendment to replace 'if' with 'of' in the following sentence: *"The resource use, unit costs and overall health state costs are summarized in table 60 of the CS."*	Typographical error.	Amended.
Page 100, section 4.2.9.6 Adverse event costs, first paragraph;	The company propose the amendment is:	Typographical error. The cross-reference to the Table number	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The incidence of grade ≥3 events (Table 41 and Table 63 of CS) for BVd and DVd are sourced from DREAMM-7, while the incidence for hKd and SVd were identified in the clinical SLR"	"The incidence of grade ≥3 events (Table 41 and Table 61 of CS) for BVd and DVd are sourced from DREAMM-7, while the incidence for hKd and SVd were identified in the clinical SLR"	in the CS is incorrect in the statement.	
Page 100, section 4.2.9.6 Adverse event costs, first paragraph; *"Only the BVd arm incurred the costs of keratopathy, blurred vision, and dry eyes (Table 64 of CS)"*	The company propose the amendment is: "Only the BVd arm incurred the costs of keratopathy, blurred vision, and dry eyes (Table 63 of CS)"	Typographical error. The cross-reference to the Table number in the CS is incorrect in the statement.	Amended.
Page 101, section 4.2.9.7 Subsequent treatment costs; *"The company noted as a limitation that SVd was not NICE approved at the time of the expert elicitation, and so subsequent SVd in 3L and 4L is not included."*	The company propose the following amendment: *"The company noted as a limitation that SVd was not NICE approved at the time of the expert elicitation, and so subsequent SVd in 3L is not included."*	Typographical error. SVd is not recommended in 4L.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 102, section 4.2.9.8 Points of critique; *"The source referenced by the company[78] reports average end of life costs of £12,727 per decedent (£13,314 per decedent for cancer diagnosis) for hospital and social care. The exact figure could not be reconciled with the original source; however, the EAG expects this to have minimal impact on the cost-effectiveness results."*	The company would like to clarify that the correct source and year for this reference is: Update reference 78 to: *Jones K, et al. Unit Costs of Health and Social Care 2022*. Kent: Personal Social Services Research Unit, University of Kent, UK; 2023 (Available from: https://kar.kent.ac.uk/100519/).	The reference from which end of life costs were sourced for this submission was the reference provided in the proposed amendment: *Jones K, et al. Unit Costs of Health and Social Care 2022*. Kent: Personal Social Services Research Unit, University of Kent, UK; 2023 (Available from: https://kar.kent.ac.uk/100519/) (4)	Amended.
Page 103, Third paragraph; *"1. Correction of an error in the estimation of the costs of ocular AEs for belantamab;* *2. Exclusion of SVd as a comparator for the DVd eligible subpopulation."*	Inclusion of additional model amendments impacting cost-effectiveness outcomes; "1. Correction of an error in the estimation of the costs of ocular AEs for belantamab; 2. Exclusion of SVd as a comparator for the DVd eligible subpopulation. 3. Implementation of estimates of the median absolute median PFS:OS ratio	Clarification of the amendments to the revised economic model with implications for the cost-effectiveness.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	for the treatments under comparison using WLS regression and fixed and random effect meta-regression”		

Issue 5 Confidential markings

EAG response: all confidential marking was changed as requested.

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th></tr>
<tr><td>Section 3.2.6.1 OS, PFS, DOR, and ORR. Page 37</td><td>The results for ORR should be marked confidential</td><td>The ORR was [redacted] higher in the BVd arm than the DVd arm ([redacted]</td></tr>
<tr><td>Section 3.4.4. NMA Results. Page 51, Table 17 Results of Fixed Effect NMAs for comparators of interest</td><td>There are values in Table 17 which are currently not marked as confidential information which is inaccurate. All values in Table 17 should be marked as confidential.</td><td>
<table>
<tr><th></th><th></th><th colspan="4">HR/OR[a] (95% CrI)</th></tr>
<tr><th>Outcome</th><th>Population</th><th>BVd vs. DVd</th><th>BVd vs. hKd</th><th>BVd vs. SVd</th><th>BVd vs. Vd</th></tr>
<tr><td rowspan="4">PFS</td><td>ITT[b]</td><td rowspan="2">[redacted]</td><td rowspan="2">[redacted]</td><td rowspan="2">[redacted]</td><td rowspan="2">[redacted]</td></tr>
<tr><td>Lenalidomide-exposed[c]</td></tr>
<tr><td>Lenalidomide-refractory[b]</td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>1 Prior LOT[b]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>OS</td><td>ITT[d]</td><td rowspan="3">[redacted]</td><td rowspan="3">[redacted]</td><td rowspan="3">[redacted]</td><td rowspan="3">[redacted]</td></tr>
<tr><td rowspan="2">ORR</td><td>ITT[b]</td></tr>
<tr><td>Lenalidomide-exposed[c]</td></tr>
</table>
</td></tr>
</table>

Location of incorrect marking	Description of incorrect marking	Amended marking
		Lenalidomide-refractory[b] [redacted] [redacted] [redacted] [redacted]
Section 3.4.4.1 PFS results. Page 52.	"In the ITT population, belamaf was superior to all three comparators of interest, DVd (Hazard Ratio, HR: 0.41; 95% Credible Interval, CrI: 0.31 to 0.53), hKd (HR: 0.24; 95% CrI: 0.17 to 0.35), and SVd (HR: 0.13; 95 CrI: 0.09 to 0.18) (Table 17)."	"In the ITT population, belamaf was superior to all three comparators of interest, DVd [redacted], hKd [redacted], and SVd [redacted] (Table 17)."
Section 3.4.4.2 OS results. Page 52.	"Only one NMA was conducted for OS, in the ITT population. A benefit in OS was observed in belamaf compared to DVd (HR: 0.57; 95 CrI: 0.41 to 0.80), hKd (HR: 0.55; 95% CrI:0.36 to 0.88), and SVd (HR: 0.50; 95% CrI: 0.29 to 0.87) (Table 17)."	"Only one NMA was conducted for OS, in the ITT population. A benefit in OS was observed in belamaf compared to DVd [redacted], hKd [redacted], and SVd [redacted] (Table 17)."

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th></tr>
<tr><td>Page 95, Section 4.2.8.3 Adverse event utilities Points for critique.</td><td>“The CS states that for the first occurrence of grade ≥2 keratopathy visual acuity events, median time to onset was 58.0 days, and median duration was 106.0 days (page 89 of CS). The equivalent figures are not reported for grade 3+.”</td><td>“The CS states that for the first occurrence of grade ≥2 keratopathy visual acuity events, median time to onset was [redacted], and median duration was [redacted] (page 89 of CS). The equivalent figures are not reported for grade 3+.”</td></tr>
<tr><td>Page 95, Section 4.2.8.3 Adverse event utilities Points for critique.</td><td>“The DREAMM-7 clinical study report lists keratopathy events of grade 1 and 2 as occurring in 3% and 7% of BVd patients respectively, where grade 3+ occur in 74%”</td><td>“The DREAMM-7 clinical study report lists keratopathy events of grade 1 and 2 as occurring in [redacted] and [redacted] of BVd patients respectively, where grade 3+ occur in [redacted]%”</td></tr>
<tr><td>Page 143, Table 51 Results for all NMAs conducted for progression-free survival (PFS)</td><td>All values the ITT population were not marked up as confidential information and all values in the table should be marked as confidential.</td><td>
<table>
<tr><th rowspan="2">BVd vs.HR (95% CrI)</th><th colspan="3">ITT Population</th><th colspan="2">1 Prior Line of Therapy</th><th colspan="2">Lenalidomide-Refractory</th><th>Lenalidomide-Exposed</th></tr>
<tr><th>CS Results[a]</th><th>Company Update[b]</th><th>EAG Update[c]</th><th>CS Results[a]</th><th>EAG Update[c]</th><th>CS Results[a]</th><th>EAG Update[c]</th><th>CS Results[d]</th></tr>
<tr><td>CyKd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>CyVd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>DVd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>EVd</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>hkDd</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>IhKd</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Kd</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr><td>Page 145, Table 53 Results for all NMAs conducted for overall response rate (ORR)</td><td>All values the ITT population were not marked up as confidential information and all values in the table should be marked as confidential.</td><td>
<table>
<tr><th rowspan="2">BVd vs. OR (95% CrI)</th><th colspan="3">ITT Population</th><th colspan="2">Lenalidomide-Refractory</th><th>Lenalidomide-Exposed</th></tr>
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<tr><td>PanoVd</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>PVd</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr><td>Vd</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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References

1. Raab MS, Fink L, Schoen P, Gonzalez-McQuire S, Flinois A, Cavo M, et al. Evolution of multiple myeloma treatment practices in Europe from 2014 to 2016. British Journal of Haematology. 2019;185(5):981-4.
2. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. British journal of haematology. 2016;175(2):252-64.

3. Myeloma UK. New life-extending treatment knocked back by NICE. 2023 [Available from: https://www.myeloma.org.uk/news/new-life-extending-treatment-knocked-back-by-nice/ [Accessed: August 2024].
4. Jones K, et al. Unit Costs of Health and Social Care 2022 Manual. 2023.

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External Assessment Group Report
Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Produced by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Authors Eleonora Uphoff, Research Fellow, CRD, University of York
Rojé Layne, Research Fellow, CHE, University of York
Naomi Kate Gibbs, Research Fellow, CHE, University of York
Sumayya Anwer, Research Fellow, CRD, University of York
Hollie Melton, Research Fellow, CRD, University of York
Helen Fulbright, Information Specialist/Research Fellow, CRD, University of York
Christopher Parrish, Associate Professor of Haematology, Leeds Institute of Clinical Trials Research, University of Leeds and Honorary Consultant Haematologist, Leeds Teaching Hospitals NHS Trust
Mark Corbett, Research Fellow, CRD, University of York
Claire Rothery, Professor of Health Economics, CHE, University of York
Sofia Dias, Professor of Health Technology Assessment, CRD, University

of York
Ana Duarte, Research Fellow, CHE,
University of York

Correspondence to Ana Duarte, University of York,
ana.duarte@york.ac.uk

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Contributions of authors
Eleonora Uphoff performed the critical review of the clinical effectiveness evidence and contributed to the writing of the clinical effectiveness section. Rojé Layne performed the critical review of the economic analyses, validated the economic model, conducted the EAG additional analyses and contributed to drafting Sections 4 and 6 of the report. Naomi Kate Gibbs performed the critical review of the economic analyses, validated the EAG additional analyses and contributed to drafting Sections

4, 5 and 7 of the report. Sumayya Anwer critiqued the indirect treatment comparisons and contributed to the writing of the clinical effectiveness section. Hollie Melton contributed to the writing of the background and clinical effectiveness section of the report. Helen Fulbright reviewed the company's search strategies and provided editorial support. Christopher Parrish shared his clinical expertise, which the EAG used to inform the background, clinical effectiveness, and cost effectiveness section of the report. Dr Parrish shared his feedback on the draft report. Mark Corbett advised on the critical review of the clinical effectiveness evidence. Claire Rothery performed the critical review of the economic analyses, contributed to drafting Section 4 of the report, co-led the economic analyses, reviewed the report as a whole, and takes joint responsibility for the report as a whole. Sofia Dias provided advice, commented on drafts of the report, reviewed the whole report, and takes joint responsibility for the report as a whole. Ana Duarte performed the critical review of the economic analyses evidence, contributed to drafting sections 1, 4, 6 and 7 of the report, co-led the economic analyses, reviewed the report as a whole, and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CON) data have been [redacted].

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List of abbreviations

Abbreviation	Definition
1L, 2L, etc	First line, second line…
1L+, 2L+, etc	First line and further lines, second line and further lines
AE	Adverse event
BCMA	B-cell maturation antigen
BVd	belantamab mafodotin with bortezomib and dexamethasone
CI	Confidence interval
CS	Company Submission (Document B)
CyKd	Cyclophosphamide with carfilzomib and dexamethasone
CyVd	Cyclophosphamide with bortezomib and dexamethasone
DOR	Duration of response
DVd	Daratumumab with bortezomib and dexamethasone
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ-5D	Standardised instrument for use as a measure of health outcome
EVd	Elotuzumab with bortezomib and dexamethasone
hKd	High dose carfilzomib and dexamethasone
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IKd	Isatuximab with carfilzomib and daratumumab
IMWG	International Myeloma Working Group
IRC	Independent review committee
ITC	Indirect treatment comparison
K	Carfilzomib
Kd	Carfilzomib and dexamethasone
KDd	Carfilzomib with daratumumab and dexamethasone
KM	Kaplan-Meier
MRD	Minimal residual disease
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PICOS	Population, intervention, comparator, outcomes, study design
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSS	Personal social services
PVd	Pomalidomide with bortezomib and dexamethasone
PanoVd	Panobinostat with bortezomib and dexamethasone
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RoB	Risk of bias
RR	Relative risk
RRMM	Relapsed or refractory multiple myeloma
SCT	Stem cell transplant

SLR	Systematic literature review
SmPC	Summary of product characteristics
SVd	Selinexor with bortezomib and dexamethasone
TA	Technology Appraisal
TTD	Time to treatment discontinuation
Vd	Bortezomib and dexamethasone
WHO	World Health Organisation

Glossary

Abbreviation	**Active substance**	**Commercial name**
B	Belamaf (belantamab mafodotin)	Blenrep
V	Bortezomib	Velcade
K/hK	Carfilzomib	Kyprolis
D	Daratumumab	Darzalex
d	Dexamethasone	Neofordex, Glensoludex, Martapan
Isa	Isatuximab	Sarclisa
Ixa	Ixazomib	Ninlaro
R	Lenalidomide	Revlimid
Pano	Panobinostat	Farydak
P	Pomalidomide	Imnovid
S	Selinexor	Nexpovio
T	Thalidomide	Thalomid
BVd	belamaf + bortezomib + dexamethasone	
Kd	carfilzomib + dexamethasone	
KRd	carfilzomib + lenalidomide + dexamethasone	
DVd	daratumumab + bortezomib + dexamethasone	
DVTd	daratumumab + bortezomib + thalidomide + dexamethasone	
DRd	daratumumab + lenalidomide + dexamethasone	
IsaPd	isatuximab + pomalidomide + dexamethasone	
IxaRd	ixazomib + lenalidomide + dexamethasone	
Rd	lenalidomide + dexamethasone	
PanoVd	panobinostat + bortezomib + dexamethasone	
PVd	pomalidomide + bortezomib + dexamethasone	
SVd	selinexor + bortezomib + dexamethasone	

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID6212	Summary of issue	Report sections
1	Inconsistent descriptions of the population of interest.	2.3; 4.2.3
2	Proposed position of belantamab mafodotin with bortezomib and dexamethasone (BVd) in the treatment pathway.	2.2.3; 2.3; 4.2.3
3	Lack of evidence for the proposed population of second line (2L)-only in adults for whom lenalidomide is unsuitable.	3.2.6; 3.3; 3.4; 4.2.3
4	Exposure to belantamab mafodotin (belamaf) in NHS clinical practice may be lower than in the DREAMM-7 trial, with an unclear impact on effectiveness.	3.2.5; 3.2.7
5	Uncertainty in the overall survival predictions for BVd due to immature data from DREAMM-7 and optimistic long-term survival extrapolations.	3.4.4; 4.2.6.3
6	Uncertainty in the progression-free and progressive disease health state utility values.	4.2.8.2; 4.2.9.7

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Prefered distribution for the extrapolation of overall survival (OS) for BVd - an independent Weibull distribution was preferred by the company while the EAG preferred an independent exponential distribution for BVd.
- Source of network meta-analysis (NMA) results for progression-free survival (PFS) and OS in the economic model - the company applied the results of their original NMAs (initially included in the company's submission (CS), while the EAG preferred their corresponding updated results using the code provided by the company.

- Source of the progressed disease utility decrement – the company used data from the DREAMM-7, while the EAG estimated progressed disease utility by assuming a utility decrement from Hatswell et al., 2019.[1]
- Distribution of subsequent treatment received after disease progression – the company applied a different subsequent treatment distribution for patients in the DVd treatment compared to other treatments under comparison, while the EAG assumed the same subsequent treatment distribution for all treatments.

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.

The company's cost-effectiveness analysis encompasses two subpopulations, which differ only by their relevant comparators: (i) DVd eligible subpopulation (comparison with DVd and carfilzomib and dexamethasone [hKd]); and (ii) DVd ineligible subpopulation (comparison with selinexor with bortezomib and dexamethasone [SVd] and hKd).

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who are alive and progression-free over time, which is associated with improved HRQoL relative to the comparators due to a higher utility value for progression-free compared to the utility for progressive disease.
- Conferring a higher utility value for patients who are progression-free on the technology compared to patients who are progression-free on the comparator.

Overall, the technology is modelled to affect costs by:

- Increasing the time on treatment compared to the comparators and the proportion of the cohort who remain progression-free for longer, with associated drug acquisition costs (except for those progression-free and off-treatment).
- Decreasing the proportion with progressive disease and associated costs of subsequent therapies upon progression.
- Incurring the costs of monitoring for and managing ocular adverse events.

The company's cost-effectiveness analyses assume a [redacted]

[redacted] Under this price for belamaf, BVd [redacted] in the EAG analyses and the company's fully corrected base-case analysis, for both subpopulations considered. The [redacted] in the company's fully corrected base-case (on which the EAG scenarios were built) is the driver of cost-effectiveness

The modelling assumptions that have the greatest effect on the technology's total QALYs are:

- Prefered distribution for the extrapolation of OS for BVd.

The modelling assumptions that have the greatest effect on the technology's total costs are:

- Prefered distribution for the extrapolation of OS for BVd.
- Approach taken to inform frequency of admnistration of belantamab mafodotin (belamaf) (based on individual participant data vs. recommendations of the belamaf summary of product characteristics).

1.3 The decision problem: summary of the EAG's key issues

Key issue 1 Inconsistent descriptions of the population of interest.

Report section	2.2.3; 2.3; 4.2.3
Description of issue and why the EAG has identified it as important	Descriptions of the population of interest are inconsistent across the decision problem table and other information (CS, clarification response) submitted by the company. In the decision problem table the company states that the population of interest is patients "who have had one prior line of therapy", i.e. all 2L patients. In the response to EAG clarification question A5, the company states that, "The proposed population is eligible 2L patients for whom lenalidomide is unsuitable", but elsewhere in the clarification response document and in the CS, the company refers to 2L patients in general, without reference to whether these patients are lenalidomide unsuitable or not. If the population of interest is all 2L patients, as indicated in the decision problem table, then lenalidomide-based 2L treatments approved for use on the NHS are also relevant comparators.
What alternative approach has the EAG suggested?	The EAG recommends that the company clarifies the proposed positioning of BVd in the treatment pathway, by stating explicitly whether BVd is to be offered to all 2L patients for whom it may be a suitable treatment option, or whether r it is to be restricted to lenalidomide-unsuitable patients only.
What is the expected effect on the cost-effectiveness estimates?	Unclear. Additional comparators should be considered in the company's cost-effectiveness analyses if the population includes adults for whom lenalidomide is suitable.

	Clinical advice to the EAG is that the 2L population will change significantly over the coming years due to changes in first line therapies.
What additional evidence or analyses might help to resolve this key issue?	The company should provide an explicit, clear, definition of the proposed population of interest.

Key issue 2 Proposed position of BVd in the treatment pathway.

Report section	2.2.3; 2.3; 4.2.3
Description of issue and why the EAG has identified it as important	The decision problem addressed in the CS to evaluate the cost-effectiveness of BVd relative to its comparators is restricted to a 2L-only population and adults for whom lenalidomide is unsuitable. Therefore, the cost-effectiveness of BVd is only evaluated against treatments recommended by NICE and available in the NHS at 2L, and excludes lenalidomide or combination therapies that include lenalidomide, while [redacted]. Clinical advice to the EAG indicates that, at least in the next 3-5 years, a substantial proportion of 2L patients (about 30% of transplant eligible and 15% of transplant ineligible patients) will be eligible to receive combination therapies containing lenalidomide. Clinical advice further suggests clinicians would prefer for BVd to also be available in 3L. Therefore, it remains unclear to the EAG why the company has not presented separate subgroup cost-effectiveness analyses for BVd at 3L-only and 3L+, [redacted]
What alternative approach has the EAG suggested?	In clarification question A15, the EAG requested analyses stratified by line of treatment (2L, 3L, and 3L+). The company explained that "NMA results for 3L only and 3L+ are not provided due to the company's positioning BVd in 2L."
What is the expected effect on the cost-effectiveness estimates?	Unknown. The cost-effectiveness of BVd is not formally assessed at 2L in those suitable for lenalidomide as all relevant comparators are not considered. Furthermore, no evidence has been presented in the 3L-only or 3L+ subpopulations from DREAMM-7 and the relevant comparators at 3L and 3L+, as listed in the NICE scope for this appraisal, have not been considered in the cost-effectiveness evaluation of BVd.

What additional evidence or analyses might help to resolve this key issue?	A clear statement on the company's proposed position of BVd in the treatment pathway is required. If BVd is to be available at 2L in adults for whom lenalidomide is a suitable treatment option or adults at 3L or 3L+, an updated economic evaluation including all relevant comparators would be required.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Key issue 3 Lack of evidence for the proposed population of 2L-only in adults for whom lenalidomide is unsuitable.

Report section	3.2.6; 3.3; 3.4; 4.2.3
Description of issue and why the EAG has identified it as important	The company have not provided clinical evidence for BVd and its relevant comparators for the subpopulation of 2L-only in adults refractory to lenalidomide. The overall ITT population (2L+) from DREAMM-7, i.e., not restricted to the 2L-only subgroup of participants and not restricted to lenalidomide refractory or exposed subpopulations, is used to inform the treatment effectiveness for BVd and DVd in the company's base case analysis. Subgroup analyses for 2L patients and for lenalidomide-refractory patients were supplied in response to EAG clarifications, but no data on the proposed subgroup of 2L lenalidomide-unsuitable patients was provided due to its small sample size.
What alternative approach has the EAG suggested?	In the absence of 2L-only data in patients for whom lenalidomide is unsuitable, the EAG acknowledges the company's reasons for using the overall ITT population (2L+) from DREAMM-7 to inform the cost-effectiveness of BVd relative to DVd in the company's proposed population. However, this must be recognised as a limitation of the evidence.
What is the expected effect on the cost-effectiveness estimates?	Unknown due to sparse clinical evidence on the subgroup of interest for the treatments under comparison.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence for the population of interest of 2L-only in adults refractory to lenalidomide.

Key issue 4 Exposure to belantamab mafodotin (belamaf) in NHS clinical practice may be lower than in the DREAMM-7 trial, with an unclear impact on effectiveness.

Report section	3.2.5; 3.2.7; 4.2.9.4
Description of issue and why the EAG has identified it as important	In the DREAMM-7 trial patient exposure to belamaf was reduced because adverse events led to dose reductions and delays. Clinical advice to the EAG indicates that dosing may be reduced further in clinical practice, in an effort to reduce the quantity and severity of ocular side effects. Clinical and cost-effectiveness analyses reflect dose reductions as implemented in DREAMM-7, but do not take into account further reductions in dosing anticipated in NHS practice. The company and EAG explored the impact of delays and dose reductions on the drug and acquisition costs of BVd compared to receiving belamaf in accordance with the recommendations of the SmPC. Costs

	increased substantially when the frequency of belamaf administration was set in accordance with the SmPC; longer delays and further reductions are expected to lower costs. The corresponding impact on effectiveness is unknown.
What alternative approach has the EAG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	Unclear how real-world cost-effectiveness of BVd would be affected by cautious dosing in NHS practice.
What additional evidence or analyses might help to resolve this key issue?	Expert opinion or evidence of how belamaf is administered in NHS practice could help inform whether dose reductions in practice are substantially different from the DREAMM-7 trial, and whether expected effectiveness is reduced.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Key issue 5 Uncertainty in the OS predictions for BVd due to immature data from DREAMM-7 and optimistic long-term survival extrapolations

Report section	3.4.4; 4.2.6.3
Description of issue and why the EAG has identified it as important	The overall survival evidence provided by DREAMM-7 is highly uncertain, particularly for the BVd treatment arm, due to immaturity of the trial data and highly optimistic long-term survival predictions for BVd, which is likely to favour the cost-effectiveness of BVd vs. the relevant comparators. There is also uncertainty on whether the proportional hazards (PH) assumption holds for the comparison with BVd, as formal diagnostic tests did not fully allow rejecting this assumption. Importantly, the company's preferred base-case approach for BVd OS implies a time decreasing Hazaed Ratio (HR) for BVd vs. DVd (i.e., an increasing treatment effect over time) that is not supported by the empirical evidence from the DREAMM-7 trial and results in optimistic long-term OS predictions for BVd according to [redacted] EAG's clinical advisors.
What alternative approach has the EAG suggested?	The EAG considered in scenario analyses alternative modelling assumptions for the BVd OS: namely (i) BVd OS extrapolation of DREAMM-7 data with independently fitted exponential distribution; (ii) PH Weibull extrapolation of DREAMM-7 data applying the empirical OS HR for BVd vs. DVd to the DVd baseline curve; and (iii) assuming a surrogacy relationship on absolute median PFS:OS: BVd OS. All three alternative modelling approaches result in more conservative long-term OS predictions for BVd, which are more closely aligned with clinical opinion.
What is the expected effect on the cost-effectiveness estimates?	In the EAG scenario analyses, the total QALYs for BVd range from [redacted] (assuming a surrogacy relation in the absolute median PFS:OS for BVd) and [redacted] QALYs (BVd OS extrapolation using the PH Weibull distribution) compared to the company's fully corrected base-case [redacted] QALYs. [redacted]

What additional evidence or analyses might help to resolve this key issue?	More mature OS evidence from the ongoing DREAMM-7 trial should reduce the uncertainty of the long-term predictions for the BVd OS.

Key issue 6 Uncertainty in the progression-free and progressive disease health state utility values.

Report section	4.2.8.2
Description of issue and why the EAG has identified it as important	The company have modelled a higher utility value for progressive disease than progression-free survival for the comparator treatments (DVd, SVd and hKd), which is not clinically justified and external evidence (e.g., Hatswell et al, 2019)[1] shows that there is a decrement in utility for PD at each subsequent line of treatment for RRMM. Furthermore, the assumption that BVd is associated with higher utility in the PF health state than SVd and hKd is not supported by empirical evidence presented by the company.
What alternative approach has the EAG suggested?	The EAG explored in scenario analysis the use of external evidence from Hatswell et al, 2019 to estimate an alternative value for the utility decrement between the PF and PD health state for all treatments under comparison. Another scenario assumed the same PF health state utility applies to BVd, SVd and hKd.
What is the expected effect on the cost-effectiveness estimates?	Only the scenario analysis in which the PD health state utility was informed by external evidence had material impact on the total QALYs estimates. [redacted]
What additional evidence or analyses might help to resolve this key issue?	Clinical opinion on the appropriateness of the health state utility estimates and assumptions, may provide additional information and clarify whether further analyses are required.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's fully corrected base-case – assuming the unit cost of bortezomib 3.5mg and the currently approved cPAS price for belamaf.	[redacted]	[redacted]	[redacted]
OS modelling approach for BVd – Independent parametric exponential extrapolation (Issue 5)	[redacted]	[redacted]	[redacted]
Updated EAG NMA results for PFS	[redacted]	[redacted]	[redacted]
Updated EAG NMA results for OS	[redacted]	[redacted]	[redacted]
PD utility decrement from Hatswell et al., 2019[1] (Issue 6)	[redacted]	[redacted]	[redacted]
Same distribution of subsequent treatments	[redacted]	[redacted]	[redacted]
EAG's preferred base case (deterministic and probabilistic)	[redacted]	[redacted]	[redacted]

Modelling errors identified and corrected by the EAG are described in 6.1.1.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Sections 6.1.1, 6.2 and 6.3 of the main report.

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report the EAG has reviewed the company submission (CS) from GlaxoSmithKline (GSK) to NICE on the clinical effectiveness and cost-effectiveness of belantamab mafodotin with bortezomib and dexamethasone (BVd) within its marketing authorisation for treating relapsed or refractory multiple myeloma after one or more treatments.

Belantamab mafodotin, trade name Blenrep®, is abbreviated as belamaf in the company submission and in this report. Belamaf received marketing authorisation in Great Britain in January 2021. Belamaf monotherapy was previously indicated for patients with relapsed or refractory multiple myeloma after four or more previous treatments. In December 2023, the European Medicines Agency (EMA) recommended the marketing authorisation be withdrawn for this indication because evidence from the DREAMM-3 trial did not show substantial benefit in Progression Free Survival (PFS) of belamaf plus pomalidomide and dexamethasone compared to pomalidomide and dexamethasone alone.[2] The FDA had previously revoked the license for belamaf in the US in March 2023.[3]

Bortezomib (trade name Velcade®) is approved for use in the NHS for different indications and at different lines of treatment of multiple myeloma, both as monotherapy (second line, relapsed or refractory multiple myeloma) and in combination with other treatments in first (also as part of induction therapy), second, and third line.

In this section the EAG critiques the company's proposed positioning of BVd in the treatment pathway and its definition of the decision problem, compared with the NICE scope.

2.2 Background

2.2.1 Description of multiple myeloma

Multiple myeloma is a type of cancer in which abnormal plasma cells are produced in the bone marrow. This leads to the accumulation of dysfunctional antibodies at the expense of antibodies that contribute to the immune response in case of infection. A typical clinical course of the disease, as described in the CS and confirmed by the EAG's clinical experts, is one in which periods of treatment and remission are interrupted by relapses, which over time become more frequent and more challenging to treat. The company highlight the build-up of resistance to therapies as an important challenge in the treatment of multiple myeloma. In section 2.2.3, we describe how this issue of

refractory patients changes over time with the introduction of new treatment regimes, and how this may impact on treatment with BVd in clinical practice in the UK.

Section B1.3.1.2 of the CS provides an overview of the epidemiology of multiple myeloma. The estimated 5,951 new cases of multiple myeloma a year refers to the UK average for data collected in 2016 to 2018. The CS highlights that multiple myeloma is commonly, though not exclusively, diagnosed later in life. In 2017, 5% of newly diagnosed cases in England were in people under the age of fifty, 22.3% is 50-64 year olds, 29.6% in 65-74 year olds, and 42.8% in people aged 75 and over.[4]

The company estimate that 3,360 multiple myeloma patients diagnosed each year in the UK are eligible to receive second line (2L) treatment. However, the proportion of patients who would be eligible to receive BVd is smaller (see section 2.2.3).

People living with multiple myeloma experience a range of symptoms, most commonly those relating to "CRAB": hypercalcaemia, renal insufficiency, anaemia, and bone lesions (CS section B1.3.1.3). Patients with relapsed or refractory myeloma are also likely to suffer side effects and complications relating to treatments. The description of the clinical burden of multiple myeloma in the CS is in line with the submission by Myeloma UK. The patient organisation describes the impact of symptoms such as pain and tiredness on quality of life, as well as the mental health impact of living with an incurable disease, relapses, and changes to treatment, for both patients and carers.

2.2.2 Description of belantamab mafodotin with bortezomib and dexamethasone (BVd)

Table 2 of the CS (p. 10) describes the working mechanism of belamaf, a monoclonal antibody entering malignant plasma cells by binding with B-cell maturation antigen (BCMA) on the cell surface. Apart from the cytotoxic effect on the invaded cancerous plasma cells, belamaf stimulates the immune response to malignant cells by recruiting and activation effector cells.

Bortezomib is a proteasome inhibitor. By blocking the function of proteasomes in myeloma cells, an accumulation of surplus proteins within the cell disrupts normal processes, halts growth, and leads to cell death.[5]

Dexamethasone is a synthetic adrenocortical steroid. Apart from being cytotoxic for myeloma cells, it enhances the cytotoxic effects of other anti-myeloma drugs such as bortezomib, selinexor, and carfilzomib. Dexamethasone also reduces inflammation, which can lower pain caused by myeloma bone disease.

There are numerous common side effects of these drugs. All three are associated with an increased susceptibility to infections. Common side effects of dexamethasone include weight gain, insomnia, mood changes, and indigestion.[6, 7] Both belamaf and bortezomib can cause anaemia and related

symptoms, diarrhoea, fever, fatigue, nausea and vomiting.[8, 9] Tingling in hands and feet are common side effects of bortezomib, and the EAG's clinical advisor explained that re-treatment with bortezomib after relapse in an earlier line should be avoided if alternatives are available. Eye problems are a very common side effect specific to treatment with belamaf; both of the EAG's clinical advisors [redacted] highlight that eye problems are a frequent cause of changes to the frequency and dose of treatment as well as being a reason for discontinuation of treatment.[10]

2.2.3 Position of BVd in the clinical pathway

In section B1.3.2.1 (pp.18-20) of the CS, the company explain the proposed positioning of BVd in a complex clinical pathway (CS Figure 3, p. 19). The pathway has changed in the last five years with the introduction of lenalidomide and daratumumab in 1L and later lines (1L+). However, it is common for patients to become refractory to these therapies, which means viable options are increasingly exhausted as patients progress through the pathway.

This company proposes BVd for 2L patients, for whom lenalidomide is unsuitable, either because patients are refractory to lenalidomide or because it is contraindicated. Although the company argues that very few or no patients in 2L would be eligible to receive lenalidomide, advice from two clinical experts to the EAG presented a more nuanced picture.

The EAG's clinical advisors explained that lenalidomide is routinely given to both stem cell transplant (SCT) eligible and SCT non-eligible patients in first line (1L) treatment of multiple myeloma. However, lenalidomide has only been approved for use in the NHS in 1L for transplant ineligible patients from 2019 and for post-transplant maintenance in 2021.[11] The EAG understands that clinicians are still seeing patients who have relapsed on older 1L treatments, and who have not yet been exposed to lenalidomide. These patients may have received different treatments, which would have included bortezomib for most (correspondence with EAG's clinical advisors). The EAG's clinical advisors expect to continue seeing patients for whom lenalidomide is a suitable treatment option for the next three to five years, after which practically all 2L patients will have received lenalidomide previously and many will be refractory.

The NCRAS study presented in the CS, a retrospective assessment of patient data from the English National Cancer Registration and Analysis Service (NCRAS), illustrates that multiple myeloma patients exposed to lenalidomide and moving on to 2L treatment are not necessarily lenalidomide-refractory.[12] The study authors created a cohort of 10,720 patients with relapsed or refractory myeloma who received treatment between 2013 and 2020 and were similar to the DREAMM-7 study participants. From this "DREAMM-7 like cohort", a second cohort was selected of patients who had

been exposed to lenalidomide when they reached 2L treatment ([redacted]). Out of the lenalidomide-exposed patients, [redacted] were lenalidomide-refractory.

A further nuance added by the EAG's clinical advisors concerns the group of patients eligible for transplant. For newly diagnosed SCT-eligible patients the standard of care is lenalidomide maintenance therapy with a lower dose of lenalidomide (TA680[13]) as indicated in the proposed treatment pathway (Figure 3 of the CS, p. 19). This lower dose of lenalidomide may lead to patients becoming less responsive to lenalidomide over time and developing some resistance. Currently, all patients relapsing on lenalidomide maintenance are ineligible for retreatment as they are considered refractory to lenalidomide. Clinical opinion differs as to whether this is a correct assessment, however, they are less likely to be refractory than patients who received a full treatment dose of lenalidomide in 1L and subsequently relapsed. One of the EAG's clinical advisors estimates that 70% of transplant-eligible patients and 85% of transplant-ineligible patients in 2L are currently refractory to lenalidomide.

Clinical advice to the EAG further indicates that few patients are contraindicated to receive lenalidomide; side effects such as allergic reactions which would not allow further treatment with lenalidomide are a rare occurrence and in some cases could be rechallenged.

In conclusion, it is inaccurate to equate 2L with a lenalidomide-refractory status. Particularly in the next three to five years, 2L patients for whom lenalidomide is unsuitable is a subgroup of all 2L patients with relapsed or refractory multiple myeloma.

2.2.3.1 Restriction of belamaf to 2L only

In the CS, the company propose BVd for 2L only, because of the 'acute burden of unmet need in this population' and because their clinical case is thought to be strongest in 2L and this positioning would therefore lead to the most cost-effective use of NHS resources (CS pp. 18-19). [redacted]

This however does not support restriction of the population to 2L lenalidomide refractory patients.

Descriptions regarding the proposed population are inconsistent across the decision problem (2L patients), elsewhere in the CS, and in the clarification response (referring to '2L patients for whom lenalidomide is unsuitable'). The EAG considers 2L to be an appropriate position for BVd, though both clinical advisors to the EAG expressed a preference for BVd to also be available at third line (3L), for two reasons. Firstly, treatment options in 3L are extremely limited, particularly for patients who are refractory to lenalidomide and those for whom bortezomib is no longer suitable due to neuropathy.[14] [redacted][10] Secondly,

common side effects of BVd such as those related to ocular toxicity are likely to impact on patients' quality of life and may be difficult to tolerate particularly for older or less fit patients. Clinical advice to the EAG indicated clinicians may therefore wish to hold back BVd until a later line of treatment in favour of a gentler treatment if this option was available to them.

Prior appraisals of technologies with broader marketing authorisation have also restricted the population to 2L or 3L only: including TA657,[15] TA897,[16] TA695,[17] and TA586.[18] TA657 committee documents considered expanding the positioning presented by the company but committee consideration for broader use at 2L/3L was limited by lack of evidence.

2.3 Critique of company's definition of decision problem

Table 3 compares the company's definition of the decision problem to the NICE final scope.

The population in the decision problem does not match the population in the final scope issued by NICE. Descriptions regarding the proposed population are currently inconsistent across the decision problem (2L patients), elsewhere in the CS, and in the clarification response (referring to '2L patients for whom lenalidomide is unsuitable'). The EAG recommends that the company confirms that the proposed positioning of BVd is eligible 2L patients for whom lenalidomide is unsuitable.

Clinical advice to the EAG indicates that lenalidomide-based treatments are still an option for some patients in 2L, particularly over the next three to five years. If the proposed population is the one stated in the decision problem, namely '2L patients', then lenalidomide-based comparators are relevant but have not been included in the company's model. Lenalidomide plus dexamethasone was recommended by NICE in 2019 for patients with multiple myeloma who have received one previous treatment which included bortezomib,[18] and carfilzomib plus lenalidomide and dexamethasone was recommended by NICE in 2021 for the same patient population.[17] These would be relevant comparators for the general 2L population.

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	People with relapsed or refractory multiple myeloma who have had at least one prior line of therapy.	Adults (> 18 years) with relapsed or refractory multiple myeloma who have had one prior line of therapy (2L patients).	• High level of unmet need in 2L. • RCT evidence available for 2L builds the strongest clinical case.	• There is inconsistency in the proposed population across the submission; unclear whether BVd is proposed for full 2L population or only those usnuitable for lenalidomide based therapies. • Clinical advisors indicated BVd being available in 3L offers a chance to hold it back in favour of a 2L treatment with more tolerable side effects.
Intervention	Belantamab mafodotin ('belamaf', Blenrep®) in combination with bortezomib and dexamethasone.	As per scope.	N/A	As per scope.
Comparator(s)	NICE approved treatments for relapsed or refractory multiple myeloma. 2L • Bortezomib monotherapy • Lenalidomide plus dexamethasone • Carfilzomib plus lenalidomide and dexamethasone • Carfilzomib plus dexamethasone • Daratumumab plus bortezomib and dexamethasone • Selinexor plus bortezomib and low-dose dexamethasone (also 3L) 3L • Lenalidomide plus dexamethasone (also 4L) • Panobinostat plus bortezomib and dexamethasone (also 4L+)	2L • Carfilzomib plus dexamethasone • Daratumumab plus bortezomib and dexamethasone • Selinexor plus bortezomib and low-dose dexamethasone (if refractory to daratumumab and lenalidomide)	• Only 2L considered by company. • Bortezomib monotherapy not used in practice. • Lenalidomide-based therapies not suitable for almost all 2L patients as they will be lenalidomide refractory.	• The EAG agrees, informed by clinical advice, that bortezomib monotherapy is not a relevant comparator. • Clinical advice to the EAG indicated that lenalidomide-based therapies may still be used for a group of patients not refractory to lenalidomide at 2L. This group will reduce over the next 3-5 years. • If the population is not restricted to lenalidomide-unsuitable patients then carfilzomib plus lenalidomide and dexamethasone, and lenalidomide with dexamethasone are relevant comparators.

	• Ixazomib plus lenalidomide and dexamethasone (also 4L) 4L • Pomalidomide plus dexamethasone (also 5L+) • Daratumumab monotherapy 5L • Selinexor plus dexamethasone			
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope	N/A	As per scope.
Economic analysis	As per NICE reference case.			As per scope, except for the comparators and population, as noted above.
Subgroups	Not specified in NICE scope.			
Special considerations including issues related to equity or equality	Not specified in NICE scope.			

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence of the efficacy and safety of treatments for relapsed or refractory myeloma in clinical trials of adults with at least one prior line of treatment. Evidence identified in the SLR informs the indirect treatment comparisons.

Searches

The original company submission included searches to identify clinical evidence for adult patients with relapsed or refractory multiple myeloma. A description of the searches and some of the search strategies were included in Appendix D (pp. 7-21). In response to the EAG's points for clarification, the company provided additional information and corrections to errors.

Table 4 presents a summary of the EAG's assessment of the search strategy. The full assessment is available in Appendix A1 Clinical effectiveness searches.

Table 4 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	The documentation contained several errors and was also unclear in numerous respects. The company only partially corrected errors in the documentation and PRISMA flowcharts as part of their clarification response.
Were appropriate sources searched?	YES	A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases were searched.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study type.
Were appropriate search terms used?	PARTLY	Sensitivity could have been increased as follows. 1. Using additional terms for 'relapsed' and 'previously treated'. 2. Using different fields rather than only the title field for WHO ICTRP.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed. Studies were limited to English language.
Were any search filters used, validated and referenced?	YES	The Scottish Intercollegiate Guidelines Network (SIGN) randomised controlled trials filter was used and referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Study selection

Eligibility criteria for the SLR were in line with the company's decision problem, to include randomised clinical trials (RCTs) of the treatment of adults with relapsed or refractory multiple myeloma. The EAG considers the inclusion and exclusion criteria to be appropriate. No full-text papers were retrieved for non-English publications (N=2 initially, N=1 in updated PRISMA flowchart clarification response).

The final number of included studies, based on the literature review and two update searches, is not clearly reported. Quality assessment was conducted for 38 included studies; the CS mentions that 48 studies were considered in the network meta-analysis (NMA) feasibility assessment out of 70 trials (CS p. 67). DREAMM-7 is included in the NMA but not an included study in the SLR. Records of trials of belamaf, including the DREAMM-7 trial, were excluded from the SLR with reason 'no outcomes of interest'. References of these records were not shared with the EAG.

Critique of data extraction

The EAG considers the data extraction of the SLR to be adequate.

Quality assessment

Table 43 in Appendix D of the CS shows that the company used the Cochrane RoB2 tool to assess risk of bias in 38 included comparators studies. However, it appears risk of bias for all domains was assessed at study-level. This makes it difficult to interpret domains three to five (missing outcome data, outcome measurement, selection bias), for which results can vary by outcome and which should therefore be assessed separately for each outcome. It is not clear which outcomes were included in the risk of bias assessments.

The critical appraisal of the DREAMM-7 trial is reported in the CS (Table 11, p. 49) using the headings suggested in NICE process and methods guidance PMG24 rather than a published risk of bias tool. See section 3.2 for the EAG's critique of the DREAMM-7 trial.

Evidence synthesis

Results were reported for outcomes of interest of the DREAMM-7 trial, and twelve studies of lenalidomide-refractory and non-refractory patients were combined in a network meta-analysis (NMA) (see section 3.3). Studies in the NMA included the comparators listed below.

- bortezomib and dexamethasone (Vd)
- carfilzomib (K)
- carfilzomib and dexamethasone (hKd; referred to as hKd in the CS to distinguish this treatment from low-dose carfilzomib; KD)
- carfilzomib with daratumumab and dexamethasone (KDd)

- cyclophosphamide with carfilzomib and dexamethasone (CyKd)
- cyclophosphamide with bortezomib and dexamethasone (CyVd)
- daratumumab with bortezomib and dexamethasone (DVd)
- elotuzumab with bortezomib and dexamethasone (EVd)
- isatuximab with carfilzomib and daratumumab (IKd)
- pomalidomide with bortezomib and dexamethasone (PVd)
- panobinostat with bortezomib and dexamethasone (PanoVd)
- Selinexor with bortezomib and dexamethasone (SVd)

Not all included studies are relevant to this appraisal – see Section 3.3 for further details.

3.2 Critique of the DREAMM-7 trial

Data on the efficacy and safety of BVd were derived from the DREAMM-7 study; a multi-centre, open-label RCT conducted in twenty countries, comparing BVd to DVd in participants with relapsed/ refractory multiple myeloma.

3.2.1 Critical appraisal DREAMM-7

Table 5 compares the company and EAG's critical appraisal of the DREAMM-7 trial.

Table 5 A comparison of critical appraisal of the DREAMM-7 trial by the company and EAG.

Question	Company's assessment[a]	EAG's assessment
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Probably yes; [redacted][b]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Mostly yes, except for extramedullary disease.
Were the care providers, patients and outcome assessors blind to treatment allocation?	No	No
Were there any unexpected imbalances in drop-out between groups?	No	Probably yes, though the impact of this is unknown and likely to be small.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

[a] Abbreviated response; see CS Table 11, p. 49-50 for justification.
[b] Additional details obtained from company's response to clarification question A10.

Randomisation was conducted appropriately; the Clinical Study Report (CSR) reports [redacted][19]

The company considered participant characteristics to be well-balanced across study arms. The EAG agrees, except for 'extramedullary disease', which was present in 5% of the BVd arm (N=13) and 10% of the DVd arm (N=25). Extramedullary disease is associated with a poorer prognosis of multiple myeloma and was identified as a potential treatment effect modifier in the NMA (CS p. 70).

The company judged that there were no unexpected imbalances in dropouts. Details on withdrawal from the study are given in the CSR and summarised in Table 6. [redacted]

Table 6 Study withdrawals and reasons for withdrawal

	BVd study arm (N=243)	DVd study arm (N=251)
Total no. of participants withdrawn from study	[redacted]	[redacted]
Reasons for study withdrawal		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3.2.2 Selection criteria

Detailed selection criteria for trial participants are documented in the CSR and summarised in Table 5 of the CS (p. 31-32). Adults (18 or over) with relapsed or refractory multiple myeloma were eligible for inclusion. Previous treatment in first line could include autologous SCT, including the induction and maintenance phases, as long as the transplant took place more than 100 prior to study enrolment.

Only 50% of the trial sample was allowed to comprise participants with two or more prior lines of treatment.

3.2.3 Participant flow diagram

The company have shared the participant flow diagram in the CSR. Out of [redacted] patients screened, [redacted] did not meet selection criteria.

[redacted]

[redacted]

Table 7 Discontinuation of treatment due to physician decision in DREAMM-7.

Reason for discontinuation[a]	BVd study arm (N=243)	DVd study arm (N=251)
[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]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[a] More than one reason for discontinuation per patient may be provided.

3.2.4 Participant characteristics

As is commonly the case in trials, the population of the DREAMM-7 trial is not fully representative of the population of patients with relapsed or refractory multiple myeloma who would be eligible to receive BVd in NHS clinical practice. Half of the study sample had received one line of therapy prior to taking part in the trial (51% BVd, 50% DVd), with the other half having received more than one line of therapy (and therefore not eligible to receive BVd according to the company's proposed positioning at 2L).

3.2.4.1 Prior- and follow-up treatments

Participants were recruited from countries across the globe, and [redacted] of participants were from the UK (CSR).[19] Participants from other countries and healthcare systems are likely to have received healthcare and treatments prior to trial participants and afterwards which are not reflective of the NHS standard of care.

Treatment for the first participant started in May 2020, not long after the approval of lenalidomide in first line on the NHS. In the study sample, 52% of participants had previously received lenalidomide. It can be expected that, in years to come, an increasing proportion of multiple myeloma patients in 2L

will have received lenalidomide. Similarly, since daratumumab is now NHS approved for use in first line for both transplant eligible and transplant-ineligible patients the proportion of participants who had previously received daratumumab (1.4%, CS Table 8, p. 39) is not only low compared to current NHS clinical practice, but daratumumab prior exposure is likely to become near universal over the coming few years.

The EAG notes that, in the DREAMM-7 trial population, 64.6% (166/257) of patients who had previously received lenalidomide were refractory, leaving 35.4% of lenalidomide-exposed patients who were still responsive to lenalidomide after receiving it (CS Table 8, pp. 38-40).

3.2.4.2 Baseline characteristics

Clinical advice to the EAG is that the DREAMM-7 trial population was younger and fitter than the population of patients with relapsed or refractory multiple myeloma in NHS clinical practice. Only 13.6% of patients were aged 75 or over, with a median age of 65 in the BVd study arm and 64 in the DVd study arm. In the DREAMM-7 like cohort from the NCRAS study, the mean age was [redacted] years old.[12] Apart from potential differences in treatment efficacy, BVd may be a less suitable treatment option for older patients. Given the toxicity profile of BVd, one of the EAG's clinical advisors indicated that clinicians may prefer a gentler treatment in 2L for older patients. Older patients may not tolerate side effects as well; the clinical advisor explained that ocular side effects in particular can have a serious, detrimental impact on the mobility, independence, and therefore quality of life of older patients. Older patients may also experience more, or more severe, side effects. Problematic side effects are likely to lead to dose reductions, a lower frequency and treatment dose, and treatment interruptions and discontinuation, all of which can reduce the effectiveness of BVd in practice.

Nearly all DREAMM-7 participants had an ECOG performance status of 0 or 1 (96%), compared to [redacted] in the DREAMM-7 like cohort from the NCRAS study.[12] As with younger patients, patients who are fitter are more likely to tolerate the treatment and are more likely to be found suitable to receive it by their clinician.

If older or less fit patients are less likely to receive BVd in practice, the DREAMM-7 trial population may be considered representative of the multiple myeloma patients likely to receive BVd in the NHS. However, outcomes may be poorer and costs higher if the treatment is given to older or frailer patients.

3.2.5 Exposure to treatment

The planned dose of belamaf was 2.5 mg/kg every three-week cycle. In the safety population [redacted], the mean dose received in the treatment group was [redacted] mg/kg/cycle, corresponding to a

relative dose intensity of [redacted]. For the comparator daratumumab, the relative dose intensity was [redacted] for the first three cycles and [redacted] (Table 8).

[redacted] The CSR describes additional calculated data of dose delays [redacted]. In the calculated data presented in the CSR, counts of dose delays were added to the observed data if there was a higher-than-expected number of days between first doses of each cycle, and if there was a difference between date of the last dose and the date of 'end of study' (SAP p. 7189).[19] The calculated dose delays showed [redacted] between belamaf and daratumumab in the proportion of patients with a dose delay [redacted] the differences in total number of dose delays [redacted] and length of delay [redacted].

Dose interruptions, meaning an unfinished or interrupted infusion of medication, were [redacted] (Table 8). For daratumumab [redacted] of dose interruptions were due to adverse events and for [redacted] of interruptions no reason was provided. In a previous appraisal of daratumumab (TA897), the EAG's clinical advisors pointed out that administering daratumumab subcutaneously, rather than intravenously as in the DREAMM-7 trial, would be associated with fewer adverse events at the time of infusion and a similar efficacy. The daratumumab Summary of Product Characteristics (SmPC) now recommends subcutaneous administration, and the EAG's clinical advisors confirmed that daratumumab would be administered subcutaneously in practice.[20] Dose interruptions due to infusion reactions in the daratumumab arm of the DREAMM-7 trial may therefore be higher than what can be expected in practice.

Dose reductions of belamaf [redacted] of patients having a dose reduction for each of the first day cycle visits. Dose reductions for daratumumab are not reported; the SmPC does not recommend dose reductions of daratumumab.[20]

Table 8 Dose modifications of belamaf and daratumumab

	Belamaf [redacted]	**Daratumumab** [redacted]
Relative mean dose intensity	[redacted]	[redacted]
Dose delays		
Total number of dose delays	[redacted]	[redacted]
Participants with any dose delay	[redacted]	[redacted]
Median duration of dose delay in days	[redacted]	[redacted]
Dose delays > 3 weeks	[redacted]	[redacted]
Dose delays > 6 weeks	[redacted]	[redacted]
Dose interruptions		

Total number of dose interruptions	[redacted]	[redacted]
Participants with any dose interruption	[redacted]	[redacted]
Dose reductions		
Total number of dose reductions	[redacted]	
Participants with any dose reduction	[redacted]	
Participants with two or more dose reductions	[redacted]	
Dose modifications due to adverse events		
Number of dose modifications due to adverse event	[redacted]	[redacted]
Study treatment withdrawn due to adverse event	75 (31%)	46 (19%)
Number of dose modifications due to ocular adverse event	[redacted]	[redacted]
Number of dose reductions due to non-ocular adverse event	[redacted]	[redacted]

[a] Relative dose intensity in cycles 1-3.

Sources: CSR Table 17 (pp. 77-78), Table 21 (p. 80), Table 26 (p. 85), Table 44 (p. 111).

Dose modifications due to adverse events were common in both study arms (Table 8), though it was more frequently a reason for treatment withdrawal in the BVd study arm (31% vs 19% of participants) (CS Table 22, p. 84). Dose modifications due to eye problems were almost exclusively found in the BVd arm, [redacted]

The EAG's clinical advisors [redacted] (CS Appendix M) indicated that clinicians are likely to be cautious with dosing to reduce side effects and would consider starting treatment on a lower dose. As part of the response to clarification (question B11b), the company presented additional clinical expert advice, which suggests clinicians would extend the dosing interval from every four weeks to eight weeks. Dose intensity for belamaf in the DREAMM-7 trial, though lower than the planned dose, is likely to be an overestimation compared to clinical practice. It is unclear whether this could lead to a reduced efficacy of BVd in practice, particularly for those patients who experience most, or the most severe, side effects.

3.2.6 Efficacy of BVd compared to DVd

Results of the direct comparison of BVd and DVd in the DREAMM-7 trial are presented in section B2.6 (main results) and B2.7 (subgroup analyses) of the CS (pp. 50-66) and include data on the outcomes listed below for the intention-to-treat (ITT) population (N=494). Outcomes are described in more detail in Table 6 (pp. 35-36) of the CS.

- Overall survival (OS). Endpoint not met for median OS.

- Progression-free survival (PFS). Endpoint met for median PFS. Measured by an Independent Review Committee (IRC) and determined following criteria of the International Myeloma Working Group (IMWG) or death.
- Duration of response (DOR).
- Minimal residual disease (MRD).
- Overall response rate (ORR).
- Time to treatment discontinuation (TTD).
- Health-related quality of life (HRQoL).

The data-cut for analysis was 2 October 2023, approximately three years and four months after dosing the first patient. The median study follow-up at the data-cut was 28.2 months. At the data cut-off, [redacted] participants in the BVd vs. [redacted] participants in the DVd group were on study treatment (CSR, p. 12).[19] The final analysis of OS is planned [redacted].

All main analyses were conducted for the full sample of participants with one or more prior lines of therapy, including lenalidomide-exposed, not exposed, and lenalidomide-refractory patients.

3.2.6.1 OS, PFS, DOR, and ORR

A summary of clinical efficacy results for outcomes included in the NICE scope is shown in Table 9. The CS also reports on Minimal Residual Disease (MRD) and time-to-treatment-discontinuation (TTD).

Table 9 Summary of clinical efficacy results DREAMM-7

Outcome	BVd (N=243)	DVd (N=251)
OS		
Participants with an event (death)	54 (22%)	87 (35%)
1st quartile (median endpoint not reached)	[redacted]	[redacted]
OS rate at 6 months	[redacted]	[redacted]
OS rate at 12 months	[redacted]	[redacted]
OS rate at 18 months	[redacted]	[redacted]
HR	0.57 (0.40; 0.80), p<0.001	
PFS		
Participants with an event (progressed or dead)	91 (37%)	158 (63%)
Median	[redacted]	[redacted]
PFS rate at 6 months	[redacted]	[redacted]
PFS rate at 12 months	[redacted]	[redacted]
PFS rate at 18 months	[redacted]	[redacted]
HR	0.41 (0.31; 0.53), p<0.001	
DOR		
Participants with an event[a]	68 (34%)	105 (59%)

Event: disease progression *Event: death* Median	[redacted] 35.6 (30.5; -)	[redacted] 17.8 (13.8; 23.6)
ORR Participants with an event (any response) sCR CR VGPR PR	 201 (82.7%) 34 (14.0%) 50 (20.6%) 76 (31.3%) 41 (16.9%)	 179 (71.3%) 13 (5.2%) 30 (12.0%) 73 (29.1%) 63 (25.1%)
Difference in ORR	[redacted]	

[a] Progression or death after a partial response or better.
CR=complete response; sCR=stringent complete response; DOR=duration of response; HR=hazard ratio; ORR=overall response rate; OS = overall survival; PFS=progression-free survival; PR=partial response; TTD=time to treatment discontinuation; VGPR=very good partial response.

Outcome data on OS, PFS, DOR, and ORR show a greater efficacy of BVd compared to DVd (Table 9). Overall survival data is immature; follow-up was ongoing for [redacted] of participants in the BVd arm and [redacted] of participants in the DVd arm. At the data cut-off, OS was greater in the BVd than the DVd study arm (HR 0.57, 95% CI 0.40; 0.80). Participants in the BVd arm also had longer PFS at six months, 12 months, and 18 months, with a median of 36.6 months [redacted] in the BVd arm and 13.4 months (95% CI 11.1; 17.5) in the DVd arm (HR 0.41, 95% CI 0.31; 0.53). The ORR was [redacted] higher in the BVd arm than the DVd arm (95% CI 2.6%; 20.1%). As shown in Table 9, this difference is due to higher rates of sCR and CR in the BVd arm (34.6% vs 17.2%). Of those who had at least a partial response (BVd = 201, DVd = 179), follow-up was still going for [redacted] of the sample, respectively. Participants in the BVd arm had a longer duration of response (DOR) (median 35.6 BVd, 17.8 DVd).

3.2.6.2 Quality of life

In the CS, the company presented two figures (Figure 9 and 10, pp. 61-62) of quality-of-life scores, measured every six weeks using the European Quality of life-5 dimensions 3 levels (EQ-5D-3L). Additional data were supplied as part of the clarification response, though these data do not seem to match the CS figures exactly (Question A7). The mean score measured at the last follow-up ([redacted]) was identical in both arms ([redacted]) and there was no difference in either group in mean change from baseline ([redacted]). The EAG's clinical advisor noted that quality of life is likely to be affected by adverse events of BVd and thought it possible that quality of life would therefore be negatively affected during treatment for a proportion of patients. [redacted]

3.2.6.3 A priori subgroup analyses

The following subgroup analyses were planned and/or performed for PFS prior to the start of this technology appraisal.

1. Subgroup analyses pre-specified in DREAMM-7 protocol, with results reported.[21]

- number of prior lines of therapy (stratification factor)
- prior bortezomib (stratification factor)
- R-ISS staging (stratification factor)
- age (< 65, ≥ 65)
- gender

2. Subgroup analyses pre-specified in DREAMM-7 protocol; results not reported.[21]

- ethnicity
- race
- region

3. Subgroup analyses not in protocol but described in latest version of SAP; results reported.[19]

- prior lenalidomide
- lenalidomide refractory (yes, no)
- time to relapse after 1L
- cytogenetic risk
- extramedullary disease

The subgroups specified for PFS were planned to be conducted for OS, potentially at a later timepoint, when the availability of data would allow it. The company supplied interaction test results for all subgroups shown in Figure 11 (CS, p.63) as part of the clarification response (clarification question A8). The categories for the planned 'age' subgroup analysis were changed from <65 and ≥ 65 to <65, 65 to ≤ 75, and ≥ 75.

Participants in the BVd arm who received lenalidomide previously were less likely to have progressed than those who had not received lenalidomide (35% versus 41%, respectively). Prior lenalidomide was associated with an improved PFS for BVd versus DVd (HR 0.33, 95% CI 0.23; 0.48) compared to no prior lenalidomide (HR 0.57, 95% CI 0.39; 0.83)[redacted] There was no statistically significant difference for PFS in efficacy of BVd for those refractory (HR 0.37, 95% CI 0.24; 0.56) and not refractory to lenalidomide (HR 0.48, 95% CI 0.34; 0.67) ([redacted]). Median PFS in the lenalidomide-refractory subgroup was [redacted]) with BVd versus [redacted]) with DVd.

The company draw on the NCRAS study data to argue outcomes in current practice are poorer for 2L patients who are refractory to lenalidomide. Median OS was [redacted] in the overall DREAMM-7 like cohort, compared to [redacted] months for lenalidomide-exposed patients [redacted] and [redacted] for lenalidomide-refractory patients.[12] However, patients in the NCRAS DREAMM-7 like cohort who were lenalidomide-refractory were also [redacted].

Age was not associated with PFS of BVd compared to DVd in the subgroup analyses, though the point estimates showed a trend towards reduced efficacy of BVd in older age. Patients of 65 and older, who make up the majority of NHS patients particularly in second line, were underrepresented. The category of 75 and over, who made up [redacted] of the NCRAS DREAMM-7 study population, was too small to produce reliable results in a subgroup analysis.[12]

PFS for BVd was more favourable compared to DVd in the male subgroup (HR 0.35, 95% CI 0.25; 0.50) than the female subgroup (HR 0.59, 95% CI 0.40; 0.87) ([redacted]).

There was no difference in PFS for extramedullary disease at baseline (yes/no), which was more common in the DVd than the BVd arm (10% versus 5%, respectively), though the numbers are too small to draw meaningful conclusions.

3.2.6.4 Additional subgroup analyses requested by the EAG

Given that the company position the treatment in 2L, and most likely only for 2L patients for whom lenalidomide is not suitable, the EAG requested efficacy data for the population of interest (clarification question A15). In the 2L cohort of the DREAMM-7 trial, around [redacted] of participants are refractory to lenalidomide.

The data provided is summarised in Table 10. There is evidence of a benefit of BVd for PFS, but not OS, for the DREAMM-7 2L only population. In the lenalidomide-refractory group, which comprised of participants with two or more prior lines of therapy, OS at the point of the data-cut was [redacted] for BVd than DVd ([redacted]). In comparison, in the CASTOR study[22] being refractory to immunomodulators, including lenalidomide, was not an effect modifier of OS for DVd compared to Vd. It is therefore unclear whether lenalidomide refractory status would be an effect modifier for OS of BVd.

The company did not provide baseline characteristics of the lenalidomide-refractory only subgroup. Without being able to judge the comparability of subgroups across treatment arms, it is difficult to

interpret the results of these analyses and the results of the post-hoc analysis of the lenalidomide-refractory subgroup in particular.

Table 10 Additional results of PFS, OS, TTD for 2L and lenalidomide-refractory patients.

	Overall sample[a]	2L only (BVd=125, DVd=123)[b]	Lenalidomide-refractory only (all lines, BVd=79, DVd=87)
PFS	HR 0.41 (0.31; 0.53) median 36.6 vs 13.4 months	[redacted]	HR 0.31 (0.19; 0.48)[c] median 25.0 vs 8.6 months[c]
OS	HR 0.57 (0.40; 0.80) median not reached Event: death 22% vs 35%	[redacted]	[redacted]
TTD	median 15.9 vs 12.8 months Event[d] 33% vs 21%	[redacted]	not provided

2L = second line; OS=overall survival, PFS=progression-free survival; TTD=time to treatment discontinuation.
[a] As reported in section 3.2.6.1.
[b] Lenalidomide-refractory and non-refractory patients.
[c] As reported in section 3.2.6.3.
[d] Discontinued treatment or death.

3.2.7 Safety of BVd compared to DVd

The data from DREAMM-7 shows that BVd is associated with common adverse events, leading to more delayed, reduced, and interrupted doses (see section 3.2.5) as well as more discontinuation of treatment. BVd was also associated with more grade 3 or 4 adverse events [redacted].

The EAG's clinical advisors highlighted ocular side effects as particularly important for clinical practice, as they may (i) mean BVd is a less suitable option for some patients (section 3.2.4.2), (ii) be associated with increased costs of managing side effects (see section 4.2.7), (iii) lead to a reduced dose intensity (section 3.2.5), and (iv) affect quality of life. Non-ocular adverse events were also more commonly observed in the BVd than the DVd arm, including thrombocytopenia (CS Table 23, p. 85).

The company performed a post-hoc analysis which adjusted for [redacted]. Table 11 shows key data on adverse events after adjustment [redacted]

Table 11 Adverse events by study arm after adjusting for [redacted]

	BVd study arm	DVd study arm
Grade 3 or 4 adverse events (no. of events per 100 person years)	[redacted]	[redacted]
Adverse events leading to treatment discontinuation (no. of events per 100 patient years)	[redacted]	[redacted]
Any serious adverse event (no. of events per 100 patient years)	[redacted]	[redacted]

Information described in sections 3.2.7.1 and 3.2.7.2 below are not adjusted for [redacted].

3.2.7.1 Ocular adverse events

The most common ocular events observed in the DREAMM-7 trial occurring in ≥ 5% of patients included blurred vision, dry eyes, photophobia, foreign body sensation in eyes, eye irritation, eye pain, visual impairment, increased lacrimation, reduced visual acuity, and diplopia.

Corneal adverse events relating to study treatment were observed in [redacted] (CSR).[19]

Corneal adverse events related to belamaf were measured using the investigator-assessed KVA scale; 84% of patients in the BVd arm experienced a corneal adverse event as per KVA criteria (N=203) (CS Table 26, pp. 89-90). Of these events, 74% were grade 3 or 4 (N=178). [redacted] (CSR).[19] These events lasted a median of [redacted] were resolved at the time of data collection [redacted]

3.2.7.2 Other adverse events

Thrombocytopenia, including reduced platelet count, was an adverse event of special interest and occurred more commonly in the BVd arm (87% of patients) than the DVd arm (65% of patients). Grade 3 or 4 thrombocytopenic adverse events (including reduced platelet count) were reported for 73% of patients in the BVd arm and 46% of patients in the DVd arm. Most of these adverse events were resolved, or patients recovered, after study medication was adjusted (dose interrupted, delayed, or reduced). The most common other adverse events (excluding ocular events) which led to a dose change in study medication are reported in Table 12.

Table 12 Summary of the most frequent adverse events (>5% in either study arm) leading to dose changes in the DREAMM-7 safety population.[a]

Adverse event	BVd study arm (N=[redacted])	DVd study arm (N=[redacted])
Any event	[redacted]	[redacted]
Thrombocytopenia[b]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Peripheral sensory neuropathy/ neuropathy peripheral	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Infusion-related reaction	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]

[a] Excluding ocular events.
[b] Including decreased platelet count.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The DREAMM-7 trial and 11 trials identified through the SLR were considered eligible for the indirect treatment comparison (ITC; CS Table 19, p. 68). Due to the structure of the network, seven of these trials do not contribute evidence to the estimates on the comparisons of interest(ARROW,[23] CANDOR,[24] IKEMA,[25] OPTIMISMM,[26] PANORAMA-1,[27] NCT01478048,[28] and NCT00813150[29]). The EAG's critique therefore focusses on the network including only studies that contribute evidence on the comparisons of interest (BVd versus SVd, DVd, hKd): DREAMM-7,[30, 31] BOSTON,[32] CASTOR,[22, 33] ENDEAVOR[34] and LEPUS.[35, 35] Table 13 lists key selection criteria for these trials. All trials included adults only, ECOG Performance Status 0-2, and all excluded participants who were refractory or unsuitable to receive the study intervention or comparator.

Table 13 Trials included in the ITC critique

Trial	Intervention	Comparator	Key selection criteria
DREAMM-7[30, 31]	BVd	DVd	• RRMM • 2L+ • No autologous SCT ≤ 100 days prior • No allogeneic SCT
BOSTON[32]	SVd	Vd	• Refractory multiple myeloma • 2L, 3L, 4L • No autologous SCT ≤ 1 month prior • No allogeneic sCT ≤ 4 months prior
CASTOR[22,33]	DVd	Vd	• RRMM • 2L+ • At least partial response to prior treatment • No autologous SCT < 12 weeks prior • No allogenic SCT
ENDEAVOR[34]	hKd	Vd	• RRMM • 2L, 3L, 4L
LEPUS[35, 36]	DVd	Vd	• RRMM • 2L+ • At least partial response to prior treatment • No autologous SCT < 12 weeks prior • No allogenic SCT

Abbreviations: 2L+ = at least one prior line of treatment; BVd = belantamab mafodotin with bortezomib and dexamethasone; DVd = daratumumab in combination with bortezomib and dexamethasone; hKd = high dose carfilzomib and dexamethasone; RRMM = relapsed or refractory multiple myeloma; SCT = stem cell transplant; SVd = Selinexor in combination with bortezomib and dexamethasone; Vd = bortezomib and dexamethasone.

Trials were generally similar in terms of selection criteria, with some differences in (partial) response required in prior treatment in some trials and variation in inclusion or exclusion of patients with recent SCT (Table 13). Clinical advice to the EAG pointed out that patients who previously received a SCT are likely to be fitter.

Table 14 gives an overview of characteristics of trial designs of the trials included in the ITC. All interventions of interest were given in treatment cycles until progression, unacceptable toxicity or adverse events, pregnancy, or withdrawal. The CASTOR study had the longest follow-up; final analyses were conducted when median follow-up was 72.6 months. In the CASTOR and LEPUS studies, non-compliance was specifically mentioned as a reason for treatment discontinuation. Cross-over from the control arm to the treatment of interest, also called treatment switching, was allowed in the BOSTON, CASTOR, and LEPUS after disease progression. The protocol of the DREAMM-7 trial states cross-over was not allowed. However, 8% of participants in the DVd arm received an antibody-drug conjugate as a subsequent treatment (CS Table 9, p. 41), and it is unclear whether this includes belamaf.

Table 14 Design characteristics of trials included in ITC

Trial	Treatment stopping criteria	Follow-up at last published data-cut	Cross-over of study arms
DREAMM-7	• Disease progression • Unacceptable toxicity • Safety stopping criteria relating to liver chemistry, corneal event, infusion-related reactions, and allergic or anaphylactic reactions. • Pregnancy	Median 28.2 months	No cross over allowed.
BOSTON	• Disease progression • Unacceptable toxicity • Pregnancy • Withdrawal of consent, or death, or Sponsor decision to terminate study.	Median 13.2 for SVd and 16.5 months for Vd	63/207 (30%) Vd group crossed over to SVd after disease progression.
CASTOR	• Disease progression • Dose delay of > 28 days, or ≥ 3 consecutive planned doses of daratumumab missed for reasons other than toxicity. • Safety or unacceptable toxicity • Pregnancy	Median 72.6 months	87/247 (35%) Vd group crossed over to DVd after disease progression. Median time to crossover after disease progression 20.5 months (5.7-68.3).
ENDEAVOR	Not clearly reported; hKd until disease progression (unless toxicity, and so on)	Median 37.5 for hKd and 36.9 for Vd	NR
LEPUS	• Disease progression • Adverse event • Non-compliance • Other; not clearly reported	Median 25.1 months	Crossover possible after disease progression (amendment 3). Unclear what proportion of participants crossed over.

Appendix Table 49 and Table 50 summarise the baseline characteristics and prior lines of therapies for the studies included in the EAG's simplified network. The included studies were generally consistent across these patient characteristics.

3.3.1 Critical appraisal of studies relevant to the ITC

The company conducted critical appraisals of the studies identified in the SLR using the Cochrane Risk of Bias (RoB) 2 tool and presented results in Appendix D3 (pp. 358-363). It is unclear on which outcome(s) the results are based. Justifications of risk of bias per rating were not provided. The RoB2 tool was not used for the DREAMM-7 study (see section 3.2.1 for DREAMM-7 critical appraisal). Table 15 highlights the most important findings from the company's assessment and EAG's assessment of risk of bias. The EAG agrees with the company that most concerns around risk of bias are due to missing information in the trial reports. All included trials were open-label studies, which carries a risk of bias if there is a patient or clinician preference for the intervention rather than the control treatment.

Table 15 Comparison of critical appraisal ITC studies

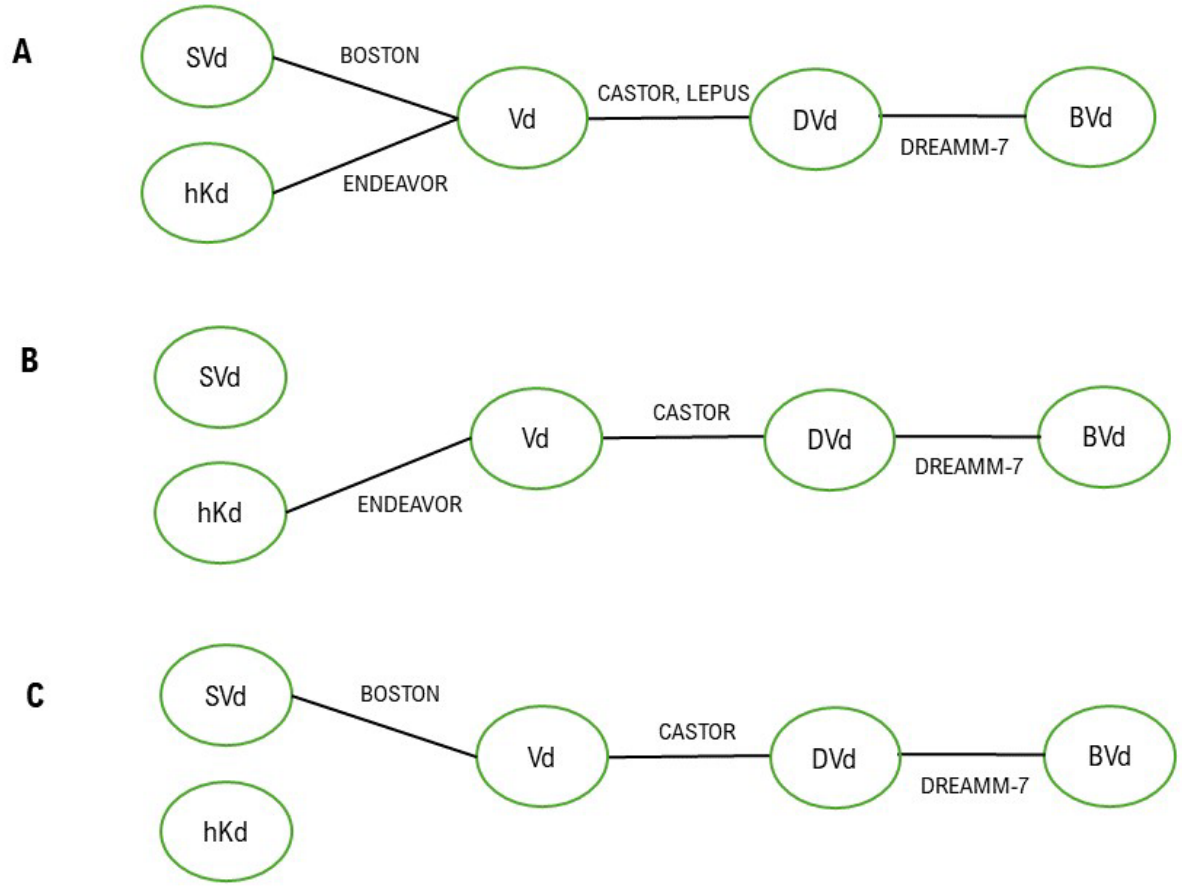
	Company's assessment	**EAG's critique**[a]
BOSTON	Overall judgement: some concerns. • Deviation from intended intervention: some concerns.	Overall judgement: some concerns. • Randomisation some concerns; insufficient information. • Deviation from intended intervention: some concerns as no blinding.
CASTOR	Overall judgement: some concerns. • Randomisation: some concerns.	Overall judgement: some concerns. • Randomisation some concerns; insufficient information. • Deviation from intended intervention: some concerns as no blinding.
ENDEAVOR	Overall judgement: low risk.	Overall judgement: some concerns. • Deviation from intended intervention: some concerns as no blinding. • Missing outcome data: some concerns as more participants in the control arm withdrew consent (2% vs 5%).
LEPUS	Overall judgement: some concerns. Randomisation: some concerns.	Overall judgement: some concerns. • Randomisation some concerns; insufficient information. Some baseline imbalances. • Deviation from intended intervention: some concerns as no blinding. • Missing outcome data: some concerns as insufficient information available.

[a] Information is only provided for those risk of bias domains with a difference between the company's and EAG's assessment, or where the EAG judged the domain to be at risk of bias. For outcome-specific domains, the EAG has considered OS and PFS.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company's indirect treatment comparisons (ITCs) are outlined in Section B.2.9 of the CS. The company's final overall network consisted of 12 studies that provided evidence on 11 comparisons (CS, Figure 15). There are no loops in this network, meaning no comparisons are informed by both direct and indirect evidence and inconsistency between direct and indirect evidence cannot be checked. The company's network can, therefore, be simplified to include only the three comparators of interest: SVd, hKd, and DVd, with comparisons to Vd used to connect the network, as evidence from other comparators does not contribute to the estimation of the comparisons of interest (Figure 1). A summary of all the ITCs conducted by the company with a list of the studies included in the simplified networks is presented in Table 16.

Figure 1 Simplified network diagrams for different outcomes and populations



A. Network for the ITT population for PFS, OS, and ORR and the 1 prior line of therapy population for PFS. **B.** Network for the lenalidomide-refractory population for PFS (comparisons to SVd are not possible). **C.** Network for the lenalidomide-refractory population for ORR (comparisons to hKd are not possible).
Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; ITT, intention-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SVd, Selinexor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

The EAG also requested NMAs for the 3L and 3L+ populations as they had been considered in TA974[37] and would be relevant to the NICE scope. In their response to clarification question A17 the company specified that they would not be exploring subsequent treatment lines after 2L and therefore did not provide these analyses.

Table 16 Studies included in the NMA for each outcome.

Outcome	Population	Models	Studies Included (simplified network)
PFS	ITT	FE, RE	BOSTON CASTOR LEPUS ENDEAVOR DREAMM-7
	Lenalidomide-exposed	FE, RE	BOSTON CASTOR ENDEAVOR DREAMM-7
	Lenalidomide-refractory	FE, RE	CASTOR ENDEAVOR DREAMM-7
	1 prior line of therapy	FE, RE	BOSTON CASTOR LEPUS ENDEAVOR DREAMM-7
OS	ITT	FE, RE	BOSTON CASTOR LEPUS ENDEAVOR DREAMM-7
ORR	ITT	FE, RE	BOSTON CASTOR LEPUS ENDEAVOR DREAMM-7
	Lenalidomide-exposed	FE, RE	BOSTON CASTOR ENDEAVOR DREAMM-7
	Lenalidomide-refractory	FE, RE	BOSTON† CASTOR DREAMM-7

†This trial was not included in the company's original network in CS Document B Figure 24, but data for this comparison was included in the datafile provided by the company in their response to clarifications.

Abbreviations: FE, fixed effect model; ITT, intention to treat; PFS, progression-free survival; RE, random effects model; ORR, objective response rate; OS, overall survival

3.4.1 Consistency and similarity of studies included in the company NMA

As there were no loops in the network it was not possible to statistically assess the consistency between the direct and indirect evidence. As there were only one or two studies per comparison in the network, between-study heterogeneity cannot be estimated.

The company's NMA feasibility assessment is outlined in Section B.2.9.2 of the CS, providing more detail in Appendix D, Section 4.1. In this assessment the company investigated similarities in study design, patient populations, the distribution of baseline characteristics, outcome definitions and the measurement and duration of follow-up. The feasibility assessment provided by the company considers the overall network and does not assess the feasibility of conducting an NMA on each outcome of interest for all populations of interest as recommended by Cope et al.[38]

The studies included in the company's network are consistent with those used in recent STAs conducted in MM, namely TA897[16] (daratumumab in combination with bortezomib and dexamethasone) and TA974[37] (selinexor in combination with bortezomib and dexamethasone), with the exception that both these STAs exclude the LEPUS study. In TA897, the company explain that LEPUS is excluded from their NMAs because the study population consists exclusively of Chinese patients and they believed that LEPUS would not be generalisable to other included studies with more mixed population demographics. They also had concerns that variations in Asian ethnicity would introduce effect modification. No reason is provided for its exclusion in TA974. The EAG does not think that these concerns are valid and, in the absence of evidence that ethnicity is an effect modifier, agree with the company's decision to include LEPUS in the current NMAs. The EAG in TA897 asked for a sensitivity analysis that included LEPUS and found that the results were consistent with the original NMA.

3.4.2 Proportional Hazards Assumption

The company assessed the proportional hazards (PH) assumption for the time-to-event outcomes in Section D.4.2 of the CS.

For DREAMM-7, the PH assumption was assessed through visual inspection of the log-cumulative hazard plots and Schoenfeld residuals, and the Grambsch-Therneau statistical test. For comparator studies the company digitised all available KM plots and constructed plots of hazard functions from the pseudo-IPD that was generated. The PH assumption was assessed through visual inspection of these plots.

For DREAMM-7, the company concluded that the PH assumption for PFS may be a reasonable assumption. The company expressed uncertainty about the validity of the PH assumption for OS as the log-cumulative hazards crossed at multiple points (CS Appendix D, Figure 6) but the Schoenfeld

residuals test and plot did not indicate violations in the assumption, therefore the company concluded that it may be reasonable to assume PH for OS too. For studies involving the comparators of interest, BOSTON, CASTOR, ENDEAVOR, and LEPUS, the company believed that the plots for the hazard functions for OS and PFS suggested that the PH assumption was also reasonable. The EAG agrees that for both PFS and OS, PH cannot be ruled out for DREAMM-7 or the comparator studies.

3.4.3 NMA Methods

The company detail the methodology for the network meta-analyses in Appendix D (Section D.4.4.5) of the CS. However, methods detailed there do not match the code supplied to the EAG in response to clarification question A14. For example in Appendix D the company state that the NMAs were conducted in the Bayesian framework using WinBUGS when in fact they were conducted in R version 4.3.2[39] using the *multinma* package[40] (version 0.6.0.9) which uses Stan.[41]

A normal likelihood model with an identity link was used for time-to-event outcomes and a binomial likelihood with a logit link was used for dichotomous outcomes. The company fit both fixed-effect (FE) and random-effects (RE) models, selecting the more appropriate one of the two. In response to clarification question A14, the company provided the EAG with the code used for all their analyses. The company also provided the dataset that was used to conduct the NMAs. However, the company notes that the dataset provided in response to clarification question A13 is different from the dataset used by the company to conduct the analyses reported in the CS. The company suggested that differences between the results presented in the CS and those obtained by the EAG when re-running the code could be attributed to the differences in the dataset, without specifying what these differences were (Section 3.4.4). The EAG note that it should be standard practice to hold details of all submitted analyses so that results can be checked and reproduced, and to clearly document all changes to the data.

From the code provided by the company, the EAG could confirm that models were sampled for 1,000 iterations over 4 chains with a burn-in of 1,000 iterations. Model convergence was tested using the Gelman-Rubin statistic.[42] The company stated that the prior distribution for mean treatment effects would be adjusted if models failed to converge, however all models appeared to converge using the recommended vague Normal(0,100^2) prior.[43]

The company used informative Turner priors[44] for the between-study standard deviation of treatment effects in RE models. For the binary ORR, the company stated that they used the generic Turner prior in a healthcare setting, LN(-2.56, 1.74^2), that was truncated using methods proposed by Ren et al.[45] For OS and PFS, the company used the Turner prior for withdrawals when comparing a pharmacological vs. placebo/control comparison, LN(-2.99. 1.74^2).

The EAG agrees that truncated Turner priors can be useful for fitting models where there is insufficient data in a network. However, the priors selected by the company are relevant only for dichotomous outcomes, therefore their use in analyses of time-to-event outcomes is questionable. In addition, the generic prior used for ORR is not the most appropriate for this outcome. The EAG believes that the Turner prior for subjective outcomes for pharmacological vs. pharmacological treatment comparisons, LN(-2.93, 1.58^2) is a more appropriate prior. More importantly, the EAG did not find any evidence in the code provided by the company that the prior distribution for ORR was truncated according to the methods proposed by Ren et al, as stated by the company. However, the EAG agrees with the company that the simpler fixed-effect models can be used for inference, as the random-effects models do not improve the model fit. Therefore, the EAG did not explore the random-effects models any further.

3.4.4 NMA Results

The results of the NMAs are reported in Document B (Section 2.9.4) and Appendix D (Section 4.5) of the CS. However, in response to clarification question A13, the company specified that the following changes had been made to the dataset used for the NMAs:

1) A new study- GEM_KyCyDex was introduced to the ITT network which added a new comparator, CyKd to the network.
2) Data from the IKEMA study was added to the network for OS in the ITT population, which added IhKd as a comparator in that network.
3) Minor corrections were made to the data.

Neither KyCyDex and IhKd are relevant comparators and both are added as spurs to the existing network. Therefore the addition of the GEM_KyCyDex and IKEMA studies does not impact the analyses conducted for the comparators of interest and will therefore not be added to the EAG's simplified network. The company did not provide any further details on the nature of the "minor corrections" made to the data. As the EAG does not have access to the previous datafile, we are unable to comment on the impact these changes may have on the analyses conducted. On further inspection, the EAG discovered other discrepancies in the data. Most of these discrepancies occur in non-relevant comparators. Here we will focus on the two discrepancies that pertain to the relevant comparators identified in Section 3.4:

1) For the ITT network for OS, the EAG identified a conference abstract[35] that reported results for LEPUS at a later timepoint. The EAG chose to include these results in their NMA instead of the less mature data used by the company.
2) In the NMA presented in CS Section B.2.9.4.4 for ORR in the lenalidomide-refractory population, SVd was not part of the network. However, in the updated dataset provided to the

EAG, data had been extracted from the BOSTON study for the SVd vs. Vd comparison. The company did not provide any explanation regarding the inclusion of the new evidence in the network. The EAG chose to include this evidence in their analysis.

The EAG repeated all NMAs (except those conducted in the lenalidomide-exposed population as that data had not been provided) and compared the results to those presented in the CS by the company (using the old dataset). In this report, the EAG presents results generated by running the code provided by the company using the updated dataset. The EAG ran the analyses using R version 4.4.1 and *multinma* version 0.7.1. The NMA results for the comparators included in the EAG's simplified network are summarised in Table 17. For all analyses, the company and the EAG preferred the simpler FE model.

Table 17 Results of Fixed Effect NMAs for comparators of interest

		HR/OR[a] (95% CrI)			
Outcome	**Population**	**BVd vs. DVd**	**BVd vs. hKd**	**BVd vs. SVd**	**BVd vs. Vd**
PFS	ITT[b]	[redacted]	[redacted]	[redacted]	[redacted]
	Lenalidomide-exposed[c]	[redacted]	[redacted]	[redacted]	[redacted]
	Lenalidomide-refractory[b]	[redacted]	[redacted]	[redacted]	[redacted]
	1 Prior LOT[b]	[redacted]	[redacted]	[redacted]	[redacted]
OS	ITT[d]	[redacted]	[redacted]	[redacted]	[redacted]
ORR	ITT[b]	[redacted]	[redacted]	[redacted]	[redacted]
	Lenalidomide-exposed[c]	[redacted]	[redacted]	[redacted]	[redacted]
	Lenalidomide-refractory[b]	[redacted]	[redacted]	[redacted]	[redacted]

a. For PFS and OS, the treatment effect is estimated as a HR and for ORR as an OR
b. Results presented were those obtained from EAG-run analyses.
c. Results presented were those reported in the CS (Appendix D).
d. Results presented were those obtained from the EAG-run analysis using the EAG's data with more recent LEPUS results
Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; CrI, credible interval; DVd, daratumumab in combination with bortezomib and dexamethasone; hKd, high dose carfilzomib and dexamethasone; HR, hazard ratio; ITT, intention to treat; LOT, line of treatment; PFS, progression-free survival; OR, odds ratio; ORR, objective response rate; OS, overall survival; SVd, selinexor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

3.4.4.1 PFS Results

NMAs were conducted in the ITT, 2L, lenalidomide-refractory, and lenalidomide-exposed patient populations. The results for company and EAG-run analyses for all comparators in the extended network are summarised in Appendix Table 51. For the ITT and 2L populations the results of the EAG analyses were consistent with those presented by the company in CS Document B Figure 17 and Appendix D Figure 35. There were some discrepancies in the results of the EAG's analyses compared to those presented in CS Figure 23. As the EAG did not have access to the original dataset used by the company to run their analyses, it is unclear whether these discrepancies are due to corrections to the

data or the methods of analysis. The EAG is therefore unable to comment on the reason for these discrepancies.

In the ITT population, belamaf was superior to all three comparators of interest, DVd (Hazard Ratio, [redacted] hKd [redacted], and SVd [redacted] (Table 17). The results were consistent across the three patient populations (Figure 2). As more patients are included in the ITT population, the 95% CrI for the estimates from the ITT analyses were narrower than in all other populations.

Figure 2 Forest plot of the comparators of interest for PFS for all NMAs conducted (EAG analyses)

Abbreviations: 2L, Second-line; BVd, belamaf in combination with bortezomib and dexamethasone; CrI, credible interval; DVd, daratumumab in combination with bortezomib and dexamethasone; hKd, high dose carfilzomib and dexamethasone; HR, hazard ratio; ITT, intention to treat; LEN-Ref, Lenalidomide-refractory; PFS, progression-free survival; SVd, selinexor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone

3.4.4.2 OS Results

Only one NMA was conducted for OS, in the ITT population. A benefit in OS was observed in belamaf compared to DVd [redacted], hKd [redacted], and SVd [redacted] (Table 17). Results for the extended network are presented in Appendix Table 52. The results from the EAG's analysis were not consistent with the results

presented by the company in CS Figure 19 or the results presented by the company using their updated dataset (Table 52). These small differences are due to the inclusion of more mature data from the LEPUS study. As all comparators in the network except for DVd are connected to BVd via the CASTOR and LEPUS studies, changes in data from LEPUS will result in changes to all these comparisons.

3.4.4.3 ORR Results

NMAs were conducted in the ITT, lenalidomide-refractory, lenalidomide-exposed patient populations. For the ITT and lenalidomide-refractory populations, results were not consistent between those presented by the company in CS Document B, Figures 21 and 25, those presented by the company in response to clarification question A13,[46] and those run by the EAG. As the EAG were not provided the exact data used to conduct each analysis, we were unable to check the reason for the discrepancy in the results. As mentioned in Section 3.4.4, the original network for the lenalidomide-refractory population (CS Document B, Figure 24) did not include SVd as a comparator. As the dataset provided to the EAG had data for SVd from the BOSTON study the EAG results include this comparator.

Results for the company and EAG analyses for all comparators in the extended network are reported in Appendix Table 53. Figure 3 shows that the estimates from NMAs differ between the ITT and lenalidomide-refractory populations, although the 95% CrIs are very wide for the lenalidomide-refractory population, due to the sparsity of the network.

Figure 3 Forest plot of the comparators of interest for ORR for all NMAs conducted (EAG analyses)

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; CrI, credible interval; DVd, daratumumab in combination with bortezomib and dexamethasone; hKd, high dose carfilzomib and dexamethasone; ITT, intention to treat; LEN-Ref, Lenalidomide-refractory; OR, odds ratio; ORR, overall response rate; SVd, selinexor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

3.5 Conclusions of the clinical effectiveness section

Direct evidence on the clinical effectiveness of BVd comes from one unblinded RCT comparing BVd to DVd; the DREAMM-7 study. Trial participants may not be fully representative of NHS practice. Most importantly, patients were younger and fitter in the trial. Trial participants also did not match the population specified by the company. Around 50% had only one prior line of therapy, and 34% were refractory to lenalidomide. As a result, no evidence on key outcomes is available for 2L patients for whom lenalidomide is unsuitable.

Data on OS for BVd versus DVd are immature. Median OS was not reached in either treatment group (HR 0.57, 95% CI 0.40; 0.80). PFS assessed by IRC was better for BVd than DVd (HR 0.41, 95% CI 0.31; 0.53). Median DOR was higher for BVd than DVd and the ORR was 11.4% higher for BVd.

BVd caused more, and more severe, common adverse events than DVd, both ocular and non-ocular, which frequently resulted in changes to the dose of the treatment and treatment delays. Adverse events associated with BVd may impact on treatment discontinuation and quality of life whilst on treatment.

Evidence for the subgroup of 2L patients showed a benefit of BVd for PFS but not OS (immature data), nor for TTD. The lenalidomide-refractory subgroup included 2L+ patients and showed a benefit of BVd for PFS and OS (immature data).

The NMA included 12 studies. Networks of evidence were sparse and apart from one exception, only one study provided all the evidence for each comparison. There were no loops in the networks so all comparisons were informed only by the direct evidence from relevant studies. The NMA methods used by the company were appropriate albeit poorly described in the CS documents. As there were few studies included in the network, heterogeneity could not be estimated adequately. However, the fixed-effect models fitted the data well. The EAG repeated the company's analyses with an updated dataset but as the company did not detail the changes made in the dataset, the EAG could not account for the small inconsistencies between results. Although the overall conclusion remains unchanged in their analysis, the EAG prefer the NMA that uses data from a later cut-off point for the LEPUS study.

In the ITT population, a benefit was seen for BVd in PFS, OS, and ORR compared to the three comparators of interest. No meta-analyses could be conducted in the LEN-refractory and 2L populations for OS, or the 2L population for ORR. For PFS, BVd could not be compared to SVd for the LEN-refractory population, and for ORR, BVd could not be compared to hKd for the LEN-refractory population. There is therefore some uncertainty in the relative effectiveness of BVd compared to DVd, hKd and SVd.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

4.1.1 Summary of company's submission

The company undertook a systematic literature review to identify economic evaluations in adults with MM who had received ≥1 prior line of therapy, i.e., in a 2L+ RRMM population, for any of the interventions in the clinical care pathway, either alone or in combination, for the period 2008 to present (see Appendix G of the CS for a detailed description of the searches, inclusion criteria, study selection process, and results of the review). A total of 72 publications that described cost-effectiveness analyses conducted for RRMM were identified; of which 19 were conducted for a UK setting and 53 for a non-UK setting. The studies for the UK setting included previous NICE Technology Appraisals (TAs) in the last 10-years' time limit; including, TA870,[47] TA897,[16] TA783,[48] TA695,[17] TA658,[49] TA657,[15] TA586,[18] TA427,[50] and TA380.[51] Summary details of the published studies for the UK and non-UK settings are provided in Table 7 and Table 8, respectively, of Appendix G of the CS. The company did not identify any economic evaluations of belamaf in combination with bortezomib and dexamethasone, or belamaf in combination with other agents.

4.1.2 Points for critique

The literature searching for the company's review of cost-effectiveness evidence appears to have been conducted to a high standard and is well reported – See Appendix AA2 for details. The EAG considers that all relevant publications are likely to have been identified; however, due to the search cut-off date of January 2024, the search did not identify the previous NICE Technology Appraisals of TA974 [37], TA970[52] (Selinexor with dexamethasone for treating RRMM after 4 or more treatments, 2024) and the review of TA658, which is guidance in development, GID-TA10979 [53]. In addition, the company did not include the paused appraisal of GID-TA10568 [54].

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a *de novo* model to evaluate the cost-effectiveness of BVd versus DVd, and the comparators of hKd and SVd, in adult patients with RRMM who have had one prior therapy, and whose disease has progressed on the last therapy, i.e., as a second line treatment (2L-only), and for whom lenalidomide is unsuitable. The effectiveness evidence informing the model is largely based on the DREAMM-7 trial from the overall ITT population (2L+), i.e., not restricted to the 2L-only subgroup, and not restricted to lenalidomide refractory or exposed subpopulations.

A partitioned survival analysis (PartSA) is used to estimate the long-term health outcomes and costs associated with progression and the clinical pathway of RRMM in the UK. In the PartSA, the time-dependent risk associated with disease progression and death is modelled by extrapolating clinical trial endpoints from DREAMM-7 to independently determine the proportion of patients alive and in the progressed (or progression-free) health state over time for BVd and the comparator of DVd, while survival outcomes for the other comparators of hKd and SVd are based on hazard ratios from the NMA applied to a baseline of DVd (see section 3.4.4). Treatment discontinuation is informed by the time-to-treatment discontinuation (TTD) from DREAMM-7 for BVd and DVd and a proxy for hKd and SVd (see Section 4.2.6.4). When patients discontinue treatment, a switch to another treatment is not directly modelled in the PartSA but the impact of treatment switching is implicit in the survival outcomes and the changes to health state membership. The costs of subsequent therapies are included in the model.

BVd is modelled to affect QALYs by increasing the proportion of patients who are alive and progression-free over time, which is associated with improved HRQoL relative to the comparators due to a higher utility value for progression-free compared to the utility for progressive disease. In addition, the company's base case analysis assumes a higher utility value for patients who are progression-free on BVd compared to patients who are progression-free on the comparator treatments (DVd, hKd and SVd). Therefore, individuals treated with BVd will accrue higher number of QALYs

than the comparators while in the PFS health states. Furthermore, the company have modelled a higher a utility value for progressive disease than progression-free for the comparator treatments.

BVd is modelled to affect costs by increasing the time on treatment compared to the comparators and the proportion of the cohort who remain progression-free for longer, with associated drug acquisition costs (except for those progression-free and off-treatment), while decreasing the proportion with progressive disease and associated costs of subsequent therapies upon progression. The largest component of cost difference between BVd and its comparators is drug acquisition costs, health state (progression-free and progressed disease) resource use and costs of subsequent treatments, while only a small difference in costs is associated with adverse events.

The company's *de novo* model uses a very similar approach to that used in previous NICE TAs for RRMM, with the same PartSA model structure and a lifetime horizon. The source of data used to inform treatment effectiveness, time on treatment, and utility values in the model is based on evidence from the relevant treatment-specific clinical studies and clinical expert input (see Table 30 of CS for a comparison of key features of the company's analysis with previous TAs for a population of 2L RRMM).

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 18.

Table 18 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon is lifetime.
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate but there is uncertainty about the appropriateness of using evidence from a 2L+ population, rather than a 2L-only subpopulation, to inform the cost-effectiveness of BVd as a second line treatment. The systematic review identified one clinical trial for BVd in the relevant patient population: DREAMM-7, which compared BVd

		with DVd. The NMA was used to assess the relative efficacy of BVd to the other comparators.
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 (HRQoL) in adults.	The CS is appropriate. HROoL was measured with EQ-5D-3L and valued using the UK tariff.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
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	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The base case model is a PartSA that is used to simulate the time in four mutually exclusive health states: progression-free (PF) on-treatment, PF off-treatment, progressed disease (PD) and death (see Figure 27 of CS). The cohort enters the model in the PF on-treatment health state and the transitions to the other health states are governed by parametric models fitted to time-dependent PFS, OS and TTD curves over a lifetime horizon, which are informed by data from the DREAMM-7 trial and hazard ratios derived from the NMA (note that in the absence of a TTD NMA, the company assumed the PFS NMA HR for the non-trial comparators as a proxy for the corresponding TTD ones). The PF health state is subdivided into 'on-treatment' and 'off-treatment' because some patients in DREAMM-7 withdrew from active treatment before disease progression, which results in cost and adverse event differences for the proportions of the cohort on- and off-treatment. The PD health state captures the costs and consequences of subsequent treatments following discontinuation from initial treatment, while the OS curve reflects the effects of subsequent treatment use. Transitions to the death state capture end of life care costs. A model cycle length of one week is used to capture differences in the frequency and timing of the different drug components of BVd and its comparators.

4.2.2.2 Points for critique

The company's base case model structure is consistent with the models used in previous NICE TAs for a population of 2L RRMM,[16, 37 15, 17, 18] except that the PF health state was not subdivided into on- and off-treatment in previous TAs (except TA897[16] for DVd), while, in TA897, the PD (or post-progression) state was also subdivided into on- and off-treatment. The EAG considers the company's approach of subdividing the PF health state to be reasonable in light of the evidence from the DREAMM-7 trial, where a number of participants in the trial discontinued treatment before disease progression (i.e., for reasons other than progression) and remained PF. The EAG also considers the company's approach of not subdividing the PD health state into on- and off-treatment to be reasonable because of a lack of reliable evidence from DREAMM-7 on discontinuation rates (or TTD) for subsequent therapies post-progression in those treated with BVd and DVd at 2L. However, it means that the company's model does not explicitly consider survival outcomes for separate clinical events at subsequent steps of disease progression (e.g., PFS-2), which are likely to be affected by subsequent treatment use after discontinuation from 2L treatment.

The appropriateness of the company's PartSA is largely dependent on how complete and mature the observed data informing survival outcomes are, especially OS, and the extrapolation of these outcomes over a lifetime horizon (see Section 4.2.6); uncertainty about the long-term OS extrapolations will lead to uncertainty in the estimates of cost-effectiveness of BVd relative to its comparators.

4.2.3 Population

The population included in the model aligns with the DREAMM-7 trial population for adults with RRMM who have had one prior therapy. The overall ITT population (2L+) from DREAMM-7, i.e., not restricted to the 2L-only subgroup of participants and not restricted to lenalidomide refractory or exposed subpopulations, is used to inform the treatment effectiveness for BVd and DVd in the company's base case analysis. This population is [redacted]. However, the decision problem addressed in the CS to evaluate the cost-effectiveness of BVd relative to its comparators is restricted to a 2L-only population and in adults for whom lenalidomide is unsuitable (see Section 2.2.3.1). Therefore, the cost-effectiveness of BVd is only evaluated against treatments recommended by NICE and available in the NHS at 2L, and excludes lenalidomide or combination therapies that include lenalidomide. Furthermore, the cost-effectiveness covers two subpopulations, which differ only by their relevant comparators (see Section 4.2.4): (i) DVd eligible subpopulation; and (ii) DVd ineligible subpopulation.

The modelled population is based on the baseline characteristics of participants in the ITT population of DREAMM-7, with a mean age of 64 years, percentage of males 55%, mean weight of [redacted] kg and body surface area of [redacted] m^2 (see Table 28 of CS).

Subgroups by number of prior lines of therapy are not considered in the economic analyses. In response to EAG clarifications (question B2), the company provides additional subgroup data for a lenalidomide refractory subpopulation and a 2L-only subpopulation from DREAMM-7, but a cost-effectiveness analysis in these subgroups is not presented.

4.2.3.1 Points for critique

The EAG's primary concern in relation to the company's proposed population for the cost-effectiveness analysis (i.e., adults at 2L-only and for whom lenalidomide is unsuitable) is that it represents a more restrictive population than the [redacted] NICE scope that includes adults who have had at least one prior therapy, i.e., includes second and subsequent lines of treatment (2L+) and is not restricted according to suitability for lenalidomide treatment. In response to the EAG's clarification question A5, the company state that the proposed population is eligible 2L patients for whom lenalidomide is unsuitable due to the high unmet need identified in this specific patient subgroup. However, as discussed in more detail in Sections 2.2.3 and 2.2.3.1, the EAG clinical advisors expect to treat patients at 2L for whom lenalidomide is a suitable treatment option over the next three to five years and, therefore, the EAG considers it inaccurate to equate 2L with lenalidomide-refractory status.

The evidence informing the cost-effectiveness of BVd is informed by the ITT population of DREAMM-7 (2L+) rather than the subgroup-specific evidence for the 2L-only population in line with the decision problem defined by the company in their submission. In response to EAG clarification question A5, the company state that the most appropriate subgroup to inform cost-effectiveness would be 2L-only patients who are lenalidomide refractory; however, the EAG is concerned that this means that there is a mismatch between the data informing the cost-effectiveness of BVd from the overall ITT population (2L+) from DREAMM-7 and the positioning at 2L for patients in UK clinical practice for whom lenalidomide is unsuitable.

The company have provided separate subgroup data for a lenalidomide refractory subpopulation and a 2L-only subpopulation from DREAMM-7. The EAG agrees with the company that the latter 2L-only subpopulation data is not generalisable to 2L patients receiving treatment in the NHS given that only approximately 20% of patients overall are lenalidomide refractory in the 2L-only subgroup. The lenalidomide refractory subpopulation (2L+) accounts for 34% of all participants from DREAMM-7 (n=79 in the BVd arm and n=87 in the DVd arm); therefore, it represents a suitable alternative source of data, rather than the overall ITT population, to inform the cost-effectiveness of BVd in line with the

company's proposed population. However, the company were unable to conduct an NMA for OS in a lenalidomide refractory subpopulation to inform a comparison of BVd with hKd and SVd, due to a lack of available data (see Section 3.4.4), and, therefore, a cost-effectiveness analysis in this subpopulation was not presented. The EAG also considers that splitting the overall population data from DREAMM-7 to reflect a subgroup of lenalidomide refractory only is unlikely to be helpful because the data, especially OS, is already immature. Furthermore, the company did not use extrapolation approaches using external data from the CASTOR trial to adjust the DVd OS in the two subgroups, as they did to increase the robustness of DVd OS extrapolation for the ITT population (see Section 4.2.6.3 for a description of this approach). Therefore, the EAG considers that the OS data for the subgroups are likely to be highly uncertain and they present additional challenges in handling the immaturity of the OS data compared to the overall ITT population (2L+).

In the absence of suitable alternative 2L-only data in patients for whom lenalidomide is unsuitable, the EAG acknowledges the company's reasons for using the overall ITT population (2L+) from DREAMM-7 to inform the cost-effectiveness of BVd relative to DVd in the company's proposed population. However, it remains unclear to the EAG why the company has not presented separate subgroup cost-effectiveness analyses for BVd at 3L-only and 3L+, [redacted] In response to EAG clarifications (question A5b), the company states that *"the strongest clinical case is in 2L since the DREAMM-7 trial is a head-to-head with the current 2L standard of care, DVd and that positioning BVd at 2L results is the most cost-effective use of NHS resources compared to other possible positionings."* The EAG is unable to formally critique this statement because no evidence has been presented in the 3L-only or 3L+ subpopulations from DREAMM-7 and the relevant comparators at 3L and 3L+, as listed in the NICE scope for this appraisal, have not been considered in the cost-effectiveness evaluation of BVd.

The EAG highlighted in Section 2.2.3 that given that lenalidomide was only approved for use at 1L in 2019, lenalidomide-based treatments are still an option for some patients in 2L and that clinical advice received by EAG suggests that the BVd would be a potential treatment option for these patients. The cost-effectiveness evidence presented by the company does not allow include the population of patients for whom lenalidomide is unsuitable and have received only 1 previous line of therapy (2L-only).

In summary, the EAG considers that evidence has only been presented for the use of BVd in the NHS after just 1 previous line of therapy (2L-only) and in patients for whom lenalidomide is unsuitable (i.e., refractory to lenalidomide or previously exposed to lenalidomide at 1L), while recognising the limitations of the evidence informing the cost-effectiveness of BVd relative to DVd, which is informed by outcomes from the overall ITT population of 2L+ of DREAMM-7.

4.2.4 Intervention and comparators

4.2.4.1 Summary of company's submission

The intervention is belamaf in combination with bortezomib and dexamethasone, BVd. Belamaf is available in 100mg and 70mg vials which are administered as an IV infusion. The dosage used in the model for belamaf is the SmPC recommended dose of 2.5mg/kg once every 3 weeks, with dose modifications recommended for ocular or other adverse reactions. The company have incorporated dose reductions and delays in the model to manage toxicity and tolerability of the therapies for MM, which is accounted for via a 'relative dose intensity' (RDI) parameter (see Section 4.2.9.4). For BVd, individual patient-level data from DREAMM-7 was used to track belamaf doses received by patients over time to account for dose delays and reductions, which was used in the company's base case analysis. The dosage for bortezomib is 1.3mg/m^2 administered through a SC injection, four times every three weeks, while the dosage for dexamethasone is 20mg oral tablets, eight times every three weeks.

The SmPC recommends that treatment should be continued until disease progression or unacceptable toxicity. Participants in the DREAMM-7 trial discontinued treatment mainly due to disease progression or intolerability (see section 3.2.3). Therefore, the model does not incorporate a stopping rule for BVd and patients are assumed to remain on treatment until discontinuation, which is defined by the time on treatment or progression-free survival curve, whichever comes first.

The comparators included in the company's model are the NICE-approved treatments at 2L for whom lenalidomide is unsuitable, which includes:

- Daratumumab with bortezomib and dexamethasone, DVd (approved by NICE in TA897 after just 1 previous line that included lenalidomide or lenalidomide unsuitable as 2L);
- Selinexor with bortezomib and dexamethasone, SVd (approved by NICE in TA974 at 2L after just 1 previous line and refractory to both daratumumab and lenalidomide);
- Carfilzomib with dexamethasone, hKd (approved by NICE in TA657 after just 1 previous line).

The company presents cost-effectiveness results separately for two subpopulations, which differ only by their relevant comparators:

- DVd eligible subpopulation - Patients who were eligible for transplant at 1L or who were ineligible for transplant before the approval of daratumumab in combination with lenalidomide and dexamethasone (DRd) as a 1L treatment. In this subpopulation, the CS states that BVd can be compared against any approved lenalidomide-sparing 2L treatment. However, at EAG points for clarification (question B1), the EAG pointed out that SVd is only approved by NICE in the 2L population for patient's refractory to both daratumumab and lenalidomide; therefore, SVd cannot be included in the 2L population where DVd is included as a relevant comparator. In response, the company updated its base case analysis to exclude SVd as a comparator in the DVd eligible population.
- DVd ineligible subpopulation – Patients in 2L who were ineligible for transplant following the approval of daratumumab in combination with lenalidomide and dexamethasone (DRd), will almost certainly be refractory to daratumumab and, therefore, BVd cannot be compared against DVd, but can be compared against any other approved lenalidomide-sparing regimen (i.e., SVd and hKd).

In summary, the following comparators are included for the two subpopulations:

- In the DVd eligible subpopulation, BVd is compared with DVd and hKd.
- In the DVd ineligible subpopulation, BVd is compared with SVd and hKd.

Subsequent treatment use after discontinuation from primary treatment is not explicitly modelled, but a one-off subsequent treatment cost (accounting for two further lines of treatment) is applied upon progression from 2L treatment. These subsequent costs are the same for BVd, SVd and hKd but differ for DVd (see Section 4.2.9.7).

4.2.4.2 Points for critique

The NICE scope for this appraisal included six treatment combinations as potential comparators for patients who have had one prior therapy, including those with lenalidomide regimen. The EAG considers the exclusion of comparators with a lenalidomide regimen to be reasonable in light of the company's proposed population (i.e., 2L-only for whom lenalidomide is unsuitable); however, as discussed in Sections 2.2.3 and 2.2.3.1, the EAG considers it inaccurate to equate 2L with lenalidomide-refractory status and some patients at 2L may be suitable for lenalidomide. Based on the company's proposed position, the 2L treatments in the NICE treatment pathway of carfilzomib with dexamethasone and lenalidomide (TA695) and lenalidomide plus dexamethasone (TA586) are ruled out as potential comparators. In addition, the NICE scope included bortezomib monotherapy (TA129). The EAG agrees with the company that bortezomib monotherapy is no longer relevant as it is rarely used in the NHS for the treatment of RRMM. Therefore, the EAG considers the three comparators,

DVd, SVd and hKd, to be the most relevant comparators at 2L in patients for whom lenalidomide is unsuitable.

The company's separation of the population into two subpopulations for DVd eligible and DVd ineligible seems appropriate in light of the approval of DRd as a 1L treatment.

The NICE scope for this appraisal also included comparators for people who had two prior therapies and people who had three or more prior therapies. The CS has not presented evidence for the cost-effectiveness evaluation of BVd in RRMM at third and subsequent lines. Therefore, it is not possible to comment on the cost-effectiveness of BVd at any other position in the treatment pathway because the relevant comparators have not been included.

In section 3.2.5, the EAG highlighted that clinical advice to the EAG suggested that in NHS clinical practice the belamaf dose is likely to be lower (particularly at treatment initiation) than the SmPC recommendation and the dose observed in the DREAMM-7 trial. The company's cost-effectiveness base-case analysis is considered reflective of the belamaf observed dose reductions in DREAMM-7 and allows exploring the impact on costs of applying the SmPC recommended dose for belamaf (see Section 4.2.9.4). However, it is not possible to assess how different belamaf dosages, including lower doses than in the DREAMM-7 trial would impact treatment effectiveness.

The EAG also noted in section 3.2.5 that, while daratumumab in DREAMM-7 (and in other studies included in the ITC, such as the CASTOR trial) was administered as an IV treatment, its SmPC currently recommends SC administration. Clinical advice to the EAG in TA897[55] suggested that the SC administration route would be preferred in clinical practice as fewer AEs would be expect for daratumumab SC vs. IV but that efficacy should not be different between administration routes. The EAG notes company has implicitly assumed equivalence between the treatment effectiveness and safety for DVd administered via IV and SC. In section 4.2.9.4, the administration costs for DVd are consistent with the SC route.

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) in England and Wales over a lifetime time horizon of 36 years (starting age of 64 years). A 3.5% annual discount rate is used for both costs and health effects.

4.2.5.2 Points for critique

The CS adheres to the NICE health technology evaluations manual[56] and the EAG considers the approach used by the company to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of company's submission

The model includes three elements relating to treatment effectiveness and extrapolation of effects over time, for BVd and comparator treatments:

(i) Progression-free survival (PFS), i.e., the probability of not progressing to the progressive disease health state;
(ii) Overall survival (OS), i.e., the probability of all-cause death; and
(iii) Time to treatment discontinuation (TTD), i.e., the expected duration on treatment until discontinuation due to disease progression, intolerability, or other reasons.

The data sources informing each of these elements for each treatment are described below and the corresponding time-dependent curves used in the company's base case analysis are presented in Figure 4 (PFS),Figure 5 (OS), Figure 6 (TTD) for BVd, DVd, SVd, and hKd.

Figure 4 Company's base-case PFS curves

Figure 5 Company's base-case OS curves

Figure 6 Company's base-case TTD curves

The effectiveness of BVd and DVd in the model is based on time-to-event Kaplan-Meier (KM) data from DREAMM-7 (overall ITT population, October 2023 data cut-off) for the outcomes of OS, PFS and TTD. Parametric survival distributions were independently fitted to the observed data to extrapolate each of the survival outcomes over the modelled lifetime horizon. Table 31 in the CS summarises the company's base-case extrapolation approach and alternative scenarios for PFS, OS and TTD. The company states that parametric survival modelling used to extrapolate DREAMM-7 trial data followed the steps outlined in NICE Decision Support Unit (DSU) technical support document (TSD) 14:[57]

- Fitting of six standard parametric distributions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) to KM data from the trial.
- Assessment of goodness-of-fit for each parametric distribution based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
- Appropriateness of using parametric distributions justified by assessment of the (i) proportional hazards (PH) assumption based on examination of log cumulative hazard plots, Schoenfeld residual plots, and empiric hazards over time; and (ii) assessment of the constant acceleration factor (AF) assumption through quantile-quantile predicted survival time plots.

- Validation of clinical plausibility and visual goodness of fit of the long-term extrapolations by three UK external clinical experts, from whom BVd and DVd at 5, 10, and 15 year landmarks had been previously elicited.

The effectiveness of hKd and SVd for the outcomes of OS and PFS were based on the NMAs reported in the CS, where HRs were derived for the comparison of these treatments with DVd (see Section 3.4). In the company's base case analysis, the HRs were applied to the extrapolated DVd survival curves to obtain extrapolated long-term survival outcomes for the non-trial comparators. The company considered the DVd extrapolation curve to be the most appropriate survival baseline because *"the DREAMM-7 trial…is a pivotal registrational phase 3 study directly comparing BVd to DVd. DVd is the current standard of care at 2L in the NICE pathway for patients who are unsuitable for lenalidomide, and it is therefore the most relevant comparator for this appraisal."* The company also highlighted that DREAMM-7 allowed establishing indirect treatment comparisons (NMAs) versus the non-trial comparators (hKd and SVd) using Vd as an anchor. An alternative survival baseline informed by the BVd arm of DREAMM-7 was considered in a scenario analysis.

In the absence of TTD HRs for non-trial comparators from the NMA, HRs for hKd and SVd derived from the company's PFS NMA were used as as a proxy for the TTD HRs and applied to the extrapolated DVd TTD curve based on DREAMM-7 to estimate the TTD for hKd and SVd.

4.2.6.2 Progression free survival

The company' base case approach to extrapolate PFS estimates from DREAMM-7 for BVd and DVd consisted of fitting independent exponential models to observed KM data in each treatment arm (see Figures 28 and 29 of CS for visual fit of alternative parametric extrapolated curves for BVd and DVd, respectively).

The company justified the use of independently fitted models on the basis that the PH assumption (i.e., the assumption that hazard ratios between comparators are constant over time) might not conclusively hold for PFS. The company considered that the Schoenfeld plot assessment (see Figure 8, Appendix O) indicated that the PH hypothesis cannot be rejected. Furthermore, the relationship between Schoenfeld residuals and time was also not statistically significant [p-value = 0.98]). However, the log cumulative hazard plots (see Figure 7) crossed at some time points, suggesting, according to the company, a violation of the PH assumption. The company also noted that the empiric hazard plot suggests a change in the hazards around 26 months (see Figure 8). Thus, the company considered that there was uncertainty on whether the PH assumption is plausible, and preferred to fit independent parametric distributions to extrapolate the PFS for BVd and DVd.

Figure 7 BVd and DVd PFS log-cumulative hazard plot (Figure 7, Appendix O)

Figure 8 BVd and DVd empiric PFS hazard plot (Figure 9, Appendix O)

The company considered that there is good agreement between statistical fit and clinical opinion on the long-term predictions of the preferred extrapolation models for both trial treatments (with independent exponential distributions). Statistical measures of goodness of fit and long-term PFS predictions for the different extrapolation models are reported in Tables 33 and 34 of the CS for BVd

and DVd, respectively. The long-term fit of different extrapolation models is illustrated in Figure 9 and Figure 10 for BVd and DVd, respectively.

Figure 9 Long-term PFS parametric extrapolations and KM - BVd (Figure 28, CS)

Figure 10 Long-term OS parametric extrapolations and KM - DVd (Figure 29, CS)

PFS curves for the non-trial comparators were derived by using the extrapolated PFS curve for DVd and applying the PFS HRs for each comparator vs. DVd from the company's original NMA for PFS in the CS (see Section 3.4.4). This approach implicitly assumes that there are proportional PFS hazards over time between DVd and the non-trial comparators. At the clarification stage, the company presented updated results for their NMAs (see Section 3.4.4, CRD), which were not implemented in

the economic model for the ITT population. The EAG was not able to fully reproduce the company's PFS NMA updated results, but differences between the NMAs results replicated by the EAG using the company's code and evidence were marginal.

In addition to testing alternative parametric distributions in scenario analyses, the company also explored scenarios assuming proportional PFS hazards would hold between DVd and BVd. These scenarios modelled the following alternative PFS extrapolations:

i. BVd PFS extrapolated using the HR for BVd vs. DVd from the DREAMM-7 trial applied to DVd PFS baseline;
ii. DVd PFS extrapolated using the HR for DVd vs. BVd from the DREAMM-7 trial applied to BVd PFS baseline.

The company's base-case cost-effectiveness estimates were robust to the scenario analyses assuming proportional hazards between DVd and BVd.

Points for critique

The EAG agrees with the company that the PH assumption cannot be ruled out for the PFS of DVd and BVd. Further to the company's interpretation of the PH assumption assessment, the EAG notes that, although there is crossing between the log cumulative hazard plots (see Figure 7), this occurs mostly in the initial time points, with the lines looking parallel for the majority of the follow-up. The company highlighted the change in hazards around 26 months in the empiric hazard plot (see Figure 8), as indicative that the PH assumption may not hold. However, the empiric hazards for BVd and DVd appear to be parallel up to 26 months. It is unclear whether the empiric hazard plot turning point at 26 months indicates a true change in the hazards or is just an artifact driven by low numbers at risk at longer follow-ups.

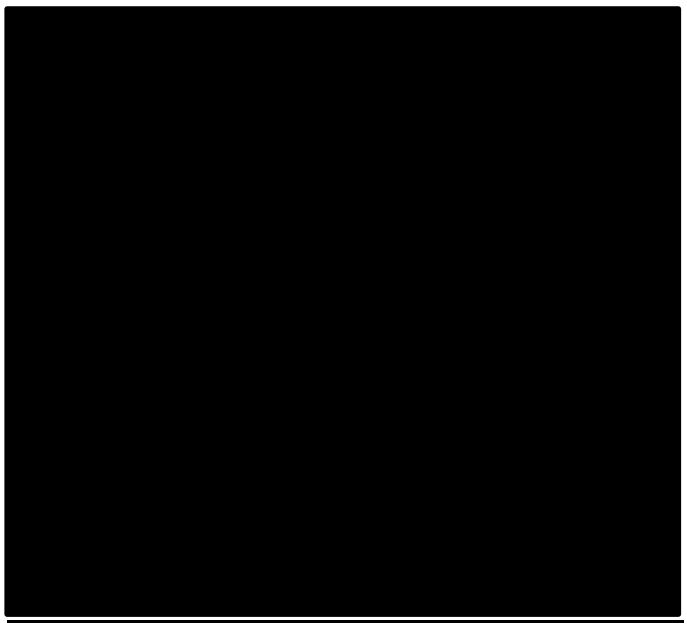
Given the relative maturity of the observed PFS estimates in DREAMM-7, clinical opinion and robustness of results to scenario analyses (i) and (ii), the EAG is reassured that the company's approach to modelling PFS for BVd and DVd with independently fitted models is likely to be reasonable. However, there remains a potential case that the PH assumption is also reasonable between BVd and DVd.

4.2.6.3 Overall survival

The company' base case approach to extrapolate OS estimates from DREAMM-7 trial for BVd and DVd consisted of fitting independent parametric models to observed data in each treatment arm and selecting the Weibull distribution as the best fitted model. Similarly, to the company's extrapolation approach for PFS, the fitting of independent parametric extrapolation models to observed data was due to concerns that the PH assumption might not hold. The company noted that the curves in the log-

cumulative hazard plots crossed at multiple points (see Figure 11) and the empiric hazard plot indicates that the hazards are not constant over time (see Figure 13, Appendix O), which were indicative that the PH assumption might not hold. However, the company also recognised that the other diagnostic tests did not rule out the PH assumption (Schoenfeld residuals test and plot; see Figure 12, Appendix O).

Figure 11 BVd and DVd log-cumulative hazard plot (Figure 11, Appendix O)



As highlighted in Section 3.2.6, the observed OS from the DREAMM-7 trial is immature, with median survival not yet observed over the trial follow-up (maximum [redacted] months), and the BVd arm data being less mature (22% events) than the DVd arm (35% events). The long-term extrapolations with standard parametric models informed by these data, are, thus, considered highly uncertain both by the company and the EAG. Since the immaturity of the OS data is one of the key issues with the CS and is a key driver for the cost-effectiveness estimates, the EAG discusses in detail below how the different extrapolation approaches taken by the company were used to explore and reduce the uncertainty in the OS extrapolations for the treatments under comparison.

Overall survival of DVd

For the extrapolation of OS for DVd in the company's base-case analysis, the company did not use the standard parametric survival extrapolation based on the follow-up data of the trial. Instead, the company used a Bayesian approach to provide an informative prior distribution for the shape parameter of the OS curve estimated from an external source. The source of external evidence was from the DVd arm of the CASTOR trial (which had 59% events over a maximum follow-up of 79.8 month).[22] The informative prior distribution was combined with the less mature DREAMM-7 data to inform the DVd OS extrapolation in the company's base-case analysis. The approach taken was based on the informative Bayesian priors method previously applied by Soikkeli et al., 2019,[58] and Palmer et

al., 2023[59] in MM. The company justified their preference for the DREAMM-7 DVd OS extrapolation with informative priors over uninformed extrapolations (i.e. standard parametric survival extrapolations) on the basis that this allowed suitable and transferable external evidence with longer follow-up to increase the robustness of the OS estimates for DVd.

The steps taken to implement this approach were described by the company as follows:

1. Published OS KM for the DVd arm of the CASTOR trial were digitized to reconstruct OS pseudo-IPD (using the Guyot et al. 2012 algorithm[60] and considering the reported number of patients at risk at each time interval).
2. Standard parametric survival models were fitted to the reconstructed OS pseudo-IPD (Weibull, Gompertz, log-normal, log-logistic, Gamma and generalised Gamma). The exponential model was not considered as it does not have a shape parameter, and the Gompertz was excluded due to clinically infeasible long-term projections resulting from a negative shape parameter.
3. Bayesian parametric survival models were fitted to the OS IPD for the DVd arm in the DREAMM-7 trial using informative priors for the shape parameters that were defined based on the results of the fitted models in Step 2. The Bayesian informative prior analyses assume that the shape parameter of the Weibull, log-logistic, Gamma and generalised Gamma distribution follow a Gamma distribution with parameters a and b ($G(a,b)$), while the shape of the log-normal distribution is assumed to follow a uniform distribution ($Uniform(a,b)$). The package specifies a and b, so that the mean and variance of the $Gamma(a,b)$ distribution or $Uniform(a,b)$ distribution used as priors, matched the mean and variance of the shape parameter that was estimated using standard parametric survival analysis in the CASTOR study (Step 2).

By using the informative prior approach for the shape parameter, the company is implicitly assuming that evidence on the scale parameter of the OS DVd extrapolation is transferable across the CASTOR and DREAMM-7 trials, and thus, that the rate of change of the hazards for DVd is transferable across these data sources. Assuming transferability of the scale parameter is in line with how this methodology has been previously applied in MM.[58, 59]

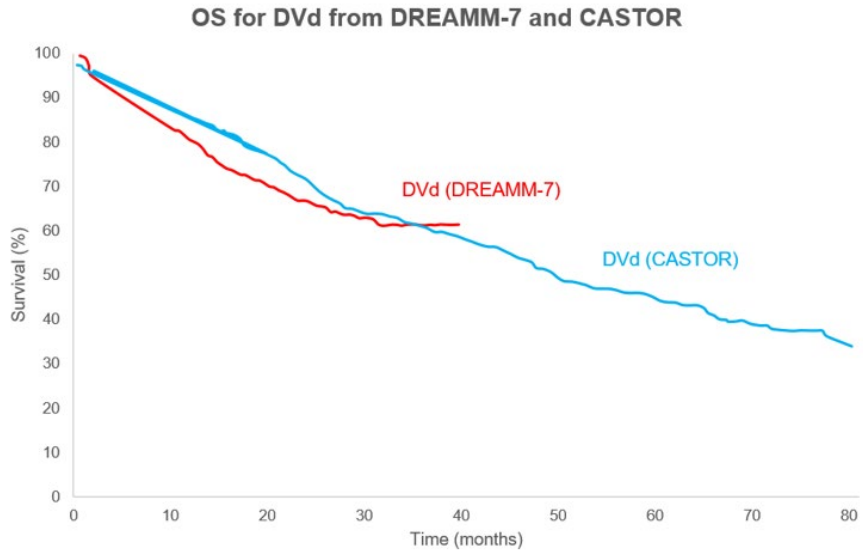
The company conducted a feasibility study to assess the appropriateness of assuming exchangeability of the shape parameter of OS between the CASTOR and DREAMM-7 trials specifically. In this study, the company compared CASTOR and DREAMM-7 based on four main domains: study design, eligibility criteria, patient characteristics, and the definition of OS. CASTOR and DREAMM-7 are both phase III, randomised, open-label trials that share a similar design. Compared to DREAMM-7 (conducted between 2020 and 2023) CASTOR was an older trial, conducted between 2014-2016, and

changes in clinical practice between the two studies may have resulted in differences between subsequent treatments. Another notable difference between the two studies is that while patients in the DVd arm of DREAMM-7 were not allowed to crossover after disease progression, patients in the DVd arm of CASTOR were allowed to switch to daratumumab monotherapy after disease progression or after a washout period if they were already receiving subsequent therapy after disease progression. The company did not think that this would influence the results in the DVd treatment arm. The treatment dose and schedule for DVd was similar in both studies.

Patient eligibility criteria was similar in both studies. Patients in the CASTOR study were required to have achieved partial response, or better, to at least one prior treatment in addition to having documented disease progression (Table 13). Additionally, patients in the CASTOR study were excluded if they were refractory to any PIs (such as ixazomib and carfilzomib) as well as bortezomib or if they had any prior daratumumab/anti-CD38 exposure, irrespective of whether they were refractory or not. Patient demographic baseline characteristics were similar between DREAMM-7 and CASTOR (Appendix Table 49). Both studies were also comparable in the number of prior lines of therapy patients had received (Appendix Table 50). However, more patients in the DREAMM-7 trial had prior exposure to bortezomib (86%) compared to CASTOR (65%).

As CASTOR had a similar trial design as DREAMM-7 with a longer follow-up, the company concluded that the assumption that the shape parameter is exchangeable for both studies was valid. Whilst it is hard to judge which study characteristics would influence the shape parameter of the parametric distributions fitted to the DVd OS data (and whether they would be the same for each distribution), the study designs and populations are broadly similar although differences in prior and subsequent therapies between CASTOR and DREAMM-7 could influence the shape of the OS distribution. At clarification stage, the company also contrasted graphically the OS KM curves for the DVd arms of the DREAMM-7 and CASTOR trials, as illustrated in Figure 12. The OS trajectory for DVd appears fairly similar across the two trials, although the OS curve from the CASTOR trial seems slightly more optimistic than DREAMM-7 up to 40 months of follow-up.

Figure 12 OS Kaplan-Meier curves for DVd (Figure 8, response to clarification question B5)



With CASTOR informative priors used to inform the shape parameter for OS, the company considered that the Weibull distribution (see Figure 13) provided the most appropriate extrapolation for DVd OS on the basis of an assessment of long-term predictions, diagnostic plots (see Section O.2.2., Appendix O), and clinical expert opinion. The Weibull distribution was also the best fitted distribution to the CASTOR trial pseudo-IPD. Table 19 summarises the long-term observed and predicted OS over time for DVd across different sources, including clinical expert opinion. the Weibull extrapolation with CASTOR trial informative prior appears to be less optimistic than the corresponding standard parametric extrapolation with Weibull beyond 5 years, although the differences are small over the time horizon. Importantly, when comparing the differences in long-term survival predictions between the different extrapolation distributions, there appears to be less variation across the models with informative priors compared to standard parametric models. This suggests a reduction in the uncertainty of the long-term survival predictions with the informative prior models.

Figure 13 Long-term OS parametric extrapolations and KM for DVd using CASTOR informative priors for the shape parameter of OS (Figure 31, CS)

Table 19 Long-term observed and predicted OS over time - DVd (adapted from Table 37, CS and Table 4, Appendix O)

Source of survival predictions	Informative priors	Median	Years					
		Months	1	2	5	10	15	20
KM DREAMM-7	NA	NR	[redacted]	[redacted]	-	-	-	-
KM CASTOR	NA	49.6	NR	NR	NR	NR	-	-
Expert opinion	NA	NA	NR	NR	45%	28%	8%	NR
Weibull (BC)	Yes, DVd arm of CASTOR trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BC, base-case; NA, not applicable; NR, not reported

The company did not explore other potential sources of evidence to provide an external baseline for OS, such as the use of NCRAS data, which was used by the company to emphasise the prognostic relevance of disease refractory to lenalidomide refractoriness at 2L treatment in the UK (see Section 2.2.3). The company justified this decision based on the limitations of the NCRAS data [redacted][12]

Overall survival of BVd

For BVd, there was no suitable source of external data with more mature OS data, so the informative prior approach was not feasible. The company's preferred extrapolation model for BVd was an independently fitted Weibull distribution. The choice of Weibull was justified by the company as being the least optimistic curve of those with adequate statistical fit (i.e., lognormal, Gompertz, log-logistic, generalised gamma and Weibull). Clinical advice to the company stated that the extrapolations with adequate statistical fit, including the company's preferred distribution, were overly optimistic in the long-term. The company's clinical experts considered that the exponential model provided the most plausible predictions at 5, 10 and 15 years (followed by the Weibull).

Another reason why the company preferred the Weibull distribution to extrapolate BVd OS in their base-case analysis, was due to the fit of the exponential distribution to the observed OS data in the initial part of follow-up (see Figure 14). The company stated that exponential distribution did not align with the early positive trend seen in the BVd OS KM and the exponential extrapolation would suggest a severe drop off in survival over the longer term.

Figure 14 Long-term OS parametric extrapolations and KM - BVd (Figure 30, CS)

Table 20 Long-term observed and predicted OS over time - BVd (adapted from Table 36, CS)

Source of survival predictions	Median	Years					
	Months	1	2	5	10	15	20
KM DREAMM-7	NR	[redacted]	[redacted]	-	-	-	-
Expert opinion	NA	NR	NR	NR	NR	NR	NR
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BC, base-case; IPCW, inverse-probability-of-censoring weighting; NA, not applicable; NR, not reported

The EAG notes that there is considerable uncertainty in the BVd OS long-term extrapolations across the different distributions. The OS projections for BVd beyond 5 years are more optimistic with the Weibull distribution compared to the exponential distribution, with the difference between curves widening considerably over time. The Weibull and exponential distributions predict that [redacted] and [redacted] of individuals would still be still alive at 20 years, respectively. Furthermore, the differences in the long-term predictions across different extrapolation models is greater for BVd compared to DVd (particularly, when considered the DVd extrapolation models with informative priors).

In order to overcome the concerns about the immature OS data from DREAMM-7, the company also considered an alternative approach that involved modelling OS by relying solely on the more mature PFS data as a surrogate for OS. In the original economic model (before EAG points for clarification) the company applied the surrogacy relationship between median PFS and OS based on 13 studies in RRMM at 2L+ lines of treatment (identified through a systematic literature review on the relationship between intermediate and final outcomes in RRMM[61]) to predict OS estimates for all treatments under comparison based on their modelled PFS outcomes. In the company's original version of the electronic model, the surrogacy relationship was estimated as a simple weighted average of the absolute median PFS:OS ratio across each treatment arm of the included studies, suggesting that 1 additional month in PFS would translate into 3.42 months in OS.

In the model, the estimated OS curves are derived based on the surrogacy relationship between median PFS and median OS for each treatment using the following steps:

1. Estimation of the median PFS from the model based on the PFS extrapolation curve (adjusted for general population mortality);

2. Estimation of the median OS by multiplying the predicted median PFS by the absolute median PFS: median OS surrogacy relationship (i.e., ratio of 3.42 months in company's original model);
3. Calculation of the HR for OS vs. PFS that needs to be applied to the PFS curve in order to obtain an OS curve with the corresponding estimated median OS ;
4. The derived HR for OS vs. PFS was then applied to the PFS curve in the model to derive the corresponding OS curve.

The company conducted scenario analyses applying the derived HR for OS vs. PFS to (i) the DVd PFS baseline and the (ii) BVd PFS baseline, which resulted in more conservative cost-effectiveness results compared to the company's base case analyses for the BVd vs. SVd and BVd vs. DVd comparisons (22.9- 24.7% and 14% increase on the incremental cost-effectiveness ratio [ICER], respectively).

The documentation submitted by the company also included an assessment of the surrogacy relationships between multiple potential surrogate (PFS, ORR, DoR, PFS-2, or minimal residual disease) and final endpoints (PFS or OS) in 2L+ RRMM, which was updated with additional studies included at the clarification stage.[61, 62] The company's surrogacy assessment report included a systematic review of RCTs and assessed surrogacy relationships using several statistical methods, including Spearman's correlation, Weighted Least Squares (WLS), fixed and random effect meta-regression, and Bayesian bivariate meta-analysis. The report also included a targeted review of published studies investigating surrogacy relationships in RRMM. The surrogacy assessment report concluded that the PFS median performed well as a surrogate for OS median in the 2L+ population. Despite using more sophisticated analytic methods to estimate the surrogacy relationship between PFS and OS in the report, the company chose to use the simple weighted average of PFS:OS absolute median ratios in their scenario analysis. At the EAG's request during the clarification stage, the company updated the electronic version of the model to allow using estimates of alternative surrogacy relationships derived from the company's report. Although the EAG did not specify the surrogacy relationship metrics to use (e.g. absolute medians vs. HRs) that should be included in the model, the company implemented estimates of the median absolute median PFS:OS ratio for the treatments under comparison using WLS regression and fixed and random effect meta-regression only. The median PFS:OS ratio estimated by these analyses are highlighted in grey in Table 21. (all values in this table reflect the update report submitted at the clarification stage), alongside estimates from the targeted literature review and one study identified by the EAG. The median PFS:OS ratios estimated by the company using a regression framework suggested that one month increase in median PFS is associated with [redacted] increase in median OS; this is within the range reported in the published literature and less optimistic than the company's simple weighted average of absolute median PFS:OS ratios (3.42 months). The surrogacy absolute median PFS:OS

estimates from the company's surrogacy report were implemented in the model using the same steps as described for the simple weighted average approach.

Table 21 Key surrogacy relationships in the company's surrogacy assessment report

	Population	Estimation method	Median PFS:OS ratio
Felix et al. 2013[*]	MM	2 stage GMM with IV	2.45 (95% CI :1.71; 3.20)[**]
Dimopoulos et al. 2017	RRMM	2 stage regression with IV	3.10 (95% CI: 2.20; 4.00)[***]
Daniele et al. 2023	RRMM	Frequentist MA	1.12 (95% CI: 0.83; 1.40)[+]
Dimopoulos et al. 2024	RRMM	WLS	1.72 (95% CI: 1.26; 2.17)[***]
Company's surrogacy assessment report	RRMM	WLS	[redacted]
		Meta-regression	[redacted]

[*]This study considered the relationship between time-dependent endpoints (PFS, event-free survival and time to progression) and OS, thus values on the table refer to this relationship unless otherwise stated. [**]Adjusted for demographics, patient type, surrogate endpoint type, publication year, and MM treatments, with censored observations. [***]Adjusted for age, sex, and publication year. [+] Adjusted for age, relapsed vs refractory, and study year.

Abbreviations: CI, confidence interval; CrI, credibility interval; FE, fixed effects; GMM, generalised method of moments; IV, instrumental variable; MA, meta-analysis; MM, multiple myeloma; NA, not applicable; NR, not reported; RE, random effects; RR, relapsed refractory; SE, standard error; WLS, weighted least-squares regression

Overall survival of hKd and SVd

The OS curves for the non-trial comparators were derived by using the extrapolated OS curve for DVd and applying the OS HRs for each comparator vs. DVd from the company's original NMA in the CS (see Section 3.4.4). As for PFS (see Section 4.2.6.2), this approach implicitly assumes that there are proportional hazards over time between DVd and the non-trial comparators for OS. The OS HRs derived from the original company's OS NMA and applied in the model are reported in Table 38 of the CS. Similarly to scenario analyses performed on the PFS extrapolation, the company's model is set up to run scenario analyses assuming proportional hazards for all treatments and using either the DVd or BVD OS extrapolation as baseline. The company did not present cost-effectiveness results for these scenario analyses. At the clarification stage, the company presented updated results for their NMAs (see Section 3.4.4), which were not implemented in the economic model for the ITT population. The EAG, identified longer follow-up OS data for the LEPUS trial[35] (see Section 3.4.4), which was used to inform the EAG's updated OS NMA. The updated EAG NMAs results were not incorporated into the following sections, but the EAG considers these in Section 6.

Points for critique

The EAG considers that the issue of greatest concern affecting the treatment effectiveness of BVd compared to the other treatments being evaluated is the immaturity of the DREAMM-7 OS data, resulting in uncertain long-term OS predictions (particularly for BVd).

The company's approach to increase the robustness of the DVd OS extrapolations by incorporating more mature external trial evidence appears appropriate to the EAG. The assumption of transferability of the shape parameters between the CASTOR and DREAMM-7 trials, which is key to the use of the informative priors approach, is supported by the company's feasibility assessment and the methodology that has been previously applied in MM.[58, 59] The EAG highlighted above that it is difficult to judge which study characteristics would influence the shape parameter of the parametric distributions fitted to the DVd OS data (and whether they would be the same for each distribution), but the study designs and populations are broadly similar. Importantly, the DVd OS predictions with the Weibull and the informative prior on the shape parameter appear to be consistent with the observed data in the CASTOR and DREAMM-7 trial, and, were considered clinically valid by the company's experts. The EAG is also reassured that the DVd OS extrapolation in the company's base-case provides an appropriate survival baseline for comparison with treatments for which the PH assumption holds.

As highlighted above, the EAG considers that the company's preferred approach using the BVd OS Weibull extrapolation results in overly optimistic OS predictions for this treatment, given clinical advice provided to the company which showed preference for the more conservative exponential extrapolation. Importantly, the EAG is concerned that the company's BVd OS extrapolation may overestimate the treatment effect of BVd compared to DVd. The use of independent Weibull distributions to extrapolate the OS for BVd vs. DVd in the company's base-case suggests that the treatment effect increases over time. This is illustrated in Figure 15, where the EAG plots the implied OS HR for BVd vs. DVd over time with the company's base-case extrapolations. The company's preferred extrapolations suggest a time decreasing OS HR (i.e., an increasing treatment effect), which goes below the empirically estimated HR for BVd vs. DVd (HR=0.57, illustrated as the horizontal dotted line in Figure 15) at approximately 5 months and then lies considerably below the empirical HR for the majority of the time horizon. The EAG considers that the assumption of a time increasing treatment effect lacks clinical rationale and is likely to overestimate the OS gain for BVd. While the empirical hazard rates observed for these treatments in DREAMM-7 (see Figure 16) suggest that hazards may not be constant, it does not appear to support the assumption that the HR for BVd vs, DVd would increase over time. Thus, the EAG considers that the empiric hazard plot assessment does not support the use of independent Weibull distributions to extrapolate OS for BVd and DVd.

The EAG also plotted in Figure 15 the implied OS HR for BVd vs. DVd over time when an exponential distribution is used to extrapolate the BVd OS (while maintaining the company's preferred extrapolation for DVd). These set of extrapolations also suggest time varying hazard ratios but, in contrast with company's preferred extrapolations for BVD and DVd, the implied hazard is increasing in time (i.e. a decreasing treatment effect) crossing the empirical hazard line at approximately 34 months and then remaining steadily above this line.

Figure 15 Time varying OS HR for BVd vs. DVd* implied by alternative extrapolations

*Not adjusted for general population mortality

Figure 16 BVd and DVd empiric OS hazard plot (Figure 13, Appendix O)

Abbreviations: BOR, bortezomib; DARA, daratumumab; DEX, dexamethasone; [redacted], belamaf; OS, overall survival.

The EAG considers that the extrapolation of BVd OS with an independent exponential distribution is more plausible than with an independent Weibull based on the assessment of the implied hazards over time and the empirical HR from the DREAMM-7 trial. The independent exponential OS extrapolation was also considered the most clinically plausible according to the company's experts.

Given the assessment of the PH assumption for the OS of BVd and DVd and the immaturity of the DREAMM-7 trial, the EAG considers that the PH assumption cannot be excluded. The company also recognises that there is uncertainty on whether this assumption holds due to conflicting results across different statistical tests. Therefore, the EAG considers that extrapolations assuming that PH holds should not be excluded from consideration, particularly for the OS extrapolation obtained by applying the empirical HR for BVd vs. DVd from DREAMM-7 (HR=0.57; 95% CI: 0.40, 0.80) to the DVd OS curve baseline. This extrapolation is henceforth referred to as PH Weibull, for simplicity.

In Figure 17, the EAG shows the alternative OS extrapolations for BVd alongside the company's preferred base- case OS curves for BVd and DVd. The BVd OS extrapolation with the independent exponential distribution results in the most conservative OS predictions, while the company's Weibull extrapolation provides the most optimistic predictions of the alternatives explored in the graph. The BVd PH Weibull has a similar fit to the BVd OS exponential extrapolation up to [redacted]). Beyond this time point, the curves separate with the potential hazards Weibull curve being more optimistic than the independent exponential curve. The long-term OS predictions with the PH Weibull curve are still less optimistic (approximately [redacted] alive at 20 years) than the company's preferred extrapolation for BVd, which predicts approximately [redacted] alive at 20 years). By building in dependency between the BVd and DVd OS extrapolations, this approach allows incorporation of external evidence from the CASTOR trial in the BVd OS curve, which will also contribute to reducing some of the uncertainty in the extrapolation for BVd (provided that PH assumption holds). The EAG believes that both the independent exponential and PH Weibull BVd OS extrapolations allow for more clinically plausible OS predictions over time, even if the initial visual fit to the observed OS data from DREAMM-7 is not as good as for the independent Weibull model. Furthermore, clinical advice to the EAG suggested the independent exponential BVd OS extrapolation is the most clinically plausible.

Figure 17 Long-term predictions for OS with alternative extrapolation approaches (extracted from the model)

Given the considerable uncertainty in the BVd OS extrapolation, the EAG considers that it is appropriate to consider in scenario analyses the OS estimates informed by the PFS:OS surrogacy relationship as an alternative to using immature DREAMM-7 OS data. However, the evidence provided by the median PFS:OS surrogacy relationship has a number of limitations. First, the majority of the company's surrogacy analyses focus on the 2L+ RRMM population and not on the 2L-only and refractory to prior lenalidomide subpopulation proposed by the company. While the population of the surrogacy assessment matches the ITT population of the DREAMM-7 trial, which is used to inform the company's base-case OS analysis, using the PFS:OS surrogacy relationship as a source of OS data requires stronger assumptions about the exchangeability of the data across populations (i.e., an assumption that the relationship between OS and PFS is maintained across lines of treatment and different classes of treatments). Second, the company's simple weighted average surrogacy approach does not allow capturing uncertainty in the surrogacy relationship. This limitation can be overcome by using regression and meta-analytic approaches to estimate the surrogacy relationship that the company reports in their surrogacy assessment report. A third limitation of the surrogacy estimates in the company's model is that these were estimated based on the surrogacy between absolute median PFS and OS. The NICE DSU TSD 20[63] recommends that surrogacy relationships are established on relative treatment effects (i.e., treatment hazard ratios) using Bayesian bivariate meta-analysis of treatment effects on a surrogate and final outcome, as this allows for both the validation of a surrogate

endpoint and for making predictions of an unobserved treatment effect on the final clinical outcome from observed treatment effects on a surrogate endpoint. While the company's surrogacy assessment report presented one analysis of the surrogacy between PFS and OS HR using Bayesian bivariate meta-analysis this was not implemented in the economic model.

Despite the limitations noted above, the EAG considers that modelling the BVd OS based on the company's absolute median PFS:OS surrogacy estimate ([redacted]) derived by WLS may still be informative as a scenario analysis, given that this estimate is consistent with other published estimates (using the same analytic method; see Table 21). In Figure 18, the EAG plotted the OS BVd as estimated by assuming an absolute median PFS:OS ratio of [redacted] alongside the other alternative approaches to extrapolate OS based on observed DREAMM-7 trial data discussed above. The BVd OS modelled based on the absolute median PFS:OS surrogacy relationship is consistently more conservative than the BVd independent exponential and PH Weibull, but seems to follow a similar trend to the other curves. In Section 6, the EAG assesses the cost-effectiveness of BVd versus comparators in scenario analyses for the alternative BVd OS curves shown in Figure 18.

Figure 18 Long-term predictions for OS in the EAG scenarios (extracted from the model)

4.2.6.4 Treatment discontinuation

Using a similar approach to that used for PFS and OS, the company' base case extrapolated TTD estimates from the DREAMM-7 trial for BVd and DVd by fitting independent parametric models to observed data in each treatment arm (see Figures 32 and 33 of CS for visual fit of the alternative extrapolated models for BVd and DVd, respectively). The company's base-case analysis used

independent Weibull models to extrapolate TTD for BVd and DVd. These models were considered to be clinically plausible and consistent with previous NICE TAs. The Weibull distribution also showed good statistical fit based on AIC and BIC for the DVd treatment group, but not for BVd. In the BVd treatment group, goodness-of-fit was better for the extrapolation curves of lognormal, log-logistic and generalised gamma, but they were considered by the company to lack face validity due to crossing the PFS curve at around 10 years.

TTD data was not available for the non-trial comparators. The HRs for hKd and SVd derived from the company's PFS NMA were used as a proxy for the HRs for TTD and applied to the extrapolated DVd TTD curve to estimate TTD curves for hKd and SVd. In a scenario analysis, the company applied the assumption that TTD is equal to PFS for all treatments under comparison.

The EAG shows in Figure 19 the company's base-case TTD extrapolated curves for each treatment comparison alongside the respective PFS and OS curves. For all treatments except BVd, the TTD curve almost overlaps with the corresponding PFS curve, which suggests that individuals will spend less time in the PF-off treatment health state before transitioning to PD. For all treatments except BVd, the TTD curve almost overlaps with the corresponding PFS curve, which suggests that individuals will spend less time in the PF-off treatment health state before transitioning to PD. In contrast, the BVd TTD curve is considerably lower than the corresponding PFS curve, so individuals who are initially treated with BVd spend a considerable proportion of their time on PFS in the PF-off-treatment health state. Table 22 shows the QALY's accrued in the model in the PF health states.

Figure 19 Company base-case PFS, OS and TTD curves (extracted from the model)

Table 22 Disaggregated total discounted QALYs accrued in the model in the PF health states in the company's base-case analysis

	QALYs BVd	QALYs DVd	QALYs SVd	QALYs hKd
PF (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]
PF (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
% QALYs accrued in PF (off-treatment)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PF, progression free.

Points for critique

The EAG considers the company's extrapolation approach for TTD to be appropriate, as clinical advice to the EAG validated the assumption that individuals will remain untreated until progression once they discontinue the primary 2L treatment is clinically plausible.

4.2.7 Adverse events

The model includes 17 treatment specific grade 3 and above AEs, three of which are ocular AEs and only apply to BVd. The company includes grade 3+ adverse events experienced by at least 5% of the population in either the BVd or DVd arm of the DREAMM-7 trial. Incidence data for BVd and DVd are sourced from DREAMM-7, incidence for hKd and SVd are sourced from their respective RCTs as identified in the clinical SLR (Table 61 of the CS). Table 23 shows the AEs incidence rates applied in the company's model for each treatment.

Table 23 AEs incidence rates applied in the company's model

	Incidence			
Adverse events	**BVd**	**hKd**	**SVd**	**DVd**
Neutropenia	[redacted]	0.07	0.19	[redacted]
Anaemia	[redacted]	0.16	0.04	[redacted]
Thrombocytopenia	[redacted]	0.16	0.31	[redacted]
Lymphopenia	[redacted]	0.07	0.00	[redacted]
Pneumonia	[redacted]	0.09	0.00	[redacted]
Peripheral neuropathy	[redacted]	0.01	0.00	[redacted]
Hypertension	[redacted]	0.18	0.00	[redacted]
Leukopenia	[redacted]	0.00	0.00	[redacted]
Nausea	[redacted]	0.01	0.00	[redacted]
Diarrhoea	[redacted]	0.01	0.04	[redacted]
Fatigue	[redacted]	0.05	0.23	[redacted]
Dyspnoea	[redacted]	0.03	0.00	[redacted]
Back pain	[redacted]	0.01	0.00	[redacted]
Hypokalaemia	[redacted]	0.03	0.00	[redacted]

Keratopathy	[redacted]	-	-	-
Blurred vision	[redacted]	-	-	-
Dry eyes	[redacted]	-	-	-

The AEs included in the model have associated cost and HRQoL decrements, which are reported in Sections 4.2.9.6 and 4.2.8.3, respectively. The company apply a one-off cost and HRQoL decrement in the first model cycle for AEs, which assumes that they occur shortly after treatment initiation and only require acute care. The company does not provide any detail on the duration of AEs.

Points for critique

Ocular adverse events are very common for BVd patients. In the CS the company states that the number of patients who experienced a keratopathy event of grade 3 or more for BVd patients in the DREAMM-trial is [redacted] (Table 63 of the CS). However, in the company's model the probability of experiencing a keratopathy event is just [redacted], blurred vision [redacted], and dry eyes [redacted], all of which were applied only in the first model cycle (Appendix F, table 9). In the DREAMM-7 clinical study report (page 116) [redacted], which does not reflect the true incidence, as it was only reported as an AE prior to the institution of Protocol Amendment 1. Following Protocol Amendment 1, investigators were not required to report corneal exam findings as AEs.

In addition, it may not be reasonable to apply the AEs, particularly the ocular events, as a one-off event in the first model cycle. The CS states that for the first occurrence of keratopathy events of grade 2 or more, median time to onset was [redacted] days, and median duration was [redacted] (page 89 CS); the equivalent figures are not reported for grade 3+. The DREAMM-7 clinical report [19] [redacted] (Table 3.0062). It is currently unclear how the company have taken account of the length or frequency of ocular adverse events.

4.2.8 Health-related quality of life

4.2.8.1 Summary of company's submission

The CS considers HRQoL relating to (i) health state utility values, stratified by treatment; and (ii) disutilities associated with AEs. Health state utility values are applied to time spent in health states in the model in order to calculate quality-adjusted life years (QALYs) that reflect the improvement in health-related quality of life (HRQoL) associated with treatment.

The company conducted a SLR to identify studies reporting HRQoL for patients with RRMM who have received at least one prior line of treatment (see Appendix H of CS for details about the

systematic literature review, including methodology, inclusion criteria and results). Out of the 146 studies identified in the SLR, three were selected to inform HRQoL for either disutilities associated with AEs or health state utility values in scenario analysis. The EAG appraisal for the identification of health-related quality of life evidence is presented in Appendix AA3.

The model incorporates a reduction in HRQoL due to aging by applying age-adjustment factors to health state utilities using the general population EQ-5D weights published by Hernández Alava et al. 2022.[64]

Health-related quality of life decrements are applied to as a one-off at the start of the model to account for patients experiencing AEs whilst on treatment.

4.2.8.2 Health state utilities

The base case treatment specific health state utility values for BVd and DVd used in the economic model are derived using the UK value set [65] and EQ-5D-3L data from the ITT population of the DREAMM-7 trial, collected over 32 time points. EQ-5D data was collected at baseline and then every 6 weeks until the end of the trial. In total there were [redacted] observations collected from patients in the progression free health state and [redacted] observations in the progressed disease state, while missing data was not reported and the company states that no imputation of missing data was performed. The data was analysed using mixed-effects linear regression, where utility values were estimated by exponentiating the least squares mean estimates for the relevant health state. Details of the regression method and results are presented in response to the EAG's clarification question B9.

The company uses a differential utility value for the progression-free health state for BVd compared to the other comparators (while no utility differences were considered between PF-on treatment and PF-off treatment) as the DREAMM-7 data supported a statistically significant difference for BVd and DVd. A common utility value for the progressed disease state was applied in the model based on DREAMM-7. For hKd and SVd, the utility values were assumed to be the same as DVd. Table 24 reports the health state utility values used in the company's base case analysis.

Table 24 Health state utility values used in the company's base case analysis

Health state	Treatment	Utility		Source
		Mean	Standard Error	
PF	BVd	[redacted]	[redacted]	DREAMM-7
	DVd	[redacted]	[redacted]	DREAMM-7
	hKd	[redacted]	[redacted]	Assumed same as DVd
	SVd	[redacted]	[redacted]	Assumed same as DVd
PD	All	[redacted]	[redacted]	DREAMM-7

Points for critique

Progression free health state utility value

Utility values for the PF health state in the CS are estimated by treatment arm. Previous submissions have also taken this approach [15, 17, 51]) and the evidence from DREAMM-7 appears to support this approach for BVd and DVd given a statistically significant difference in PFS utilities. However, there is no evidence to support differential utility between BVd and SVd or hKd for progression free utility.

Utility values in the CS are not explicitly conditional online of therapy. In TA974[37] the EAG and committee requested revised 2L- and 3L-specific utilities, for both the PF and PD state, citing Hatswell et al. 2019,[1], a systematic review and meta-analysis for multiple myeloma combining registry data and 13 published studies to estimate utility values for each line of therapy. Hatswell et al. 2019[1], which indicate different utilities dependent upon line of therapy with utility values decreasing with each subsequent therapy (Table 25). The EAG also cited clinical expert advice that given length of time on treatment and toxicity of treatments, HRQoL is likely to reduce for each subsequent line of therapy. The EAG requested additional analysis from the company (question B9d) including line of therapy as an additional interaction term in their estimation of utilities; however, the company's response indicated that they did not have time to complete this analysis.

Given the evidence available the EAG applying PFS utilities by treatment rather not by line of therapy is appropriate for BVd and DVd. However, the company has not presented empirical evidence to justify the assumption that SVd or hKd to have differential utilities in PF from BVd. Therefore, the EAG considers this to be an area of uncertainty and explores alternative assumptions in Section 6.

Progressed disease health state utility value

The EAG notes that the utility value for the progressed disease health state is higher than the progression-free health state utility value for all three comparator treatments, which implies that there is a utility increase of 0.003 upon progression of the disease. for DVd, SVd and hKd. The increase in the PD health state utility value is clinically implausible according to clinical advice received by the EAG. In addition, this difference ([redacted]) is substantially smaller than the difference in utility between BVd and DVd in the progression free health state ([redacted]) (Table 24).

For BVd the decrement in utility for progressive disease, relative to progression free in the base case is [redacted]. This is lower than all previous estimates used in submissions which range from 0.035 to 0.122 (Table 25). In the scenario analysis the company use utilities from previous submissions (TA897 and TA695) with decrements relating to the progression of disease of 0.055 and 0.072.

In a submission related to RR MM[37] a scenario analysis used evidence from Hatswell et al., 2019. [1] They used the estimates for the progression free health state utility of 2L patients (0.62) and the

progressed disease utility as the mean utility of 3L, 4L and 5L+ patients (0.55), implying a progressive disease decrement of 0.070. health state utility decrement of 0.070. The EAG considers the estimates reported in Hatswell et al., 2019, [1] to be more representative of the disutility associated with moving to a subsequent line of therapy than those estimated in the DREAMM-7 trial. The EAG do not expect the treatment specific uplift in utility, seen in the progression free state, to be sustained in the progressed disease state and prefer a single health state utility for progressive disease based on the DVd PFS utility minus the decrement.

Table 25 Health state utilities for PF and PD in previous submissions for RR MM

	Line of treatment	PF	PD	Progression decrement	Data source	Notes
Company submission						
Base case in CS	2L	[redacted]	[redacted]	[redacted]	DREAMM-7 trial	Utilities estimated directly from EQ-5D-3L data.
Previous submissions or evidence for utilities in RR MM patients*						
Selinexor with bortezomib and dexamethasone (TA974 2024) [37]baseline scenario	2L & 3L 2L 3L	0.697 0.706 0.694	0.660 0.668 0.659	0.037 0.038 0.035	BOSTON trial	Utilities were taken from EQ-5D-5L and mapped to EQ-5D-3L using the Hernandez-Alava mapping algorithm. A backwards stepwise regression approach was used to determine the final mixed effect regression model. The final list of covariates included treatment arm (Vd), age, baseline ECOG, baseline EQ-5D-3L and progression status. Of these covariates, treatment arm was found to have a non-significant p value (Pr[>F]) but was retained in all models until the EAG and committee requested it be revised to exclude treatment arm and include line of therapy.
Selinexor with bortezomib dexamethasone (TA974 2024) [37]scenario analysis using Hatswell et al. 2019	2L 3L	0.620 0.590	0.550 0.520	0.070 0.070	SLR	This is a scenario analysis from TA974 (row above) using evidence from Hatswell et al. 2019. For the 2L subgroup the company assumed that the PF health state utility was equal to 2L patients (0.62) and the PD utility was calculated as the mean utility of 3L, 4L and 5L+ patients (0.55). For the 3L subgroup, the progression free utility was equal to 3L patients (0.59) and the PD utility was calculated as the mean utility of 4L and 5L+ patients (0.52).
Daratumumab with bortezomib (TA897 2023) [16]	2L	0.737	0.665	0.072	ENDEAVOR trial	The company had wanted to use data from the CASTOR trial but the utilities were unrealistically high according to the EAG and so ENDEAVOR data (TA573) was recommended. Scenario analysis one in the CS.
Carfilzomib with dexamethasone and lenalidomide, (TA695 2021) [66]	2L	0.714 (cycle 1 and 2) 0.761 (cycle 3 plus, CRd) 0.745 (cycle 3 plus, Rd)	0.698	0.055	ASPIRE trial	Utilities were mapped from patient-reported EORTC QLQ-C30 outcomes to EQ-5D-3L utilities using the Proskorovsky et al. 2014 ordinary least squares mapping algorithm model. The company base case used treatment specific utility values from cycle 3 in the PF health state citing TA657 as justification. The ERG and committee preferred to remove treatment-specific utilities on advice from the clinician that there is no clinical benefit beyond the gain to PFS. The ERG also noted ASPIRE was an open-label trial which might influence patient's response to health-related quality of life questionnaires. ASPIRE included patients who had received 1 to 3 lines of therapy. Line of therapy was not adjusted for.

						Scenario analysis two in the CS. Simplified using an unweighted mean of the cycle 3+ treatment specific utilities for the PF state, (0.761 + 0.745)/2 = 0.753.
Carfilzomib with dexamethasone, (TA657 2020) [15]	2L	0.737 (cycle 1 and 2) 0.741 (cycle 3 plus, Cd) 0.714 (cycle 3 plus, Vd)	0.638	0.099 (cycle 1 and 2) 0.103 (cycle 3 plus, Cd) 0.076 (cycle 3 plus, Vd)	ENDEAVOR trial	EORTC QLQ-C30 data was transformed to EQ-5D-3L utilities values using the mapping algorithm from Proskorovsky et al., 2014. Treatment specific utility values were used from cycle three of the PF disease state.
Hatswell et al., 2019. [1]	All lines	2L 0.620 (0.46 – 0.79) 3L 0.590 (0.57 – 0.61) 4L 0.578 (0.28 – 0.88) 5L+ 0.469 (0.02 – 0.92)			SLR	A SLR and network meta-analysis combined with registry data to produce utility estimates for MM by line of treatment.
Panobinostat (TA380 2015) [51]	3L	0.706 (PANO/BTZ/DEX) 0.725 (BTZ/DEX) 0.762 (off treatment)	0.64	0.066 (PANO/BTZ/DEX) 0.085 (BTZ/DEX) 0.122 (off treatment)	PANORAMA-1 trial and van Agothoven et al. (2004)	EORTC QLQ-C30 questionnaire was mapped to obtain the corresponding EQ-5D-3L utility value for PF on treatment, by treatment arm. The PF off-treatment health state utility was assumed to be equal to the mean utility value (0.762) mapped from the last HRQL assessment while still on treatment and was based on pooled data from both treatment groups. No PD utility was collected during the trial so utility values were informed by van Agthoven et al (2004) following previous submissions TA228 and TA171.
*Lenalidomide plus dexamethasone for 2L+ (TA586 2019) and Ixazomib with lenalidomide and dexamethasone for 3L (TA870 2023) were also explored but the health state utilities were not found in the documents listed on the NICE submission page.						

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; SVd, selinexor in combination with bortezomib and dexamethasone; PD, progressed disease; PFS, progression free state; SLR, systematic literature review

Other issues

Despite health state utilities being derived from a single regression output, independent beta distributions were fitted to capture parameter uncertainty in these inputs. Thus, these parameters were varied independently in the probabilistic sensitivity analysis (PSA) and the correlation between the inputs not considered. The EAG notes that it would be preferable to fit probability distributions that allow maintaining the correlation between these parameters in the PSA (e.g., multivariate normal distribution informed by the Cholesky decomposition of the regression variance-covariance matrix). Despite this, the EAG is not concerned that this will have considerably affected the cost-effectiveness estimates.

4.2.8.3 Adverse event utilities

There are 17 adverse events included in the model (see section 4.2.7 for more detail). Disutilities associated with adverse events were taken from previous appraisals and the academic literature (see Table 26). The company apply the HRQoL decrement in the first cycle of the model only.

Three of the disutilities relate to ocular adverse events (keratopathy, blurred vision and dry eyes), and are applied to BVd only. The disutility used for all three is sourced from NICE TA369: Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears.[67] The company do not include disutilities to account for adverse events of grade 2 or less.

Table 26 Adverse event disutility applied in the company's model

Adverse events	**Disutility**	**Source**
Neutropenia	0.15	TA695 [17]
Anaemia	0.31	TA695[17]
Thrombocytopenia	0.31	TA695[17]
Lymphopenia	0.07	TA897[16]
Pneumonia	0.19	TA695[17]
Peripheral neuropathy	0.07	TA897[16]
Hypertension	0.00	TA695[17]
Leukopenia	0.07	TA510 [48], Brown et al. 2013[68]
Nausea	0.10	TA510[48], Brown et al. 2013[68]
Diarrhoea	0.10	TA510[48], Brown et al. 2013[68]
Fatigue	0.12	TA695[17]
Dyspnoea	0.12	TA510[48], Brown et al. 2013[68]
Back pain	0.09	Sullivan et al. 2011[69]
Hypokalaemia	0.20	TA695[17]
Ocular events applied only to BVd		
Keratopathy	0.16	TA369[67]

Blurred vision	0.16	
Dry eyes	0.16	

Points for critique

It is unclear from the source of the ocular disutility (TA369) what time period the 0.16 applies to and how that compares with ocular adverse events experienced by BVd patients in the DREAMM-7 trial. The CS states that for the first occurrence of grade ≥2 keratopathy visual acuity events, median time to onset was [redacted] days, and median duration was [redacted] days (page 89 of CS). The equivalent figures are not reported for grade 3+.

The CS argues that ocular events of grade 2 and below will be captured by the treatment specific progression free utilities from DREAMM-7. The DREAMM-7 clinical study report lists keratopathy events of grade 1 and 2 as occurring in [redacted] and [redacted] of BVd patients respectively, where grade 3+ occur in [redacted][19] Mild ocular events are therefore a less critical issue having both a low incidence and a likely low cost and impact on disutility.

The EAG ran the company's economic model excluding adverse events and the impact on cost-effectiveness was minimal.

4.2.9 Resource use and costs

4.2.9.1 Confidential pricing arrangements

The EAG notes that there are confidential commercial arrangements in place for comparator treatments and treatments delivered at post-progression. The drug acquisition cost used in the CS and in Sections 5 and 6 of this report include only the confidential pricing agreement for Belamaf.

Table 27presents details of the treatments with confidential price which differs from the publicly available list price used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices are correct as of July 9, 2024.

Table 27 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Daratumumab	Simple PAS
Carfilzomib	Simple PAS*
Selinexor	Simple PAS
Pomalidomide	Simple PAS

Isatuximab	Simple PAS
Panobinostat	Simple PAS

*when in combination with dexamethasone

4.2.9.2 Summary of company's submission

The company's base case analysis includes resource use and costs relating to: (i) drug acquisition and drug administration; (ii) health state (i.e., routine disease management); (iii) subsequent treatments; (iv) adverse events; and (v) end of life care.

Table 28 and Table 29 summarise the costs applied in the company's base case analysis for the drug and acquisition and remaining cost categories, respectively. Table 68 in the CS provides more detailed information.

Table 28 Drug acquisition and administration costs per cycle in the company's base-case analysis

Treatment cycle	Acquisition cost per treatment cycle (£)	Admin cost per treatment cycle (£)	Total cost per treatment cycle (£)
Belamaf			
Average 3W Cycle	[redacted]	[redacted]	[redacted]
Median 3W Cycle	[redacted]	[redacted]	[redacted]
Bortezomib and Dexamethasone			
Treatment cycle 1	[redacted]	[redacted]	[redacted]
Treatment cycles 2-8			
Treatment cycles 9+	[redacted]	[redacted]	[redacted]
DVd			
Treatment cycle 1	[redacted]	[redacted]	[redacted]
Treatment cycles 2-3		[redacted]	[redacted]
Treatment cycles 4-8	[redacted]	[redacted]	[redacted]
Treatment cycles 9+	[redacted]	[redacted]	[redacted]
SVd			
Treatment cycle 1	[redacted]	[redacted]	[redacted]
Treatment cycles 2+		[redacted]	[redacted]
hKd			
Treatment cycle 1	[redacted]	[redacted]	[redacted]
Treatment cycle 2+	[redacted]	[redacted]	[redacted]

Table 29 Health state costs and one-off costs in the company's base-case analysis

Health state	Cost per cycle (£)			
	BVd	hKd	SVd	DVd
PFS (on treatment) - Disease Management	[redacted]	[redacted]	[redacted]	[redacted]
PFS (off treatment) - Disease Management	[redacted]	[redacted]	[redacted]	[redacted]
PD - Disease Management	[redacted]	[redacted]	[redacted]	[redacted]

Ophthalmologist (cycles 1-4) - Disease Management	[redacted]	[redacted]	[redacted]	[redacted]
	One off costs (£)			
First subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
Second subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]
End of Life	12,397.00	12,397.00	12,397.00	12,397.00

4.2.9.3 Resource use and cost evidence in the published literature

The company conducted a systematic review of the literature to identify existing cost-effectiveness, cost and resource use, and health-related quality of life evidence for patients with RRMM who have had at least one prior line of therapy (2L+).

The search strategies, the original (January 2023), and updated (January 2024) SLR results of this review were reported in Appendix I of the CS. The original review included 142 studies (25 UK-based, 117 non-UK-based publications) which reported cost and resource use. The SLR update added 23 studies, out of which 2 were UK-based and 21 were non-UK-based publications. A summary of the studies identified is provided in Appendix I of the CS.

Points for critique

The EAG presents an appraisal of the evidence identification search strategy in Appendix AA4 of this report. In brief, the EAG identified issues with the clarity of reporting on records identified from each source, lack of provision of documented search strategies, and filters being used but not referenced. The EAG also considered that additional databases could have been searched for economic evidence. Nevertheless, the EAG did not identify any additional relevant evidence that the company may have missed and does not consider this issue to affect the conclusions of the cost-effectiveness.

4.2.9.4 Drug acquisition and administration costs

Table 53 in the CS summarises the treatment schedule based on SmPC for all comparators.

The list price of a 100mg vial of belamaf proposed by the company is £[redacted]. In the model the company assumed a 70mg vial was also available and this is proportionally priced at [redacted] These prices were discounted in the model according to the company's proposed PAS ([redacted]%) discount resulting in unit costs of [redacted] and [redacted] respectively. [redacted]

The CS utilizes a formulation for Bortezomib (1mg) which only has a British National Formulary (BNF) list price (£217.82) [7] but does not have an electronic market information tool (eMIT) price. Prices on EMIT suggest significantly less than the BNF list price is paid by the NHS and therefore the EAG decided that a correction should be made to the formulation acquired in the model, updating the unit size to 3.5mg and price to £66.29 as per eMIT[70] to better reflect NHS practice.

Belamaf acquisition costs were applied based on IPD dose information [redacted]) from the DREAMM-7 trial to the proportion of patients on treatment in each weekly cycle in the company's base case analysis. When patients on treatment in DREAMM-7 was reduced to 50 patients, the distribution of patients receiving each dosage was assumed constant over the remaining model time horizon.

The model base case assumes drug wastage on all administrations of all treatments to resemble UK clinical practice. The company implements a method of moments (MoM) approach to estimate drug acquisition costs. The MoM estimates the probability distribution of size of doses required for each drug based on the ITT population average patient weight and body surface area, and the SmPC dose adjusted using IPD dosage information (Belamaf) or RDI (all other drugs). The sum product of this distribution for each dose and the number of vials required to administer the dose informs the units acquired and the acquisition costs per model cycle.

Administration costs in the base case are applied for belamaf based on the proportion of patients on treatment who receive a belamaf dose. Administration costs for bortezomib and dexamethasone are applied irrespective of the proportion who receive a Belamaf dose. The 'IV treatment: Subsequent administrations in a treatment cycle' cost appears to be applied to all cycles (including the first). For DVd, SVd and hKd, acquisition and administration costs are applied at the start of their respective treatment cycles according to their treatment schedules. The unit costs are their BNF list price [7, 71-74] and the units of resource use for each drug (except Selinexor and Dexamethasone) are based on the MoM calculations. Units of Selinexor and Dexamethasone acquired are based on the dose per regimen divided by the unit size. The acquisition cost of each drug is then the product of the units acquired and the cost per unit. Administration costs are applied based on administration method for each drug in the regimen, and number of administrations per cycle.

Points for critique

The company's model utilises the IPD dosage information as used in DREAMM-7 when calculating acquisition and administration costs for belamaf. The company provides evidence to support the use of IPD data for belamaf rather than apply a constant RDI approach as with the other drugs in the regimen and comparators. The company illustrates the relationship between time and cumulative doses administered over time in the DREAMM-7 trial (Figure 11 in response to EAG clarifications)

which shows that the initial SmPC dose (2.5mg/kg) is less common over time in the trial. The 1.9mg/kg dose (which is the SmPC recommended dose if moderate corneal adverse events occur with the full dose), however, shows a relatively constant increase in cumulative doses over time. The off-label doses increase slowly over time, however, the SmPC doses still account for approximately 75% of the doses applied in the trial. The EAG considers a scenario in Section 6 where the SmPC dosage is applied over time. [redacted]. The company also illustrates that the average dose of Belamaf in 3-week cycles reduced quickly following the first administration cycle and remained low over the remainder of the trial (see Figure 13, response to EAG clarifications). Evidence is also provided which indicates that the SmPC planned dosage (2.5mg/kg) and the mean RDI approach to dosage for patients on treatment overestimates Belamaf acquisition costs as time progresses (Figure 14, response to EAG clarifications). The EAG considers the use of IPD dosing from DREAMM-7 to calculate belamaf acquisition costs to be a reasonable approach given that the dosage modelled is consistent with the actual dosage received in the trial. The EAG's clinical advisors noted that a more caution approach to dosing of belamaf is taken in NHS practice due to ocular adverse events associated with belamaf, with dosage typically lower than SmPC guidance, and delays being common in clinical practice.

The company base case assumed that a 70mg belamaf vial which is currently unavailable in the NHS will become available alongside the 100mg. When assuming that 70mg vial is not available (and using the version of the company's model submitted at the clarification stage) the ICER of [redacted] (BVd vs. DVd) and [redacted] per additional QALY (BVd vs. SVd), for the DVd eligible and DVd ineligible subpopulations, respectively. While this is a considerable increase in relation to company's base-case results of the ICERs of BVd vs. the relevant comparators, NICE has not indicated in the pricing tracker for this appraisal that the 70mg belamaf vial is unlikely to be available.

4.2.9.5 Health state costs

Health state costs, consisting of routine monitoring and disease management costs, varied by treatment group for the PFS (on-treatment) state, driven by differential resource use estimates across treatments. PFS (off-treatment) and PD costs were the same across all treatments. The resource use, unit costs and overall health state costs are summarized in Table 60 of the CS.

Unit costs for each cost category were sourced from NHS reference costs 21/22[75], while resource use estimates were based on expert clinical opinion.

The same cost categories are applied to all treatments except BVd, where an additional cost is incurred for ophthalmologist visits. The ophthalmologist costs were only applied for the first 4 treatment cycles when patients were on treatment. Health state costs are applied weekly over the lifetime horizon for patients in the PFS and on-treatment.

Points for critique

Ophthalmologist visits are only considered in the first 4 treatment cycles. The SmPC guidance for belamaf suggests that further visits can occur if clinically indicated. However, the EAG notes that this could potentially be covered through the AE costs, and the company also suggests the combination of the two could result in some double counting. Therefore, the EAG is reasonable satisfied with the company's assumptions for health state resource use and costs.

4.2.9.6 Adverse event costs

Costs associated with grade ≥3 adverse events were considered in the model. The incidence of grade ≥3 events (Table 41 and Table 61 of CS) for BVd and DVd are sourced from DREAMM-7, while the incidence for hKd and SVd were identified in the clinical SLR. Only the BVd arm incurred the costs of keratopathy, blurred vision, and dry eyes (Table 63 of CS). Unit costs for treating each AE were sourced from the NHS reference costs 21/22.[75]

Adverse events costs were applied in the first cycle of the model as a one-off-cost, which was calculated as a sum product of the incidence rates and the costs associated with each event (see Section 4.2.7). The cost categories are the same (except eye-related adverse events) across all comparators. As in the paused appraisal for belamaf at 4L+ [54], frequency per patient per episode of ophthalmologist visits for mild and moderate keratopathy were [redacted] whereas visits for severe keratopathy were [redacted].

Points for critique

As noted in the healthcare costs section, there may be overlap with eye-related routine and AE costs. The EAG notes that evidence provided in the Clinical Study report with regards to keratopathy (described in detail in Section 4.2.7), eye-related adverse event incidence appears low. The EAG notes however, that due to the costs being applied as a one-off cost, that even a change to 100% incidence for keratopathy, blurred vision, and dry eyes, has minimal impact on the ICERs in the company's revised base-case.

4.2.9.7 Subsequent treatment costs

Subsequent treatment (3rd and 4th line) costs were applied as a one-off cost to the proportion of patients moving to the progressed disease health state in each cycle. The proportion of patients

expected to receive subsequent treatments in 3rd and 4th lines were informed by Raab et. al 2019 (ref 47 in CS) and were equivalent across all treatments. Patients were assumed to receive treatment until death, assumed at 9 months post progression. Subsequent treatment costs included acquisition and administration costs.

The company considered three different distributions of subsequent treatment options as in previous submissions.[55, 76] These distributions, elicited from clinical experts were as follows: i) likely future pathway aligned, ii) current patients pathway aligned, and iii) NICE pathway aligned. The company's base-case analysis applies option (ii) to inform the treatment distribution for 3L+. The company noted as a limitation that SVd was not NICE approved at the time of the expert elicitation, and so subsequent SVd in 3L is not included.

The treatments considered for first and second subsequent treatments by arm, the proportion expected to receive them, and the associated costs are presented in Tables 56, 58 and 59 of the CS. Table 30 summarises the distribution of subsequent treatments and corresponding costs per line of treatment and conditional on the treatment received at PFS.

Table 30 Distribution and total costs of subsequent treatments by treatment received in PFS

	Subsequent treatment distribution at							
	3L				**4L**			
Subsequent reatment	**Treatment in PFS**				**Treatment in PFS**			
	BVd	**hKd**	**SVd**	**DVd**	**BVd**	**hKd**	**SVd**	**DVd**
Dara	8.6%	8.6%	8.6%	1.1%	3.8%	3.8%	3.8%	3.8%
IxaRd	0%	0%	0%	0%	0.0%	0.0%	0.0%	0.0%
Pd	16.1%	16.1%	16.1%	61.3%	34.3%	34.3%	34.3%	27.3%
IPd	43.0%	43.0%	43.0%	5.4%	2.2%	2.2%	2.2%	2.2%
PanoVd	32.3%	32.3%	32.3%	32.3%	59.7%	59.7%	59.7%	66.7%
Palliative chemotherapy	0%	0%	0%	0%	0.0%	0.0%	0.0%	0.0%
Kd	0%	0%	0%	0%	0.0%	0.0%	0.0%	0.0%
Rd	0%	0%	0%	0%	0.0%	0.0%	0.0%	0.0%
Total cost*	85,702.58			84,441.02	79,412.48			78,815.62

*Adjusted for the proportion of patients assumed to be receiving subseqeunt treatments at each line. **Abbreviations:** BVd, belamaf in combination with bortezomib, and dexamethasone; Dara, Daratumumab; DVd, daratumumab in combination with bortezomib, and dexamethasone; IPd, Isatuximab + pomalidomide + dexamethasone; IxaRd, Ixazomab + lenalidomide +dexamethasone; hKd, high dose carfilzomib + dexamethasone; Kd, carfilzomib and dexamethasone PanoVd, Panobinostat + bortezomib + dexamethasone; Pd, Pomalidomide + dexamethasone; Rd, Lenalidomide +dexamethasone; SVd, Selinexor in combination with bortezomib, and dexamethasone

Points for critique

The company's preferred distribution of subsequent treatments does not align with the NICE pathway, which should represent NHS clinical practice. Nevertheless, when alternative treatment distributions were considered by the company in scenario analyses the cost-effectiveness results were not

substantially impacted. The EAG's clinical advisors suggested that the distribution of treatments seemed reasonable. The EAG notes that while the costs associated with subsequent treatments do not differ substantially between the treatments (the costs are the same for BVd, SVd and hKd and slightly lower for DVd (see Table 30), the timing of when these subsequent treatment costs are incurred is important due to discounting. In particular, the EAG notes that BVd is associated with a much longer period of PFS compared to the comparator treatments; therefore, the impact of the subsequent treatment costs on cost-effectiveness is driven by the timing of movement to the PD health state due to discounting rather than the difference between the treatments in terms of the distribution of subsequent treatments received.

4.2.9.8 End of Life Treatment Costs

End of life costs of £12,397 were applied as a one-off cost to patients when they moved to the dead state.

Points for critique

The source referenced by the company[77] reports average end of life costs of £12,727 per decedent (£13,314 per decedent for cancer diagnosis) for hospital and social care. The exact figure could not be reconciled with the original source; however, the EAG expects this to have minimal impact on the cost-effectiveness results.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

All analyses presented in the CS include the confidential simple PAS discount of [redacted] over the company's new proposed belamaf list price (see Section 4.2.9.4); [redacted]

A summary of the inputs and variables used in the company's base case analysis is presented in Table 68 of the CS and the assumptions used in the model are summarised in Table 69 of the CS.

At the clarification stage the company submitted a revised version of the economic model. The key revisions with implications for the cost-effectiveness results were:

1. Correction of an error in the estimation of the costs of ocular AEs for belantamab;
2. Exclusion of SVd as a comparator for the DVd eligible subpopulation;

3. Implementation of estimates of the absolute median PFS:OS ratio for the treatments under comparison using WLS regression and fixed and random effect meta-regression for scenario analyses.

The updated model also had additional functionality to simultaneously output cost-effectiveness results for the two subpopulations: (i) DVd eligible subpopulation and (ii) DVd ineligible subpopulation (i.e. patients who are refractory to daratumumab and therefore this cannot be included as a comparator). All cost-effectiveness results in Section 5.1.1 were estimated using the company's model updated at the clarification stage, unless otherwise stated. The company did not present updated results for their sensitivity analyses.

The full incremental base-case cost-effectiveness analysis is presented in Table 31 and Table 32, for the DVd eligible and DVd ineligible subpopulations, respectively. These tables include the probabilistic and deterministic cost-effectiveness results.

For the DVd eligible population the two relevant comparators for BVd are DVd and hKd, of the two comparators [redacted] The deterministic ICER for BVd relative to DVd is [redacted], while the probabilistic ICER is [redacted]. The cost effectiveness plane and acceptability curves are presented in Figure 36, and 37 of the CS (for the company's original model). These show that the probability of BVd being cost-effective is approximately [redacted] at cost-effectiveness thresholds of £20,000 and £30,000 per additional QALY, respectively.

Table 31 Company's base case results for the DVd eligible population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. DVd (/QALY)
Deterministic analysis							
DVd	[redacted]	4.97	[redacted]				
hKd	[redacted]	4.59	[redacted]	[redacted]	-	[redacted]	[redacted]
BVd	[redacted]	9.23	[redacted]	[redacted]	4.27	[redacted]	[redacted]
Probabilistic analysis							
DVd	[redacted]	5.13	[redacted]				
hKd	[redacted]	4.85	[redacted]	[redacted]	-	[redacted]	[redacted]
BVd	[redacted]	9.21	[redacted]	[redacted]	4.08	[redacted]	[redacted]

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

For the DVd ineligible population the two relevant comparators for BVd are SVd, and hKd. [redacted]. The deterministic ICER for BVd relative to SVd is [redacted], while the probabilistic ICER is [redacted]. The cost effectiveness plane and acceptability curves are presented in Figure 38, and 39 of the CS (for the company's original model). These show that the probability of BVd being cost-effective is [redacted] at cost-effectiveness thresholds of £20,000 and £30,000 per additional QALY, respectively.

Table 32 Company's base case results for the DVd ineligible population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. SVd(/QALY)
Deterministic analysis							
SVd	[redacted]	4.17	[redacted]				
hKd	[redacted]	4.58	[redacted]	[redacted]	-	[redacted]	[redacted]
BVd	[redacted]	9.23	[redacted]	[redacted]	5.07	[redacted]	[redacted]
Probabilistic analysis							
SVd	[redacted]	4.45	[redacted]				
hKd	[redacted]	4.85	[redacted]	[redacted]	-	[redacted]	[redacted]
BVd	[redacted]	9.21	[redacted]	[redacted]	4.76	[redacted]	[redacted]

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

To aid understanding of the key drivers of the cost-effectiveness results, Table 33 and Table 34 provide a summary of the disaggregated costs and QALYs, respectively. For BVd versus DVd the increase in costs is largely driven by the health state costs. The increased costs for BVd compared to SVd are predominantly driven by the increased treatment costs (drug acquisition and administration), with some of this cost offset by a reduction in subsequent treatment costs. BVd is less costly than hKd driven largely by lower treatment costs. The QALY gain for BVd is driven by both the improvements in HRQoL associated with remaining progression-free for longer relative to the comparators and living longer in the progressed disease state.

Table 33 Summary of the disaggregated costs in the company's deterministic base case results

BVd vs DVd				
Item	**Cost of BVd (£)**	**Cost of DVd (£)**	**Incremental costs (£)**	**% of absolute incremental costs**
Treatment cost (includes drug acquisition and administration)	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost*	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
BVd vs SVd				
Item	**Cost of BVd (£)**	**Cost of SVd (£)**	**Incremental costs (£)**	**% of absolute incremental costs**
Treatment cost (includes drug acquisition and administration)	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost*	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
BVd vs hKd				
Item	**Cost of BVd (£)**	**Cost of hKd (£)**	**Incremental costs (£)**	**% of absolute incremental costs**
Treatment cost (includes drug acquisition and administration)	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost*	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

*End of life costs are included in the health state costs category.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone.

Table 34 Summary of the disaggregated QALYs in the company's deterministic base case results

BVd vs DVd				
Item	**QALYs of BVd**	**QALYs of DVd**	**Incremental QALYs**	**% of absolute incremental QALYs**
Progression free (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Progression free (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
BVd vs SVd				
Item	**QALYs of BVd**	**QALYs of SVd**	**Incremental QALYs (**	**% of absolute incremental QALYs**
Progression free (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Progression free (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
BVd vs hKd				
Item	**QALYs of BVd**	**QALYs of hKd**	**Incremental QALYs**	**% of absolute incremental QALYs**
Progression free (on treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Progression free (off treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality-adjusted life years; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone.

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company reports univariate deterministic sensitivity analysis (DSA) via tornado plots of the 15 most influential parameters (Figures 41, 42 and 43 of the CS). In the absence of confidence intervals or published ranges, upper and lower bounds tested in the DSA were calculated by assuming a standard error of 0.2, These results indicate that, at a £30,000 per additional QALY threshold, for all three comparators subsequent treatment cost, percentage of patients receiving subsequent treatment and utility in the progressed disease state are amongst the top six influential parameters on the ICER. For the comparison of BVd with SVd and hKd results were also sensitive to relative treatment efficacy (HRs) for TTD and OS, which are taken from the literature.

The CS outlines 28 scenario analyses (Tables 74). It reports the deterministic results from these scenarios for SVd (Table 76) and DVd (Table 77), it does not explore scenarios for BVd compared with hKd[redacted]. For comparisons with SVd the scenario with the greatest impact on the cost-effectiveness results was applying subsequent treatment costs to all patients at the start of the model, rather than to a

proportion of patients on disease progression, increasing the ICER from [redacted] in the base case ([redacted]) to [redacted]. For comparisons with DVd the scenarios with the greatest impact were varying the DVd PFS extrapolation to log-logistic [redacted] or lognormal [redacted] as opposed to the base case extrapolation which uses the exponential curve [redacted]

No subgroup analysis was presented by the company.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company undertook both clinical and technical validation of the originally submitted economic model. For technical validation, the CS states an internal validity check was conducted systematically by completing the TECH-VER checklist. Which involved testing the selection and results of different modelling options, calculation spot checks, validation against source data and extreme value testing to assess whether the model responded logically to the tests.

The clinical inputs and assumptions were validated during a two-staged interview with three practicing UK based haematologists completed in April 2024 (Section B.2.3.3 Appendix M). They were consulted as to the patient pathway for 2L MM patients with one previous line of therapy, the extrapolation assumptions of clinical outcomes, healthcare resource utilisation, and subsequent treatment related parameters.

Points for critique

The EAG considers the company's validation procedure to be reasonable. However, the EAG reviewed the company model in detail and identified two errors at the clarification stage (described in 6.1.1.1) consequently the company submitted a revised version of the economic model. The revised model contained two additional errors. Firstly, the bortezomib price and formulation was not in line with eMIT. Secondly the company included a price for belamaf which had not been approved. Both of these errors were corrected by the EAG and results presented in section 6.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

A summary of the main issues identified and critiqued in Section 4, along with the scenario where the EAG addresses each issue in its additional analyses, is shown in Table 35. The EAG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where

possible, the EAG explored alternative assumptions and model inputs in scenario analyses to the company's corrected base-case analysis (EAG Scenarios 1-7). The EAG's base case consists of the set of assumptions and model inputs that the EAG considers to be more appropriate for assessing the cost-effectiveness of BVd relative to the relevant comparators for the (i) DVd eligible (i.e., DVd and hKd) and (ii) DVd ineligible population (i.e., SVd and hKd). Where the EAG is unable to provide a judgement in the absence of evidence (e.g., whether differential PFS utilities compared to BVd should be applied for SVd and hKd), the EAG have presented results of alternative scenarios to the EAG base case. Thorough descriptions of the EAG scenario analyses are presented in Section 6.1.1, while the impact on the cost-effectiveness results is presented in Section 6.1.1. The effect of making changes simultaneously on elements that are considered to form part of the EAG's preferred base case assumptions and alternative scenarios to the EAG base case are presented in Section 6.3.

The cost-effectiveness results presented in Section 6 do not include the confidential pricing arrangements for the comparators and subsequent treatments (see Section 4.2.9.1). Corresponding analyses including these pricing arrangements are reported in a confidential appendix to the EAR.

Table 35 Summary of the main issues identified by the EAG in Section 4 and EAG scenarios

Critique item and description The EAG considers that:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		EAG Scenarios	EAG Base-case		
1	The cost-effectiveness of BVd for individuals at 2L-only treatment for RRMM whose condition is refractory to lenalidomide is informed by the overall ITT population of DREAMM-7 (2L+), instead of the subgroup of patients in the trial relevant to the company's proposed treatment positioning of BVd (i.e., restricted to the 2L-only and lenalidomide refractory subgroup). Therefore, the company assumes that the clinical effectiveness evidence collected from the overall ITT population of DREAMM-7 is transferable to the company's proposed subpopulation of interest, but there is limited evidence to support this assumption.	No	No	Yes	Unknown
2	The cost-effectiveness of BVd has not been evaluated by the company at third and subsequent lines in the NICE treatment pathway for RRMM, [redacted] Relevant comparators have also not been considered in the economic model and, therefore, the cost-effectiveness of BVd cannot be formally assessed at 3L+.	No	No	Yes	Unknown
3	The overall survival evidence provided by DREAMM-7 is highly uncertain, particularly for the BVd treatment arm, due to immaturity of the trial data and highly optimistic long-term survival predictions for BVd, which is likely to favour the cost-effectiveness of BVd vs. the relevant comparators.	Sc. 1.1-1.3	Yes (Sc. 1.1)	Yes	No
4	The EAG could not replicate the company's PFS NMA results (updated at the clarification stage); discrepancies between company and EAG results were minor. Notwithstanding, the EAG updates the company's economic model for consistency with the EAR clinical section 3.4.4.1.	Sc. 2	Yes	No	No
5	The EAG included the results of a study reporting more mature OS data for the LEPUS tial[35] in the OS NMA instead of the less mature data from this study used by the company, and considered it appropriate to update the company's economic model with the EAG's updated OS NMA results (in line with Section 3.4.4.2).	Sc.3	Yes	No	No
6	The assumption that BVd is associated with higher utility in the PF health state than SVd and hKd is not supported by empirical evidence presented by the company; an alternative assumption that the same PF health state utility applies to these three treatments should be formally considered in the cost-effectiveness analysis.	Sc. 4	No	Yes	No
7	The company have modelled a higher utility value for progressive disease than progression-free survival for the comparator treatments (DVd, SVd and hKd), which is not clinically justified and external evidence (e.g., Hatswell et al, 2019) [1] shows that there is a decrement in utility for PD at each subsequent line of treatment for RRMM.	Sc. 5	Yes	Yes	No

Critique item and description The EAG considers that:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		EAG Scenarios	EAG Base-case		
8	The acquisition and administration costs of BVd are based on IPD-dosing evidence from the DREAMM-7 trial and do not reflect the dose and frequency of administration recommended for belamaf according to the SmPC.	Sc. 6	No	Yes	No
9	The company applied differential costs for subsequent treatments applied as a one-off cost at the point of disease progression for individuals treated with DVd compared to the other treatments under comparison. The EAG considers that it is more appropriate to model the same subsequent treatments costs regardless of the initial treatment received, because the subsequent treatment costs used in the company's model may not reflect the distribution of subsequent treatments in (i) DREAMM-7 for BVd and DVd and (ii) NHS clinical practice.	Sc. 7	Yes	No	No

Abbreviations: Sc., scenario

6.1.1 Issues explored by the EAG in additional analyses

6.1.1.1 Corrections to the company's base-case analysis

The EAG discussed in Section 4.2.9.4 that the unit cost (£217.82 per vial)[7] of the bortezomib presentation (powder for solution for injection vials, 1mg) used to inform the acquisition costs of bortezomib was likely to overestimate the costs of this component, as alternative presentations are available in the NHS at a lower cost per mg. Furthermore, in TA974[37] the unit cost £66.29 (per vial for the current price year)[70]of the bortezomib powder for solution for injection vials, 3.5mg was used. The EAG has, thus, corrected the economic model by applying the unit cost for the 3.5mg bortezomib in line with TA974.

[redacted]

The EAG presents in Table 39 and Table 40 the results of the company's corrected base-case analysis for the DVd eligible and DVd ineligible subpopulations, respectively. The EAG first presents results for the company's base-case analysis corrected for the unit price of bortezomib, and then for both the unit price for bortezomib and the approved cPAS price for belamaf; the latter analysis is, henceforth, referred to as the company's fully corrected base-case analysis. All EAG scenario analyses in subsequent sections build on the company's fully corrected base-case analysis.

6.1.1.2 Scenario 1: OS modelling approach for BVd

In Section 4.2.6.3, the EAG discussed the appropriateness of the company's approach to modelling the OS outcomes for BVd. The considerable uncertainty in OS long-term predictions across different parametric extrapolation model is a consequence of the immaturity of the DREAMM-7 OS data. There is also uncertainty on whether the PH assumption holds for the comparison with BVd, as formal diagnostic tests did not fully allow rejecting this assumption. Importantly, the company's preferred base-case approach for BVd OS implies a time decreasing HR for BVd vs. DVd (i.e., an increasing treatment effect over time) that is not supported by the empirical evidence from the DREAMM-7 trial and results in optimistic long-term OS predictions for BVd according to both the company's and the EAG clinical advisors. In this scenario analyses the EAG considers three alternative approaches to inform the BVd OS discussed in detail in Section 4.2.6.3, which result in more conservative and clinically plausible long-term predictions for this outcome:

- Scenario 1.1: Independent parametric exponential extrapolation - BVd OS extrapolation of DREAMM-7 data with independently fitted exponential distribution.

- Scenario 1.2: PH Weibull extrapolation: BVd OS extrapolation of DREAMM-7 data is performed by applying the empirical OS HR for BVd vs. DVd to the DVd baseline curve (Weibull with CASTOR trial informative prior on the shape parameter).
- Scenario 1.3: Surrogacy relationship on absolute median PFS:OS: BVd OS is modelled by assuming that a one month increase in median PFS for this treatment (as informed by the extrapolation of BVd PFS evidence from the DREAMM-7 trial) results in a proportional increase in median OS (of [redacted] months) based on the company's surrogacy assessment analysis using the WLS methodology.

6.1.1.3 Scenario 2: Updated EAG NMA results for PFS

In section 3.4.4.1 the EAG reported updated results for the PFS NMA obtained by running the code and data provided by the company at the clarification stage. As the company did not update the economic model and the EAG found some (minor) discrepancies between the results of the NMA as reported in the CS and those reported at the clarification stage, the EAG updated the economic model in line with the EAG NMAs. The estimates applied in the model are reported alongside the company's original NMA results in Table 36. In this scenario (and consistently with the company's base-case), only the HRs for SVd and hKd are applied in the model. The EAG notes that differences between the EAG and company's estimates are very small.

Table 36 PFS NMA results applied in the model

Comparison	Company's original NMA			EAG updated NMA		
	HR	95% CI LB	95% CI UB	HR	95% CI LB	95% CI UB
hKd vs DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVd vs DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BVd vs DVd*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Not applied in the model, as BVd PFS is modelled independently these results are for comparison purposes only.
Abbreviations: CI, confidence interval; HR, hazard ratio; LB, lower bound; UB, upper bound.

6.1.1.4 Scenario 3: Updated EAG NMA results for OS

In section 3.4.4.2, the EAG included the results of a study reporting more mature OS data for the LEPUS tial[35] in the OS NMA instead of the less mature data from this study used by the company. The EAG considers it appropriate to update the company's economic model with the EAG's updated OS NMA results (in line with Section 3.4.4.2), as this allows the use of more mature data to inform the NMA estimates. The estimates applied in the model are reported alongside the company's original NMA results in Table 37. In this scenario (and consistently with the company's base-case), only the HRs for SVd and hKd are applied in the model. The EAG notes that differences between the EAG's estimates suggest that hKd and SVd are slightly more efficacious compared to DVd than in the company's original NMA.

Table 37 OS NMA results applied in the model

Comparison	Company's original NMA			EAG updated NMA		
	HR	95% CI LB	95% CI UB	HR	95% CI LB	95% CI UB
hKd vs DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVd vs DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BVd vs DVd*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Not applied in the model, as BVd OS is modelled independently these results are for comparison purposes only.
Abbreviations: CI, confidence interval; HR, hazard ratio; LB, lower bound; UB, upper bound.

6.1.1.5 Scenario 4: Progression free utility values – equal for BVd, hKd and SVd

In Section 4.2.8.2, the EAG described how the company used utility estimates from DREAMM-7 to inform the health state utilities in their base-case analysis. In the absence of comparative evidence for the utilities of SVd and hKd, the company has assumed that the PF utilities for these treatments would be the same as for DVd (i.e., [redacted]) and, therefore, a lower utility than BVd ([redacted]). The assumption that BVd is associated with higher utility in the PF health state than SVd and hKd is not supported by empirical evidence presented by the company. Thus, the EAG explores in this scenario the alternative assumption that the same PF health state utility applies to BVd, SVd and hKd treatments.

6.1.1.6 Scenario 5: Progressed disease utility values – assuming utility decrement from Hatswell et al., 2019[1]

In Section 4.2.8.2, the EAG discussed how the company's estimation of the health state utility for the PD health state using DREAMM-7 data resulted in a higher utility value ([redacted]) for PD than PF for the comparator treatments (DVd, SVd and hKd), which is also substantially smaller than the difference in utility between PF BVd and DVd ([redacted]). The EAG considered that the company's PD health state utility lacked face and clinical validity, and may underestimate the HRQoL loss due to disease progression over the individuals' lifetime, where external evidence from Hatswell et al., 2019,[1] shows that there is a decrement in utility for PD at each subsequent line of treatment for RRMM.

In this scenario, the EAG uses evidence from the Hatswell et al., 2019[1] utility meta-analysis (see Section 4.2.8.2) to estimate an alternative value for the utility decrement between the PF and PD health state for all treatments under comparison. The calculation of the utility decrement is illustrated in Table 38. In brief, the EAG took an average of the health state utility across lines of treatments from the meta-analysis (3L, 4L and 5L) and assumed that the utility decrement associated with disease progression would be equal to the difference between the 2L health state utility and the estimated average health state utility for 3L+. This decrement was then applied to the PF health state utility for DVd to derive the PD health state utility applied in the EAG scenario. This approach is in line with a scenario analysis undertaken in TA974.[37]

Table 38 Utility estimates in Scenario 5 and Hatswell et al., 2019[1]

Line of MM treatment	Hatswell et al 2019[1]			Scenario 5
	Utility	Average health state utility	Utility decrement for progressed disease	PD utility
2L	0.620	0.620	-	-
3L	0.590	0.546	0.074	[redacted]
4L	0.578			
5L	0.469			

6.1.1.7 Scenarios 6: Belamaf administration frequency according to SmPC

In Section 4.2.9.2, the EAG discussed how acquisition and administration costs of BVd are based on IPD-dosing evidence from the DREAMM-7 trial and do not reflect the dose and frequency of administration recommended for belamaf according to the SmPC. Using IPD-dosing, the company attempted to capture the treatment delays and interruptions observed for belamaf in the DREAMM-7 trial. The EAG considers the company's approach to be reasonable, as clinical advice to the EAG suggests that more caution is exercised in NHS practice with belamaf due to ocular adverse events and therefore dose reductions and treatment delays and/or interruptions are expected. However, the company has not explored how administering BVd without these delays and interruptions (i.e., according to the SmPC recommendation) would impact on the estimates of cost-effectiveness. In this scenario, the EAG assumed the same frequency of administration for BVd according to the scheduled defined by its SmPC, while also assuming the mean RDI observed in the DREAMM-7 trial.

6.1.1.8 Scenarios 7: Cost of subsequent treatments – same treatment distribution

The company applied differential costs for subsequent treatments applied as a one-off cost at the point of disease progression for individuals treated in PFS with DVd compared to the other treatments under comparison. The EAG considers that it is more appropriate to model the same subsequent treatments costs regardless of the treatment received in PFS, because the subsequent treatment costs in the company's model may not reflect the distribution of subsequent treatments in (i) DREAMM-7 for BVd and DVd and (ii) the NHS clinical practice. Applying the same subsequent treatments distribution for all treatment groups allows the difference in the subsequent treatment costs across the treatments under comparison to be driven by the delay to disease progression for the more efficacious treatments (i.e., it is only the timing of movement to progressive disease that affects the relative cost-effectiveness of the treatments due to discounting).

6.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

Table 39 and Table 40 show the deterministic results of the EAG scenarios alongside the results of the company's updated base-case (see Section 5.1.1) and corrected base-case (see Section 6.1.1.1) for the

DVd eligible and DVd ineligible subpopulations, respectively. Under the currently approved PAS price for belamaf, BVd [redacted] the EAG scenario analyses and the company's fully corrected base-case analysis, for both subpopulations considered. When only the unit cost of bortezomib is corrected ("company's corrected base-case"), the average costs of all treatments under comparison are reduced compared to the company's updated base-case, with the costs of SVd and DVd reducing more than those of BVd. Thus, the incremental costs of BVd increase for both subpopulations resulting in slightly higher ICERs for BVd.

The [redacted] in the company's fully corrected base-case (on which the EAG scenarios were built) is the driver of cost-effectiveness across analyses in both subpopulations.

The EAG scenarios with the largest impact on the company's base-case total average QALYs for BVd are scenarios 1.1 to 1.3 where more conservative estimates of BVd OS are assumed. In these analyses the total QALYs range from [redacted] (Scenario 1.3, assuming a surrogacy relation in the absolute median PFS:OS for BVd) and [redacted] QALYs (Scenario 1.2, BVd OS extrapolation using the PH Weibull distribution) compared to the company's fully corrected base-case [redacted] QALYs. These scenarios also suggest considerable impact on decreasing average total costs for BVd. The decrease in total costs is greater on average for the scenarios with more conservative BVd OS estimates (i.e., Scenario 1.3) where total BVd costs decrease to [redacted] compared to [redacted] in the company's fully corrected base-case analysis.

In Scenario 6, where belamaf frequency of administration is done according to SmPC, there appears to be a substantial increase in the average total costs of BVd ([redacted]) compared to the company's fully corrected base-case analysis ([redacted]).When PD utilities are informed by Hatswell et al., 2019[1] (Scenario 5), the average total QALYs decrease for all treatments under comparison, but the absolute decrease is higher for BVd resulting in [redacted] QALYs compared to company's fully corrected base-case analysis ([redacted] QALYs).

The remaining scenarios have a modest impact on average total costs and/or QALYs of the treatments under comparison.

Table 39 Cost-effectiveness results of the EAG scenario analyses – DVd eligible population

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
NA	Company's updated base case	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	Company's corrected base-case – assuming the unit cost of bortezomib 3.5mg	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	Company's fully corrected base-case – assuming the unit cost of bortezomib 3.5mg and the currently approved cPAS price for belamaf.	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1	OS modelling approach for BVd – Independent parametric exponential extrapolation	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2	OS modelling approach for BVd – PH Weibull extrapolation	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.3	OS modelling approach for BVd – Surrogacy relationship on absolute median PFS:OS	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Updated EAG NMA results for PFS	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Updated EAG NMA results for OS	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Progression free utility values – equal for BVd, hKd and SVd	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Progressed disease utility values – assuming utility decrement from Hatswell et al., 2019[1]	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Belamaf administration frequency according to SmPC	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Cost of subsequent treatments – same treatment distribution	D-Vd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 40 Cost-effectiveness results of the EAG scenario analyses – DVd ineligible population

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
NA	Company's updated base case	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	Company's corrected base-case – assuming the unit cost of bortezomib 3.5mg	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA	Company's fully corrected base-case – assuming the unit cost of bortezomib 3.5mg and the currently approved cPAS price for belamaf.	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1	OS modelling approach for BVd – Independent parametric exponential extrapolation	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2	OS modelling approach for BVd – PH Weibull extrapolation	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.3	OS modelling approach for BVd – Surrogacy relationship on absolute median PFS:OS	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Updated EAG NMA results for PFS	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Updated EAG NMA results for OS	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Progression free utility values – equal for BVd, hKd and SVd	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Progressed disease utility values – assuming utility decrement from Hatswell et al., 2019[1]	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Belamaf dosing and administration frequency according to SmPC	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Cost of subsequent treatments – same treatment distribution	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 EAG's preferred assumptions

The EAG's preferred assumptions include the following changes from the company's fully corrected base case:

- OS extrapolation with an independent exponential distribution for BVd, which the EAG considers to result in the most clinically plausible long-term predictions, in accordance with clinical advice received by both the company and the EAG – Scenario 1.1
- Updated NMA results for PFS and OS in accordance with the analyses performed by the EAG in Sections 3.4.4.1 and 3.4.4.2 – Scenario 2 and 3
- Progressed disease utility values estimated by assuming a utility decrement from Hatswell et al., 2019[1], which the EAG considers to be more representative of the impact on HRQoL of disease progression than the company's DREAMM-7 data and result in more clinically plausible PD utility estimates – Scenario 5.
- Subsequent treatment costs assume the same treatment distribution regardless of the treatment received in 2L, which the EAG considers an appropriate simplification to allow the difference in the subsequent treatment costs across the treatments under comparison to be driven by the delay to disease progression for the more efficacious treatments – Scenario 7.

Table 41 and Table 42 show the cumulative impact of the EAG's preferred assumptions on the ICER for the DVd eligible and DVd ineligible subpopulations, respectively.

Table 41 Cumulative cost-effectiveness results for the EAG's preferred assumptions – DVd eligible population

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's fully corrected base-case results	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1	OS modelling approach for BVd – Independent parametric exponential extrapolation	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+ 2	+ Updated EAG NMA results for PFS	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3	+ Updated EAG NMA results for OS	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3+5		DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	+ PD utility decrement from Hatswell et al., 2019[1]	hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3+5+7	+ Same distribution of subsequent treatments	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3+5+7	EAG probabilistic base-case	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 42 Cumulative cost-effectiveness results for the EAG's preferred assumptions – DVd ineligible population

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's fully corrected base-case results	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1	OS modelling approach for BVd – Independent parametric exponential extrapolation	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+ 2	+ Updated EAG NMA results for PFS	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3	+ Updated EAG NMA results for OS	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3+5	+ PD utility decrement from Hatswell et al., 2019[1]	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3+5+7	+ Same distribution of subsequent treatments = EAG base-case	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.1+2+3+5+7	EAG probabilistic base-case	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The selection of changes made to the EAG base case is based on the available evidence; however, important uncertainties remain. To address the remaining uncertainties, the EAG presents two

scenarios on the EAG base case. These include alternative assumptions to the EAG's base case relating to:

- OS extrapolation for BVd: a PH Weibull distribution is assumed for BVd, which the EAG considers to be the second most clinically plausible extrapolation (albeit an optimistic one) for BVd – as per Scenario 1.2.
- Progression free utility values assumed equal for BVd, hKd and SVd, which in the absence of empirical evidence suggesting differential utilities between these treatments provides an equally plausible alternative assumption for these parameters – as per Scenario 5.

Table 43 and Table 44 show the impact of the alternative assumptions on the EAG base case for the DVd eligible and DVd ineligible subpopulations, respectively. Similarly to the EAG base-case analysis, [redacted] all the relevant comparators in the EAG additional analyses for both subpopulations considered. For the BVd OS extrapolation scenario assuming PH, average total QALYs and costs are higher for BVd compared to the EAG base-case analysis.

Table 43 Cost-effectiveness results for alternative assumptions on the EAG's base case – DVd eligible population

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	EAG base case (1.1+2+3+5+7)	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BVd – OS modelled with							
1.2	PH exponential extrapolation	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS health state utilities for hKd							
4	Same as for BVd	DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 44 Cost-effectiveness results for alternative assumptions on the EAG's base case – DVd ineligible population

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	EAG base case (1.1+2+3+5+7)	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BVd – OS modelled with							

1.2	PH exponential extrapolation	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS health state utilities for hKd and SVd							
4	Same as for BVd	SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The company submitted a (PartSa) decision model to assess the cost-effectiveness of BVd for the treatment of RRMM in adults who have had one previous line of treatment (i.e., 2L-only) and for whom treatment with lenanidomide is unsuitable due to prior treatment refractoriness. The company's cost-effectiveness analysis encompasses two subpopulations, which differ only by their relevant comparators: (i) DVd eligible subpopulation (comparison with DVd and hKd); and (ii) DVd ineligible subpopulation (comparison with SVd and hKd). The EAG considers that the comparators selected are appropriate for each subpopulation considered in the model.

The evidence informing the cost-effectiveness of BVd is informed by the ITT population of DREAMM-7 (2L+) rather than the subgroup-specific evidence for the 2L-only, lenalidomide refractory population in the company's model. In the absence of suitable alternative 2L-only data in patients for whom lenalidomide is unsuitable, the EAG acknowledges the company's reasons (see Section 4.2.3) for using the overall ITT population (2L+) from DREAMM-7 to inform the cost-effectiveness of BVd relative to DVd in the company's proposed population. However, the EAG considers that the mismatch between the population informing the model's clinical effectiveness parameters and the company's proposed population is a source of unquantifiable uncertainty. The EAG also notes that the findings of the cost-effectiveness analyses conducted by the company and the EAG cannot be generalised to the populations of RRMM adults at 2L-only and/or 2L+, as the relevant comparators for these populations have not been included in the model. The EAG is also concerned that the cost-effectiveness of BVd has not been evaluated by the company at third and subsequent lines in the NICE treatment pathway for RRMM, [redacted] Relevant comparators have also not been considered in the economic model and, therefore, the cost-effectiveness of BVd cannot be formally assessed at 3L+.

The EAG considers that the model structure used to assess cost-effectiveness of BVd is appropriate to model the natural history of RRMM. However, the clinical evidence (DREAMM-7 trial) informing the model OS outcomes is immature, which results in considerable uncertainty in the long-term OS predications, particularly for BVd, and through these the estimates of cost-effectiveness. The EAG

considers that this uncertainty in the modelled BVd OS is the main issue in assessing the treatment effectiveness of BVd compared to the other treatments being evaluated. The EAG acknowledges the company's attempts to explore and reduce the uncertainty in the modelled OS. The EAG is reassured that the use of informative prior from the CASTOR trial on the shape parameter of the DVd OS extrapolation of DREAMM-7 (with a Weibull distribution) results in clinically plausible OS predictions and provides an appropriate survival baseline for comparison with treatments for which the PH assumption holds. However, the company's preferred approach using the BVd OS Weibull extrapolation of DREAMM-7 results in overly optimistic OS predictions for this treatment, given clinical advice provided to the company which showed preference for the more conservative exponential extrapolation. Furthermore, the use of independent Weibull distributions to extrapolate the OS for BVd and DVd in the company's base-case suggests that the treatment effect of BVd vs. DVd increases over time (i.e., a time varying HR BVd vs. DVd decreasing over time). The EAG considers that the assumption of a time increasing treatment effect lacks clinical rationale, is not supported by the observed clinical evidence from DREAMM-7 and is likely to overestimate the OS gain for BVd. Alternative approaches to modelling the BVd OS (assuming (i) time increasing HRs for BVd vs. DVd as implied by an independent exponential BVd OS, (ii) PH for the BVd OS extrapolation, and (iii) a valid surrogacy relationship between BVd absolute medians for PFS:OS) all result in more conservative and clinically plausible BVd OS long-term predictions compared to the company's base-case approach. The immaturity of the BVd OS evidence informing the cost-effectiveness is, thus, a key area of uncertainty.

The company have modelled a higher utility value based on DREAMM-7 for progressive disease than progression-free survival for the comparator treatments (DVd, SVd and hKd), which is not clinically justified and external evidence (e.g., Hatswell et al, 2019[1]) shows that there is a decrement in utility for PD at each subsequent line of treatment for RRMM. Furthermore, the company's assumption that BVd is associated with higher utility in the PF health state than SVd and hKd is not supported by the empirical evidence presented by the company, and the EAG considers that an alternative assumption that the same PF health state utility applies to these three treatments is equally plausible. Thus, both the modelled PD utility and PFS utility for hKd and SVd, are areas of uncertainty.

The acquisition and administration costs of BVd are based on IPD-dosing evidence from the DREAMM-7 trial and do not reflect the dose and frequency of administration recommended for belamaf according to the SmPC. The EAG considers the use of IPD to calculate belamaf treatment costs to be a reasonable approach given the evidence provided on dose reductions and dose delays over time, and that it is consistent with DREAMM-7. Clinical advice to the EAG noted there is caution with dosage mainly due to attempts to avoid ocular adverse events associated with belamaf. This leads to the use of typically lower dosages of belamaf compared to SmPC recommendations, and

delays being common in clinical practice. There is, however, uncertainty on whether dosage in the DREAMM-7 trial is reflective of clinical practice. Importantly, it is not possible to explore in scenario analyses the impact of this on the clinical effectiveness of BVd due to lack of evidence.

The company applied differential costs for subsequent treatments applied as a one-off cost at the point of disease progression for individuals treated in PFS with DVd compared to the other treatments under comparison. The EAG considers that it is more appropriate to model the same subsequent treatments costs regardless of the initial treatment received in PFS, because the subsequent treatment costs used in the company's model may not reflect the distribution of subsequent treatments in (i) DREAMM-7 trial for BVd and DVd and (ii) NHS clinical practice. The EAG acknowledges, however, that applying the same subsequent treatments distribution for all treatment groups is a simplified approach to allow the difference in the subsequent treatment costs across the treatments under comparison to be driven by the delay to disease progression for the more efficacious treatments (i.e., it is only the timing of movement to progressive disease that affects the relative cost-effectiveness of the treatments due to discounting).

As highlighted in Section 5, [redacted] At the request of NICE, the EAG analyses include the PAS price for belamaf provided in the price tracking form, [redacted]. Under this price for belamaf, BVd [redacted] in all the EAG analyses (including scenario, base-case, and additional analysis over the EAG base-case) and the company's fully corrected base-case analysis, for both subpopulations considered. The [redacted] in the company's fully corrected base-case (on which the EAG scenarios) is the driver of cost-effectiveness across analyses in both subpopulations. The EAG scenarios with the largest impact on the company's base-case total average QALYs for BVd are scenarios 1.1 to 1.3 where more conservative estimates of BVd OS are assumed. In these analyses the total QALYs range from [redacted] (Scenario 1.3, assuming a surrogacy relation in the absolute median PFS:OS for BVd) and [redacted] QALYs (Scenario 1.2, BVd OS extrapolation using the PH Weibull distribution) compared to the company's fully corrected base-case [redacted] QALYs. These scenarios also suggest considerable impact on decreasing average total costs for BVd. The decrease in total costs is greater on average for the scenarios with more conservative BVd OS estimates (i.e., Scenario 1.3) where total BVd costs decrease to [redacted] compared to [redacted] in the company's fully corrected base-case analysis. The cost scenarios suggest that the average total costs of BVd are very sensitive to assumption on the frequency of administration for belamaf; when administration frequence is done

according to SmPC instead of IPD-dosing, the average total costs of BVd ([redacted] appear to increase compared to the company's fully corrected base-case analysis [redacted]

The EAG's preferred assumptions include the following changes from the company's base case: (i) OS extrapolation with an independent exponential distribution for BVd, (ii) updated EAG NMA results for PFS and OS, (iii) progressed disease utility values estimated by assuming a utility decrement from Hatswell et al., 2019,[1] and (iv) subsequent treatment costs assume the same treatment distribution across the treatments under comparison. The results of the EAG base-case were consistent with the EAG scenario analyses and company's fully corrected base-case. The EAG base-case was most sensitive to the additional EAG scenario in which a PH Weibull extrapolation was applied for BVd, which suggest an increase in the average total QALYs ([redacted]) and costs [redacted]) for BVd compared to the EAG base-case analysis.

Finally, the EAG notes that all analyses in Section 6 assume that a 70mg vial of belamaf is available. The EAG did not formally test this assumption, as NICE has not indicated in the pricing tracker for this appraisal that the 70mg belamaf vial is unlikely to be available. If only the 100mg belamaf vial is available in the NHS, the average total cost for BVd in the EAG base-case analysis would increase by approximately [redacted]

7 SEVERITY MODIFIER

The CS presents an assessment of whether the severity modifier applies using current NICE guidance.[56] The severity modifier does not apply in the company's base case or scenario analyses.

The EAG checked the company's base-case calculations using the web-based QALY shortfall calculator provided by using the reference case settings (https://shiny.york.ac.uk/shortfall/) and are satisfied with the company's calculations.

The EAG also checked the company's scenarios and EAG additional analyses resulting in lower LYG and/or QALYs for the comparator treatments when compared to the company's base-case analysis. None of these analyses suggested that the severity modifier applies.

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Appendix A Literature searches

A1. Clinical effectiveness searches

The original company submission included searches to identify clinical evidence for adult patients with relapsed or refractory multiple myeloma. A description of the searches and some of the search strategies were included in Appendix D (CS pp. 7-21).

In response to the EAG's points for clarification, the company provided additional information and corrections to errors.

Table 45 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	The documentation contained several errors and was also unclear in numerous respects detailed below. In the original company submission, search strategies were not provided for conference proceedings. This was raised as a point for clarification. Although the company's response provided further details, documented copies of the search strategies were not provided. The documentation reported that the searches on the Ovid platform were conducted at two different points. This was incorrect, as the Ovid platform was only searched in the original set of searches. The update searches were performed on ProQuest. In the original company submission, the specific date limits applied within the searches of MEDLINE and Embase via ProQuest were not shown. Although the dates searched were provided, the search lines did not show how the date limits were applied. The same issue applied to the documentation of the second update of the Cochrane library and the update searches for International Health Technology Assessment database (INAHTA), clinicaltrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP). This was raised as a point for clarification and the company responded with the information. In the original company submission, line 2 of the searches of the Cochrane databases was missing. This was raised as a point for clarification and the company responded with additional documentation. However, line 2 was still missing in the updated document. It was misleading to list that Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessments (HTA) were searched up to 2021. DARE hasn't been updated since March 2015. HTA hasn't been updated since March 2018. For clinicaltrials.gov there are multiple search boxes for 'Condition/disease', 'Other terms', 'Intervention/treatment' and it was not clear which box(es) were used in conducting the search. In the original company submission, there were many differences between what the results of each database listed (or added up to) and what the various PRISMA diagrams stated. Moreover, the figures reported in the text of D.1.4.1 did not always match the PRISMA diagrams. There were numerous additional errors. Additionally, it was difficult to understand the PRISMA diagrams in places: the documentation of the Embase search via Ovid did not include the conference abstracts searched on line 49, so the last results line was difficult to understand in the context of the PRISMA. Moreover, the searches of Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) were combined in the documentation but separated in the PRISMA and did not add up to the same figures. This was raised as a point for clarification. The company provided additional documentation in response. However, this still contained various errors and inconsistencies.

Were appropriate sources searched?	YES	A good range of relevant databases, conference proceedings, grey literature sources and trials registry databases were searched.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study type.
Were appropriate search terms used?	PARTLY	For all sources searched, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. For instance, on Embase alone, there were several missing subject headings to represent treatment failure, recurrent disease, etc, and there are many more synonyms that could also have been searched as free-text terms for this concept. This was raised as a point for clarification. The company responded that they were not aware of any relevant studies that were missed. Only the title field was searched for WHO ICTRP. It would have been more sensitive to perform multiple searches of this source using the different fields available.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed. Studies were limited to English language.
Were any search filters used, validated and referenced?	YES	The Scottish Intercollegiate Guidelines Network (SIGN) randomised controlled trials filter was used and referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

A2. Cost-Effectiveness Searches

The original company submission included searches to identify cost-effectiveness studies, for adult patients with relapsed or refractory multiple myeloma. A description of the cost-effectiveness searches and the search strategies were included in Appendix G (pp. 7-17). In response to the EAG's points for clarification, the company provided additional information and corrections to errors. The EAG's assessment of the evidence identification strategy is reported in Table 46.

Table 46 EAG assessment of evidence identification – SLR of cost-effectiveness studies

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission, the documentation did not include the search strategies for the grey literature or website searches. This was raised as a point for clarification. Although the company's response provided further details, documented copies of the search strategies were not provided. In the original company submission, the figures shown in the PRISMA diagrams did not correspond with the results of the database searches, and it was not clear how many records were found through each source. This was raised as a point for clarification. The company provided additional documentation in response. However, this still contained various errors and inconsistencies.

Were appropriate sources searched?	PARTLY	A small range of relevant databases, conference proceedings, and grey literature sources and were searched. It would have been better to search additional databases for economic evidence.
Was the timespan of the searches appropriate?	YES	Date limits were used (and differed according to source of evidence) and were sufficient.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study types.
Were appropriate search terms used?	YES	For all sources searched, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. For instance, on Embase alone, there are several missing subject headings to represent treatment failure, recurrent disease, etc, and there are many more synonyms that could also have been searched as free-text terms for this concept. This was raised as a point for clarification. The company responded that they were not aware of any relevant studies that were missed.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed. Studies were limited to English language.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

A3. Health-Related Quality of Life Searches

The original company submission included searches to identify health-related quality of life studies for adult patients with relapsed or refractory multiple myeloma. A description of the searches was included in Appendix H (p. 4). However, the search strategies were included in Appendix G (pp. 7-17). In response to the EAG's points for clarification, the company provided additional information and corrections to errors. The EAG's assessment of the evidence identification strategy is reported in Table 47.

Table 47 EAG assessment of evidence identification– SLR of HRQoL studies

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission, the documentation did not include the search strategies for the grey literature or website searches. This was raised as a point for clarification. Although the company's response provided further details, documented copies of the search strategies were not provided. In the original company submission, the figures shown in the PRISMA diagrams did not correspond with the results of the database searches, and it was not clear how many records were found through each source. This was raised as a point for clarification. The company provided additional documentation in response. However, this still contained various errors and inconsistencies.

Were appropriate sources searched?	PARTLY	A small range of relevant databases, conference proceedings, and grey literature sources and were searched.
Was the timespan of the searches appropriate?	YES	Date limits were used (and differed according to source of evidence) and were sufficient.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study types.
Were appropriate search terms used?	YES	For all sources searched, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. For instance, on Embase alone, there are several missing subject headings to represent treatment failure, recurrent disease, etc, and there are many more synonyms that could also have been searched as free-text terms for this concept. This was raised as a point for clarification. The company responded that they were not aware of any relevant studies that were missed.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed. Studies were limited to English language.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

A4. Cost and Healthcare Resource Identification, Measurement and Valuation Searches

The original company submission included searches to identify cost and healthcare resource identification, measurement and valuation studies for adult patients with relapsed or refractory multiple myeloma. A description of the searches was included in Appendix I (p. 4). However, the search strategies were included in Appendix G (pp. 7-17). In response to the EAG's points for clarification, the company provided additional information and corrections to errors. The EAG's assessment of the evidence identification strategy is reported in Table 48.

Table 48 EAG assessment of evidence identification – – SLR of costs and resource use SLR studies

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission, the documentation did not include the search strategies for the grey literature or website searches. This was raised as a point for clarification. Although the company's response provided further details, documented copies of the search strategies were not provided. In the original company submission, the figures shown in the PRISMA diagrams did not correspond with the results of the database searches, and it was not clear how many records were found through each source. This was raised as a point for clarification. The company provided additional documentation in response. However, this still contained various errors and inconsistencies.

Were appropriate sources searched?	PARTLY	A small range of relevant databases, conference proceedings, and grey literature sources and were searched. It would have been better to search additional databases for economic evidence.
Was the timespan of the searches appropriate?	YES	Date limits were used (and differed according to source of evidence) and were sufficient.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition with the study types.
Were appropriate search terms used?	YES	For all sources searched, the search terms for the relapsed or previously treated concept could have used several additional terms to increase sensitivity. For instance, on Embase alone, there are several missing subject headings to represent treatment failure, recurrent disease, etc, and there are many more synonyms that could also have been searched as free-text terms for this concept. This was raised as a point for clarification. The company responded that they were not aware of any relevant studies that were missed.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed. Studies were limited to English language.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not referenced.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Appendix B Additional Tables

Table 49 Baseline characteristics of studies included in the EAG's simplified network.

	BOSTON		ENDEAVOR		CASTOR		LEPUS		DREAMM-7	
	SVd (N=195)	**Vd** (N=207)	**hKd** (N=464)	**Vd** (N=465)	**DVd** (N = 251)	**Vd** (N=247)	**DVd** (N=141)	**Vd** (N=70)	**BVd** (N=243)	**DVd** (N=251)
Age, years										
Med (Range)	66 (59-72)[a]	67 (61-74)	65 (35-89)	65 (30-88)	64 (30-88)	64 (33-85)	61 (28-79)	61 (43-82)	65 (34-86)	64 (32-89)
Sex, n(%)										
Male	115 (59)	115 (56)	240 (52)	229 (49)	137 (54.6)[b]	147 (59.5)[b]	85 (60.3)	42 (60.0)	128 (53)	144 (57)
Race, n (%)										
White	NR	NR	348 (75)	353 (76)	216 (86.1)[b]	219 (88.7)[b]	NR[f]	NR[f]	206 (85)	203 (81)
Asian	NR	NR	58 (13)	57 (12)	12 (4.8)[b]	11 (4.5)[b]	NR[f]	NR[f]	28 (12)	33 (13)
Black	NR	NR	8 (2)	9 (2)	14 (5.6)[b]	6 (2.4)[b]	NR[f]	NR[f]	8 (3)	12 (5)
ECOG PS, n (%)										
0	69 (35)	77 (37)	221 (48)	232 (50)	106 (42.4)[b]	116 (47.0)[b]	64 (45.4)	27 (38.6)	232 (96)[e]	235 (96)[e]
1	106 (54)	114 (55)	211 (45)	203 (44)	131 (52.4)[b]	112 (45.3)[b]	70 (49.6)	35 (50.0)		
2	20 (10)	16 (8)	32 (7)	30 (6)	13 (5.2)[b]	19 (7.7)[b]	7 (5.0)	8 (11.4)	NR	NR
ISS Stage, n (%)										
I	173 (89)[‡]	177 (86)[c]	205 (44)	204 (44)	98 (39.0)	96 (38.9)	72 (51.1)	34 (48.6)	102 (42)	103 (41)
II			259 (56)	261 (56)	94 (37.5)	100 (40.5)	45 (31.9)	22 (31.4)	130 (53)	132 (53)
III	12 (6)[‡]	16 (8)[c]			59 (23.5)	51 (20.6)	24 (17.0)	14 (20.0)	9 (4)	14 (6)
Cytogenic Profile, n (%)										
High risk	NR	NR	97 (21)	113 (24)	41 (22.7)	37 (21.3)	46 (33.3)[d]	27 (39.7)[d]	67 (28)	69 (27)
Standard risk	NR	NR	284 (61)	291 (63)	140 (77.3)	137 (78.7)	92 (66.7)[d]	41 (60.3)[d]	175 (72)	175 (70)

a. The trial reported Median(IQR). b. EAG extracted these data from the company submission included in the committee papers for TA897. c. The revised-ISS (or R-ISS) was reported for this trial. d. The denominator for DVd and Vd were 138 and 68, respectively. e. The denominator for B-Vd and DVd were [redacted] and [redacted], respectively. f. This trial was conducted on Chinese patients in mainland China and Taiwan. **Abbreviations:** BVd; belamaf in combination with bortezomib and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; ECOG PS, Eastern cooperative oncology group performance score; hKd, high dose carfilzomib and dexamethasone; IQR, interquartile range; ISS, International Staging System; Med, median; NR, not reported; PS, performance score; SVd, selixnor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

Table 50 Summary of prior lines of therapy in studies included in the EAG's simplified network.

	BOSTON		ENDEAVOR		CASTOR		LEPUS		DREAMM-7	
	SVd (N=195)	**Vd** (N=207)	**hKd** (N=464)	**Vd** (N=465)	**DVd** (N = 251)	**Vd** (N=247)	**DVd** (N=141)	**Vd** (N=70)	**BVd** (N=243)	**DVd** (N=251)
Prior Lines of Therapy, n (%)										
Median (IQR)	NR	NR	2 (1-2)	2 (1-2)	2 (1-9)	2 (1-10)	2 (1-11)	2 (1-7)	NR	NR
1	99 (51)	99 (48)	232 (50)	232 (50)	122 (49)	113 (46)	41 (29)	19 (27)	125 (51)	125 (50)
2	65 (33)	64 (31)	157 (34)	145 (31)	70 (28)	74 (30)	45 (32)	25 (36)	88 (36)	99 (39)
3	31 (16)	44 (21)	75 (16)	87 (19)	37 (15)	32 (13)	25 (18)	8 (11)		
4	0	0	0	1 (<1)†	22 (9)	28 (11)	30 (21)	18 (26)	30 (12)	27 (11)
> 4	0	0	0	0						
Prior drug exposure, n (%)										
Bortezomib	134 (69)	145 (70)	250 (54)	252 (54)	162 (65)	164 (66)	110 (78)	57 (81)	210 (86)	216 (86)
Thalidomide	NR	NR	211 (45)	247 (53)	125 (50)	121 (49)	NR	NR	121 (50)	144 (57)
Lenalidomide	77 (39)	77 (37)	177 (38)	177 (38)	89 (36)	120 (49)	48 (34)	26 (37)	127 (52)	130 (52)
Daratumumab	11 (6)	6 (3)	NR	NR	NR	NR	NR	NR	3 (1)	4 (2)
Refractory Status, n (%)										
IMiDs	NR	NR	NR	NR	83 (33)	97 (39)	41	93	[redacted]	[redacted]
Lenalidomide	NR	NR	113 (24)	122 (26)	45 (18)	60 (24)	35 (25)	21 (30)	79 (33)	87 (35)
Thalidomide	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]
PI	NR	NR	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]
Bortezomib	NR	NR	15 (3)	19 (4)	NR	NR	NR	NR	[redacted]	[redacted]
Last LOT	NR	NR	NR	NR	76 (30)	85 (34)	96 (68)	39 (56)	NR	NR

†This was a protocol deviation. **Abbreviations**: BVd; belamaf in combination with bortezomib and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; hKd, high dose carfilzomib and dexamethasone; IMiDs, immunomodulatory drugs; IQR, interquartile range; LOT, line of therapy; NR, not reported; PI, proteasome inhibitors; SVd, selixnor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

Table 51 Results for all NMAs conducted for progression-free survival (PFS)

BVd vs. HR (95% CrI)	ITT Population			1 Prior Line of Therapy		Lenalidomide-Refractory		Lenalidomide-Exposed
	CS Results[a]	Company Update[b]	EAG Update[c]	CS Results[a]	EAG Update[c]	CS Results[a]	EAG Update[c]	CS Results[d]
CyKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CyVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hkDd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IhKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. Results that were reported in the CS. b. Results generated by the company using the updated data, reported in powerpoint file[46], c. Results generated by the EAG using updated data and the company's code. d. The company did not provide updated data for this subgroup, therefore the EAG was unable to conduct this analysis themselves.
Relevant comparators that were included in the EAG's simplified network are shaded grey. Where there was no evidence for a comparator results were not generated in the NMA, indicated by '---' in the table.
Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; CrI, credible interval; CyVd, cyclophosphamide in combination with bortezomib and dexamethasone; CyKd, carfilzomib, cyclophosphamide and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; EVd, elotuzumab in combination with bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; hkDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; HR, hazard ratio; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; Kd, carfilzomib and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; PVd, pomalidomide in combination with bortezomib and dexamethasone; SVd, selinexor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone

Table 52 Results for all NMAs conducted for overall survival (OS)

BVd vs. HR (95% CrI)	ITT Population			
	CS Results[a]	Company Update[b]	EAG Update 1[c]	EAG Update 2[c]
CyKd	[redacted]	[redacted]	[redacted]	[redacted]
CyVd	[redacted]	[redacted]	[redacted]	[redacted]
DVd	[redacted]	[redacted]	[redacted]	[redacted]
EVd	[redacted]	[redacted]	[redacted]	[redacted]
hKd	[redacted]	[redacted]	[redacted]	[redacted]
hkDd	[redacted]	[redacted]	[redacted]	[redacted]
IhKd	[redacted]	[redacted]	[redacted]	[redacted]
Kd	[redacted]	[redacted]	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]	[redacted]	[redacted]
PVd	[redacted]	[redacted]	[redacted]	[redacted]
SVd	[redacted]	[redacted]	[redacted]	[redacted]
Vd	[redacted]	[redacted]	[redacted]	[redacted]

a. Results that were reported in the CS. b. Results generated by the company using the updated data, reported in powerpoint file[46], c. Results generated by the EAG using updated data and the company's code d. Results generated by the EAG using updated data, including the most recent evidence for the LEPUS study. e. The dataset provided to the EAG included data that allowed this comparison to be included in the network, but the company did not present results in their updated analysis.
Relevant comparators that were included in the EAG's simplified network are shaded grey. Where there was no evidence for a comparator results were not generated in the NMA, indicated by '---' in the table.
Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; CrI, credible interval; CyVd, cyclophosphamide in combination with bortezomib and dexamethasone; CyKd, carfilzomib, cyclophosphamide and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; EVd, elotuzumab in combination with bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; hkDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; HR, hazard ratio; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; Kd, carfilzomib and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; PVd, pomalidomide in combination with bortezomib and dexamethasone; SVd, selinexor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone

Table 53. Results for all NMAs conducted for overall response rate (ORR)

BVd vs. OR (95% CrI)	ITT Population			Lenalidomide-Refractory		Lenalidomide-Exposed
	CS Results[a]	Company Update[b]	EAG Update[c]	CS Results[a]	EAG Update[c]	CS Results[d]
CyKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CyVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hkDd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IhKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. Results that were reported in the CS. b. Results generated by the company using the updated data, reported in PowerPoint file[46], c. Results generated by the EAG using updated data and the company's code. d. The company did not provide updated data for this subgroup, therefore the EAG was unable to conduct this analysis themselves. e. SVd was not included in the original network in the CS, but was part of the updated dataset provided to the EAG by the company during clarifications.

Relevant comparators that were included in the EAG's simplified network are shaded grey. Where there was no evidence for a comparator results were not generated in the NMA, indicated by '---' in the table.

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; CrI, credible interval; CyVd, cyclophosphamide in combination with bortezomib and dexamethasone; CyKd, carfilzomib, cyclophosphamide and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; EVd, elotuzumab in combination with bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; hkDd, high dose carfilzomib in combination with daratumumab, and dexamethasone; IhKd, isatuximab in combination with high dose carfilzomib and daratumumab; ITT, intent to treat; Kd, carfilzomib and dexamethasone; OR, odds ratio; PanoVd, panobinostat in combination with bortezomib and dexamethasone; PVd, pomalidomide in combination with bortezomib and dexamethasone; SVd, selinexor in combination with bortezomib and dexamethasone; Vd, bortezomib and dexamethasone

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Single technology appraisal

[ID6212]

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments

Further information requested

May 2025

File name	Version	Contains confidential information	Date
ID6212_Belantamab mafodotin with bortezomib and dexamethasone_further information requested document_19May2025_FINAL_v1.0.docx	V1.0	Yes	19/05/25

Context

The decision problem for this submission relates to the clinical and cost-effectiveness of belantamab mafodotin (belamaf) plus bortezomib and dexamethasone (BVd) in adults with relapsed/refractory multiple myeloma (MM) and, who have received only one prior therapy.

1. Provide the DREAMM-7 most recent data cut for 2L only population

Since the previous communications with NICE, we now have the latest IA2 overall survival (OS) data cut for the population aligned with the SACT dataset incorporated into the model (2L patients exposed to lenalidomide). We have updated the model accordingly, please find these changes in cells C85:F85 in the 'Data Store' sheet.

Notably, this data shows an improvement to the BVd OS outcomes versus the approach previously recommended by GSK (IA2 intention-to-treat [ITT]). Both sets of hazard ratios are illustrated in Table 1 below.

Table 1: OS hazard ratios (BVd versus DVd)

Population	Hazard ratio	Lower bound	Upper bound
DREAMM-7 - IA2 2L Lenalidomide-exposed	[redacted]	[redacted]	[redacted]
DREAMM-7 - IA2 ITT	0.58	0.43	0.79

The impact of implementing this change on the model is to improve the cost-effectiveness of belamaf versus using the IA2 ITT hazard ratio (Table 2).

Table 2: Impact of IA2 2L LE data for SACT population (Belamaf net vs DVd list)

Comparator	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
D-Vd	[redacted]	[redacted]	-	-	-
B-Vd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

2. Use the DVd SACT data to inform the comparison of BVd vs. KRd

The functionality for including the KRd arm within the economic model (with the SACT analysis) is already applied. Previously the switch was disabled given the SACT analysis is reflective of a 2L Lenalidomide exposed population.

The company have tweaked the model to allow KRd to be modelled within the SACT population ('Settings'!G37). Given hazard ratios are used to estimate KRd PFS, OS and TTD based on adjustments to the BVd arm of the model, the cost-effectiveness impact between KRd and BVd is relatively minor by using an approach incorporating SACT

(compared to model shared previously on the 17th February 2025). This is because any increase in the efficacy of BVd is subsequently reflected by changes to efficacy the KRd arm. Table 3 below indicates that after making this change.

Table 3: Impact on results – (Belamaf PAS vs. comparator list price)

Comparator	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
KRd	[redacted]	[redacted]	-	-	
BVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Note: These settings include SACT OS for DVd (Weibull) and IA2 ITT HR applied for BVd OS and Carfilzomib stopping rule. All other settings are aligned to the committee and EAG preferred base-case shared previously.

3. Present the impact of using other curves between Weibull and Gompertz

Table 4 shows the corrected DVd OS parametric extrapolations and goodness of fit statistics that we submitted on 17th April 2025. We apologise that our explanation of negative AIC / BIC scores was confusing, but we note that GSK did in fact correctly select the statistically best fitting curve (i.e. the curve with the lowest AIC and BIC score, the Weibull curve).

Table 4: DVd OS parametric distribution and goodness of fit statistics

Function	AIC	BIC
Exponential	-128.356	-125.188
Weibull	-256.418	-251.667
Gompertz	-207.475	-202.725
Log-logistic	-242.488	-237.737
Lognormal	-221.399	-216.648
Generalised Gamma	NA	NA

Expert validation indicates that the log-logistic and lognormal curves are optimistic and not clinically plausible. Consequently, we disagree with changing the base case curve away from the Weibull and Table 5 below justifies the Weibull curve selection and further highlights the lack of agreement between the external expert opinion and the log-logistic and lognormal curves.

Table 5: DVd SACT OS extrapolation versus DREAMM-7 DVd clinical validation (IA1)

Parametric curve (DVd)	**Survival – 5 years**	**Survival – 10 years**	**Survival – 15 years**
DREAMM-7 clinical validation (Average of 3 EE's, most likely %)	45%	28%	8%
DVd SACT – Weibull	[redacted]	[redacted]	[redacted]
DVd SACT – Log-logistic	[redacted]	[redacted]	[redacted]
DVd SACT – Lognormal	[redacted]	[redacted]	[redacted]

Regardless, the cost-effectiveness results are illustrated in Table 6, Table 7 and Table 8 below for completeness (Belamaf PAS vs. List for DVd). Given hazard ratios are applied to the DVd OS to estimate BVd OS, the choice of OS baseline DVd curve from SACT has minor impact on cost-effectiveness.

Table 6: Cost-effectiveness results - OS SACT (Weibull) – IA2 ITT HR used for BVd OS

Comparator	**Total Costs (£)**	**Total QALYs**	**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
D-Vd	[redacted]	[redacted]	-	-	
B-Vd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Table 7: Cost-effectiveness results - OS SACT (Log-logistic) – IA2 ITT HR used for BVd OS

Comparator	**Total Costs (£)**	**Total QALYs**	**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
D-Vd	[redacted]	[redacted]	-	-	
B-Vd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Table 8: Cost-effectiveness results - OS SACT (Lognormal) – IA2 ITT HR used for BVd OS

Comparator	**Total Costs (£)**	**Total QALYs**	**Inc. Costs (£)**	**Inc. QALYs**	**ICER (£/QALY)**
D-Vd	[redacted]	[redacted]	-	-	

B-Vd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

4. Add a stopping rule for KRd after 18 cycles

Given that the BluTeq criteria for KRd align with a stopping rule of 18 cycles, the company agrees that this should be incorporated into the model. We apologize for this error. While our approach was aligned with the SmPC for carfilzomib,[1] we did not check the Blueteq criteria for KRd specifically.[2]

Details of the update to the cost-effectiveness model are listed in the 'Change log – 19th May' sheet shared with this response. Table 3 (see response to question 2) indicates that after making this change.

Notwithstanding the output of Table 3, we are aware that both carfilzomib and lenalidomide have confidential discounts which could therefore results in ICERs >£25k, and potentially even >£30k. Under these circumstances, GSK proposes that it would still be a cost-effective use of NHS resources to approve belamaf in the lenalidomide naïve subpopulation.

1. **Equitable access:** For patients diagnosed prior to the introduction of lenalidomide in the front-line setting (transplant ineligible: 2019, TA587; transplant ineligible: 2021, TA680), GSK would, if possible, like to see access granted for all patients at second line (2L), regardless of prior lenalidomide exposure, due to the high unmet need for more effective treatment options with novel mechanisms of action at first relapse, and the well-established principle in myeloma management of using the most effective therapy as early as possible to maximise benefit.
2. **The lenalidomide-naïve population is small, and it will decline over the next few years:** Lenalidomide naïve patients eligible for KRd at 2L (as per current BluTeq criteria)[2] represent a small population compared to their lenalidomide-exposed counterparts, who are eligible for DVd, Kd, or SVd. Over the next few years, practically all 2L patients will have been previously treated with lenalidomide, and thus few patients – if any – will remain eligible for KRd at 2L.[3] Consequently, the risk of making an incorrect decision in this subpopulation is very low (as the subpopulation is already small and shrinking over time) and the benefits for approving in this subpopulation are high, due to the high unmet need highlighted in the previous point.
3. **The figures presented in Table 3 underestimate the cost-effectiveness of belamaf.** The KRd model presented was a simple approach to allow an estimate

to be made of the cost-effectiveness in a small subpopulation. A more complete model would, for example:

- Incorporate more realistic TTD for KRd
- Investigating independent modelling of BVd and KRd

To estimate the impact of the first scenario on outcomes, a scenario has been included to set TTD as equal to PFS, reflecting a profile more similar to DVd (available in 'Clinical Inputs'!D91) based on a scenario requested by the EAG in TA695.

In the interests of equity, the transient nature of the lenalidomide-naïve population, and in recognition of how far GSK have gone to provide lower ICERs than required in the lenalidomide-exposed population, GSK request that this lenalidomide-naïve population is nevertheless approved.

If this is not feasible, GSK requests that this appraisal focusses on the proposed population from the original submission below, in order to avoid any further delays for patients at 2L:

Proposed population:

Belantamab mafodotin with bortezomib and dexamethasone as an option for treating multiple myeloma in adults, only if they have had just 1 previous line of treatment and:

- *it included lenalidomide or*
- *lenalidomide is unsuitable as a second-line treatment*

5. Implement a starting age of 70 and ocular AE disutilities

GSK notes that they disagree with the above request on methodological grounds. Nevertheless, in the interests of swift access they have been incorporated into our results within our other responses. As acknowledged by the Committee, they have a negligible impact.

6. References

1: Kyprolis. Summary of Product Characteristics. Amgen Ltd.

2: National Cancer Drugs Fund List. Version 1.363, Page 92, 16 May 2025. Available from: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/

3: DREAMM-7, EAG report, page 23

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Single technology appraisal

[ID6212]

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments

Technical Appendix

Feb 2025

File name	Version	Contains confidential information	Date
ID6212_Belantamab mafodotin with bortezomib and dexamethasone_Technical Appendix.docx	V1.0	Yes	14/02/25

Context

The decision problem for this submission relates to the clinical and cost-effectiveness of belantamab mafodotin (belamaf) plus bortezomib and dexamethasone (BVd) in adults with relapsed/refractory multiple myeloma (MM) and, who have received only one prior therapy.

As there is considerable unmet need in current NHS practice at 2L for new, more effective options with new mechanisms of action, and both GSK and NICE agree that a path to reimbursement prior to marketing authorisation is preferred to a second Committee meeting, if this is possible. To that end, on 10/02/25, NICE communicated to GSK that they would value an opportunity to see an updated base case prior to making a decision on the indication.

The 'Committee Preferred Final Assumptions' document outlines how the Company have adapted the model to incorporate these updated base case preferences, and this technical appendix gives details on the three more technical changes which have been made to the model:

1. Details of analysis against KRd (Carfilzomib plus lenalidomide and dexamethasone)
2. Details of incorporation of SACT data as a DVd baseline curve
3. Details of DREAMM-7 Interim Analysis 2 (IA2)

1. *Analysis against KRd (Carfilzomib plus lenalidomide and dexamethasone)*

1.1. Background

The following analysis is applied to the economic model, following the Committee's preferences for an analysis incorporating comparators aligned to a broader second-line population:

"Comparators should be updated to include all currently available treatment options for the updated population submitted by the company (see positioning of BEL+BOR+DEX above)."

Cost-effectiveness analysis was undertaken using the results outputted from the Matching-Adjusted Indirect Comparison for belamaf mafodotin plus bortezomib and dexamethasone (BVd) versus Carfilzomib plus lenalidomide and dexamethasone (KRd). Further background of the methods of the MAIC are detailed in the reference pack ('DREAMM7-ASPIRE MAIC RRMM - KRd versus BVd - Methodology_17Feb2025_FINAL'), while detail of the MAIC results are available in the summary results PPT included in the reference pack ('DREAMM-7 and ASPIRE MAIC summary results IA2 v1.0').

Comparison between BVd and KRd was incorporated into the latest CEM to allow for the cost-effectiveness of BVd to be investigated for patients naïve to prior lenalidomide treatment (or otherwise suitable for lenalidomide treatment) in second-line multiple myeloma (MM) therapy.

1.2. Model functionality

In the 'Settings' sheet, a switch updates the hKd comparator throughout the model to incorporate all inputs suitable for cost-effectiveness analysis of KRd, including efficacy outputs (PFS, OS, TTD), Adverse event costs, treatment acquisition costs and administration costs.

Once this switch is set, the KRd comparator has full functionality in the model, including the functionality of the OWSA and PSA analysis. Note that inclusion of KRd

allows only for pairwise cost-effectiveness analysis between KRd and BVd; this is aligned with NHS treatment practices in 2L MM, where patients who are suitable for a lenalidomide-containing regimen will likely receive KRd while those who are unsuitable for a lenalidomide-containing regimen will likely receive DVd, and the two therapies are not reasonable alternatives for each other.

1.3. **Survival extrapolation**

The MAIC analyses KRd versus BVd arm only from the DREAMM-7 trial. Therefore, in the economic model the results of the MAIC analysis is applied to the survival extrapolations of the BVd arm (PFS, OS, TTD), using the ITT population as the reference arm.

Hazard ratios for OS and PFS were applied directly to the unweighted DREAMM-7 BVd arm for the ITT population. This method was chosen for the following reasons:

- The weighted BVd and the unweighted BVd arms (red and green curves in Figure 1 below) were considered sufficiently similar, such that incorporating a weighted BVd arm into the model was unlikely to impact results (and therefore decision making) but may have introduced unnecessary complexity into the analysis. Importantly, the OS curves are particularly close aligned, which is the main driver of the cost-effectiveness in the economic model.

- The overlapping overall survival KM curves between KRd and BVd (Figure 1) poses a challenge. This indicates the likelihood that proportional hazards do not hold, which is to say that BVd's survival advantage increases over time. Applying hazard ratios is the most conservative response to these data, as it enforces an assumption of proportional hazards and removes this long-terms survival advantage from BVd. The purpose behind this is to demonstrate that any analysis which is cost-effective using the practical hazard ratio approach would also be cost-effective using the more complex approach, and hence the Committee can confidently make decisions on the analysis.

Figure 1: PFS and OS Kaplan Meier curves from the MAIC analysis

1.4. Hazard ratios

PFS, and OS curves were estimated for KRd by applying the MAIC HRs to the extrapolated BVd ITT data of the corresponding outcome.

No published TTD data were available to inform the MAIC, and so the approach used in the main submission was applied to the MAIC analysis (similar to other indirect comparators). Specifically, KRd HRs are applied to BVd TTD extrapolation using PFS HRs from the MAIC versus BVd as a proxy, assuming PH of KRd TTD to BVd TTD.

GSK notes that this has severely conservative implications for the cost-effectiveness of BVd compared to KRd; The relationship between BVd PFS and BVd TTD is abnormal and is not expected to compare to other comparators (such as DVd). Figure 2 below illustrates the different profile of DVd and BVd in terms of relationship between PFS and TTD in DREAMM-7. PFS is shown to widely diverge from TTD for the BVd arm (indicating a substantial proportion of patients treated with BVd remain progression-free while off-treatment), whereas for DVd these curves are closely aligned (indicating the majority of patients treated with DVd and progression-free remained on treatment). That is to say, applying the same relationship to KRd that BVd has between PFS and TTD likely creates a highly conservative approach to the KRd treatment costs

Figure 2: DREAMM-7 IA2 Kaplan Meier curves - PFS, OS and TTD

Again, the purpose behind this is to adopt the most conservative assumptions possible, which will in turn give the Committee a high degree of confidence around the cost-effectiveness against KRd. GSK proposed this greatly limits the scope for decision error, and therefore reduces the need for a further delay in approval.

1.5. Efficacy data inputs

The hazard ratios used in the model from the summary MAIC report are outlined below in Table 1 - Table 3. While the 'No R-ISS' analysis was used in the base-case (detail for this is outlined in the summary results PPT), all scenarios are incorporated into the model for appropriate scenario analysis to test the robustness of the MAIC.

1.5.1. Progression-free survival

Table 1: PFS inputs from MAIC analysis

Setting	Analysis	BVd vs KRd		
		Hazard ratio	Lower bound	Upper bound
Base-case	Weighted MAIC analysis (No R-ISS)	[redacted]	[redacted]	[redacted]
Scenario analyses	Naïve (unweighted) comparison	[redacted]	[redacted]	[redacted]
	All PFs and TEMs adjusted	[redacted]	[redacted]	[redacted]
	Excluding cytogenic risk	[redacted]	[redacted]	[redacted]
	Excluding >=4 prior LOTs	[redacted]	[redacted]	[redacted]

1.5.2. Overall survival

Table 2: OS inputs from MAIC analysis

Setting	Analysis	BVd vs KRd		
		Hazard ratio	Lower bound	Upper bound
Base-case	Weighted MAIC analysis (No R-ISS)	[redacted]	[redacted]	[redacted]
Scenario analyses	Naïve (unweighted) comparison	[redacted]	[redacted]	[redacted]
	All PFs and TEMs adjusted	[redacted]	[redacted]	[redacted]
	Excluding cytogenic risk	[redacted]	[redacted]	[redacted]
	Excluding >=4 prior LOTs	[redacted]	[redacted]	[redacted]

1.5.3. Adverse events

Adverse event incidence were taken from the ASPIRE trial and are outlined in the table below.

Table 3: AE incidence rates from ASPIRE

Adverse event	Incidence of adverse events applied in the CEM		Reference
	BVd	KRd	
Neutropenia	0.12	0.31	ASPIRE trial (Siegel, et al., 2018)
Anaemia	0.14	0.19	
Thrombocytopenia	0.55	0.17	
Lymphopenia	0.10	0.00	
Pneumonia	0.12	0.16	
Peripheral neuropathy	0.05	0.03	
Hypertension	0.06	0.06	
Leukopenia	-	0.00	
Nausea	-	0.01	
Diarrhoea	0.04	0.05	
Fatigue	0.05	0.08	
Dyspnoea	0.04	0.00	
Back pain	-	0.02	
Hypokalaemia	-	0.11	

1.6. Other modelling assumptions

Except where indicated above, all modelling assumptions are as per the base-case model. Some costing data sources have been updated to align to the new comparator:

- Treatment costs (dosage, administration and administration method) was sources from the Carfilzomib SmPC (Amgen, 2024) Relative dose intensity (RDI) was taken from the ASPIRE trial, outlined in TA695 (National Institute for Health and Care Excellence, 2021), while drug costs were elicited from the Carfilzomib BNF for the 30mg vial size (National Institute for Health and Care Excellence, n.d.).

- Health state resource use was assumed to align with hKd (high-dose carfilzomib plus dexamethasone), given similar dosing scheduling between the two comparators.

- Subsequent treatment costs were adjusted to align between comparators by the EAG. Therefore, a similar approach was assumed with KRd, that subsequent treatment costs are aligned between comparators (and the only impact on results is from the delay of progression through the discounting of delayed subsequent treatment costs).

1.7. Results

The results below show BVd to dominate KRd using the methodology outlined above, and the new base-case outlined by the committee.

Summary table for ICER of BVd versus KRd using IA-2 DREAMM-7 data (new base-case) – List (KRd) versus PAS (BVd)

	Total Costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY) BVd vs comparator
KRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

2. Incorporation of SACT data as a DVd baseline curve

2.1. Background

The following analysis is applied to the economic model as a scenario following the Committee's preferences for an analysis using SACT data:

"The committees preferred base case is to use overall survival data from SACT for DAR+BOR+DEX to estimate the absolute baseline curve, with the relative effects for BEL+BOR+DEX from DREAMM-7 applied"

"Updated analyses based on the preferred population (2L only OR 2L/3L LEN exposed). The committees preferred base case is to use overall survival data from SACT for DAR+BOR+DEX to estimate the absolute baseline curve, with the relative effects for BEL+BOR+DEX from DREAMM-7 applied."

Please note the general comments made on this approach in the document 'Committee Preferred Final Assumptions'. GSK's position is that this is not a methodologically sound approach in comparison to using directly-elicited RCT data. However, the methodology and results of these analyses are presented below for completeness.

2.2. Data Source

Systemic Anti-Cancer Therapy data set (SACT) data was requested from NHS England, and a publication was identified which fit this criteria (RWE of DVd usage in the NHS 2L len-exposed setting, Lawton et al. (2024) (Lawton, Bishton, Clark, Thackray, & Smith, 2024). Real-world data on patient outcomes was collected though the SACT by the National Disease Registration Service (NDRS) for comparisons against CASTOR phase III clinical trial results.

The data used was in line with the current recommendation after the CDF exit of DVd in June 2023:

"Daratumumab with bortezomib and dexamethasone is recommended as an option for treating multiple myeloma in adults, only if they have had just 1 previous line of treatment and:

- *it included lenalidomide or*

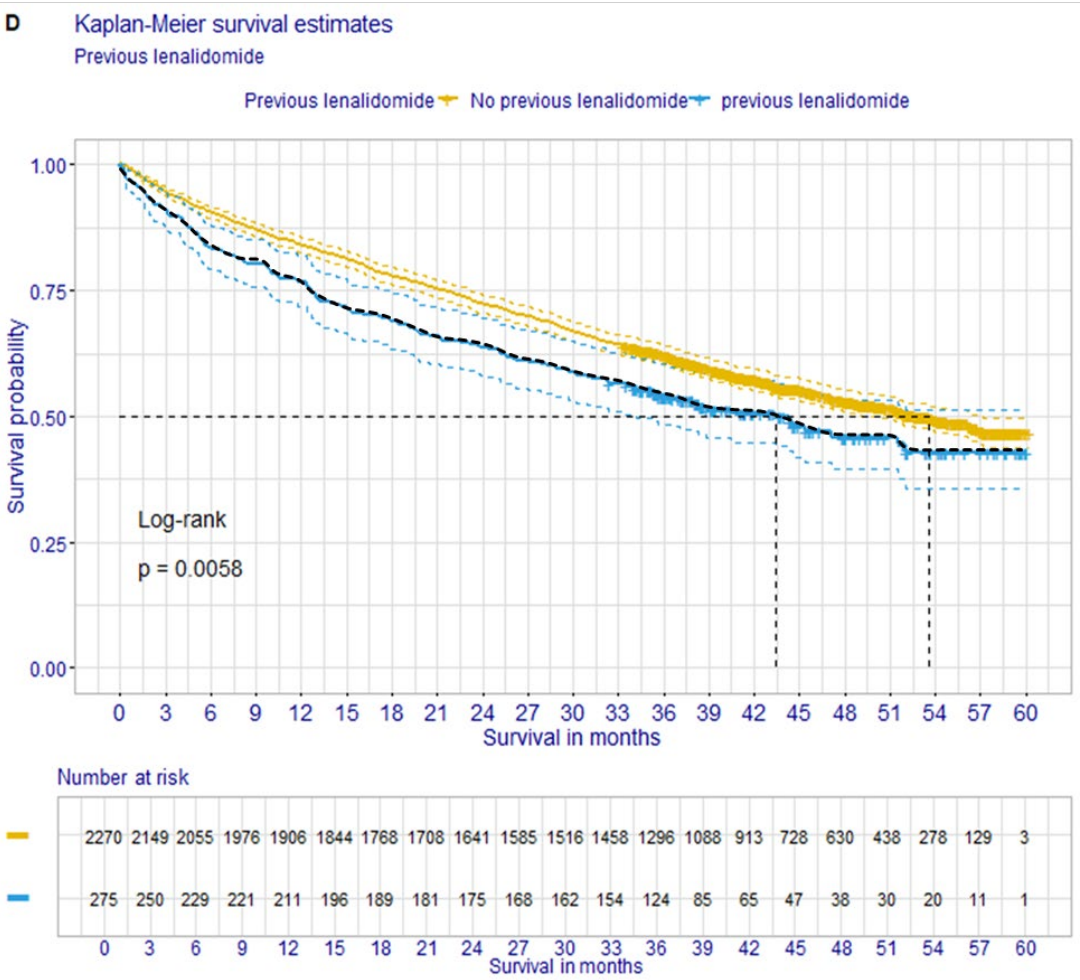
- *Lenalidomide is unsuitable as a second-line treatment"*

A suitable proxy aligning for patients eligible to receive DVd was therefore identified in the publication; patients who have received previous lenalidomide.

2.3. **Digitisation exercise**

The KM curve for SACT DVd for patients treated with prior lenalidomide was extracted from the figures in the Lawton et al. publication using digitisation and the flexsurv package in R to fit associated parametric survival curves. Figure 3 below shows the overall survival Kaplan Meier from Lawton et al., the black line overlaid onto the figure illustrates the digitised Kaplan Meier curve generated from the reconstructed digitised curve. This resulting Kaplan Meier curve was then incorporated into the economic model.

Figure 3: Lawton et al. OS KM data overlaid with the digitised KM data



To validate the approach, the KM curve generated by the digitisation exercise was overlaid onto the KM curve from the DREAMM-7 trial (ITT population). The correspondence between the two curves – displayed in Figure 4 - was excellent, implying that the DREAMM-7 trial ITT data was a good proxy for NHS clinical practice.

Figure 4: Digitised patient-level data overlaid with the DREAMM-7 KM curve

2.4. Fitting of curves to digitised KM data (PFS, OS)

Six standard parametric distributions have been fitted to the DVd SACT KM data using R software (Exponential, Weibull, Gompertz, log-logistic, log-normal and Generalised Gamma). Due to lack of convergence, the Generalised Gamma curve was excluded from the analysis. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) are used to estimate the goodness of fit for each parametric distribution.

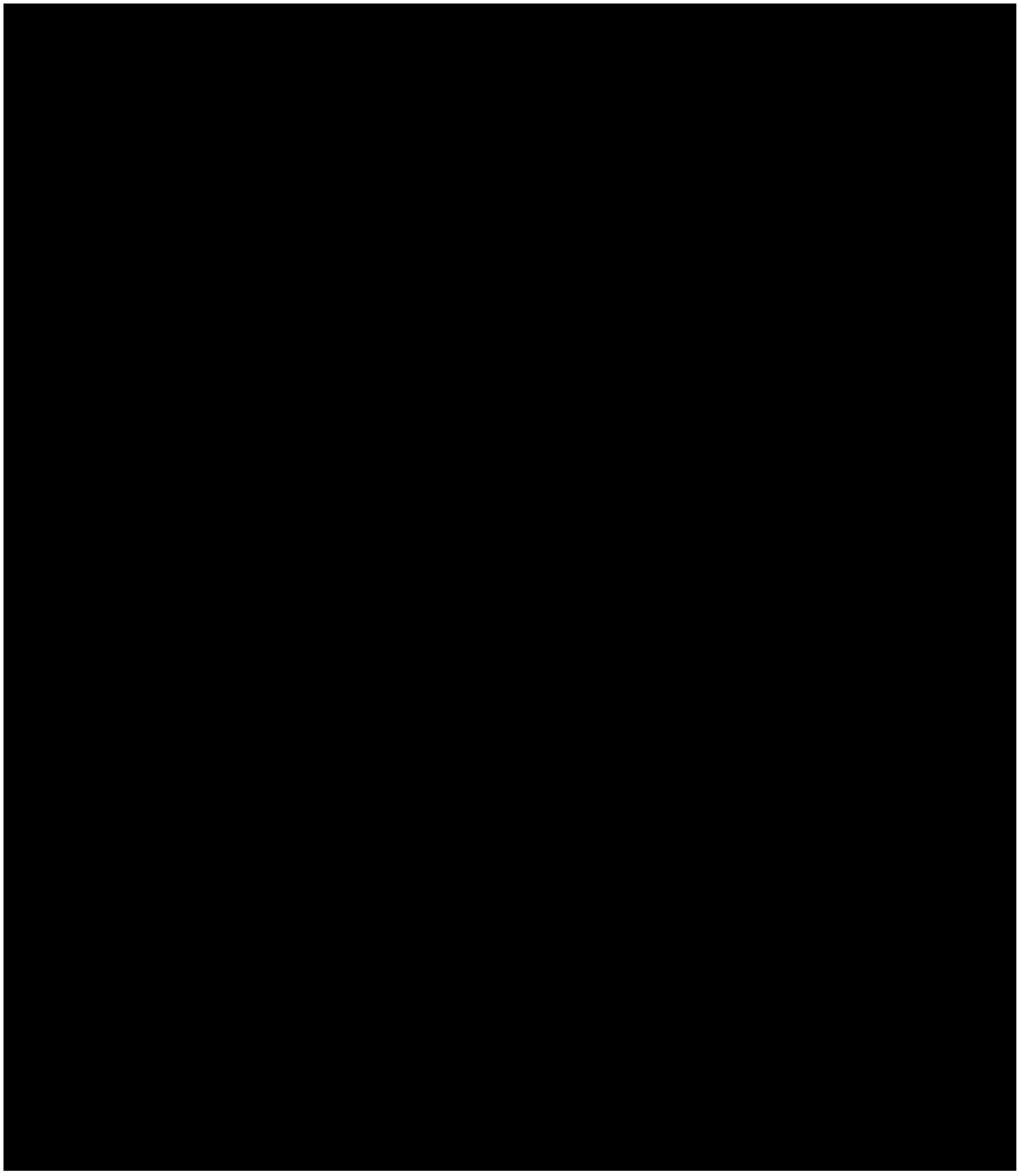
Table 4 displays the numerical outputs of this exercise, while Figure 5 visually displays these extrapolations on a graph overlaid with the SACT RWE data. Note that negative AIC / BIC have the same interpretation as positive AIC / BIC, in that smaller absolute magnitudes indicate better fit.

Table 4- DVd parametric distribution coefficients and goodness of fit statistics

Function	Parameter	Coefficient	AIC	BIC
Exponential	Rate	[redacted]	[redacted]	[redacted]
Weibull	Shape	[redacted]	[redacted]	[redacted]
	Scale	[redacted]		
Gompertz	Shape	[redacted]	[redacted]	[redacted]
	Rate	[redacted]		
Log-logistic	Shape	[redacted]	[redacted]	[redacted]
	Scale	[redacted]		
Lognormal	meanlog	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]		
	mu	[redacted]	[redacted]	[redacted]

Generalised Gamma	Sigma	[redacted]		
	Q	[redacted]		

Figure 5 – Possible parametric extrapolations of SACT data



The Weibull curve was chosen as the base-case for the following reasons:

- Best alignment to external expert validation from the original company submission (Appendix M), given extensive experience of DVd in second-line treatment.
- Good visual fit in the region with known KM data, and a conservative extrapolation in the region without known KM data
- Second-best statistical fit (the exponential curve was the best fitting statistically, but the visual fit was poor and alignment with external expert experience was very poor).

Table 5 below highlights the lack of agreement between the external expert opinion and the exponential curve, and hence justifies the Weibull curve

Table 5: DVd SACT extrapolation versus DREAMM-7 DVd clinician validation (IA1)

Parametric curve (DVd)	Survival – 5 years	Survival – 10 years	Survival – 15 years
DREAMM-7 clinical validation (Average of 3 EE's, most likely %)	45%	28%	8%
DVd SACT – Weibull	[redacted]	[redacted]	[redacted]
DVd SACT – Exponential	[redacted]	[redacted]	[redacted]

2.5. Incorporation into the CEM

The generated parametric survival curves for DVd were incorporated into the economic model, replacing the existing DVd arm from the DREAMM-7 trial. In line with the Committee's request, relative effects of BVd versus DVd from the DREAMM-7 trial were incorporated through use of a hazard ratio to adjust OS accordingly.

The hazard ratio from the most relevant population from DREAMM-7 (2L lenalidomide exposed [IA1 dataset]) was applied in the model, in line with the request to align the data to the company proposed population, regardless of limited sample size [redacted]. Detail of the PFS and OS of this subgroup are provided in Section 2.6 of this document. Given the uncertainty of this population, a toggle was included to switch to the Company preferred approach, ITT. As presented in the

submission and Committee meeting, ITT is not markedly less valid as a proxy for NHS patients than 2L len-exposed but substantially more reliable as the sample size is much greater. Notably, the ITT OS HR (aligned with the company original submission base-case) is the most conservative of these options. These are shown in Table 6 below.

Table 6: DREAMM-7 OS hazard ratios applied to the DVd SACT dataset

	Hazard ratio	Lower bound	Upper bound
DREAMM-7 - IA2 ITT	0.58	0.43	0.79
DREAMM-7 - IA1 ITT	0.57	0.41	0.80
DREAMM-7 - IA1 Len-exposed	[redacted]	[redacted]	[redacted]
DREAMM-7 - IA1 2L Len-exposed	[redacted]	[redacted]	[redacted]

2.6. 2L len-exposed DREAMM-7 trial data

Although the only element of the 2L len-exposed DREAMM-7 trial data used in the updated model is the hazard ratio, it was thought helpful to provide more background information on from where this hazard ratio was derived, in order to help assist Committee decision-making. Table 7 and Figure 6 display information relating to PFS in this subpopulation, which is provided for background only (not used in the model). Table 8 and Figure 7 display the same information but for OS, which is an important element in the SACT-updated economic model. These OS data show that despite the small sample size in the 2L len exposed subpopulation the OS HR is (nominally) statistically significant, and there is clear evidence of divergence between the KM curves. This in turn explains the substantial benefit observed for BVd in this subpopulation.

Table 7: Summary of progression-free survival in 2L lenalidomide exposed sub-population

Figure 6: Kaplan Meier curves of progression-free survival in 2L lenalidomide exposed sub-population

Table 8: Summary of overall survival in 2L lenalidomide exposed sub-population

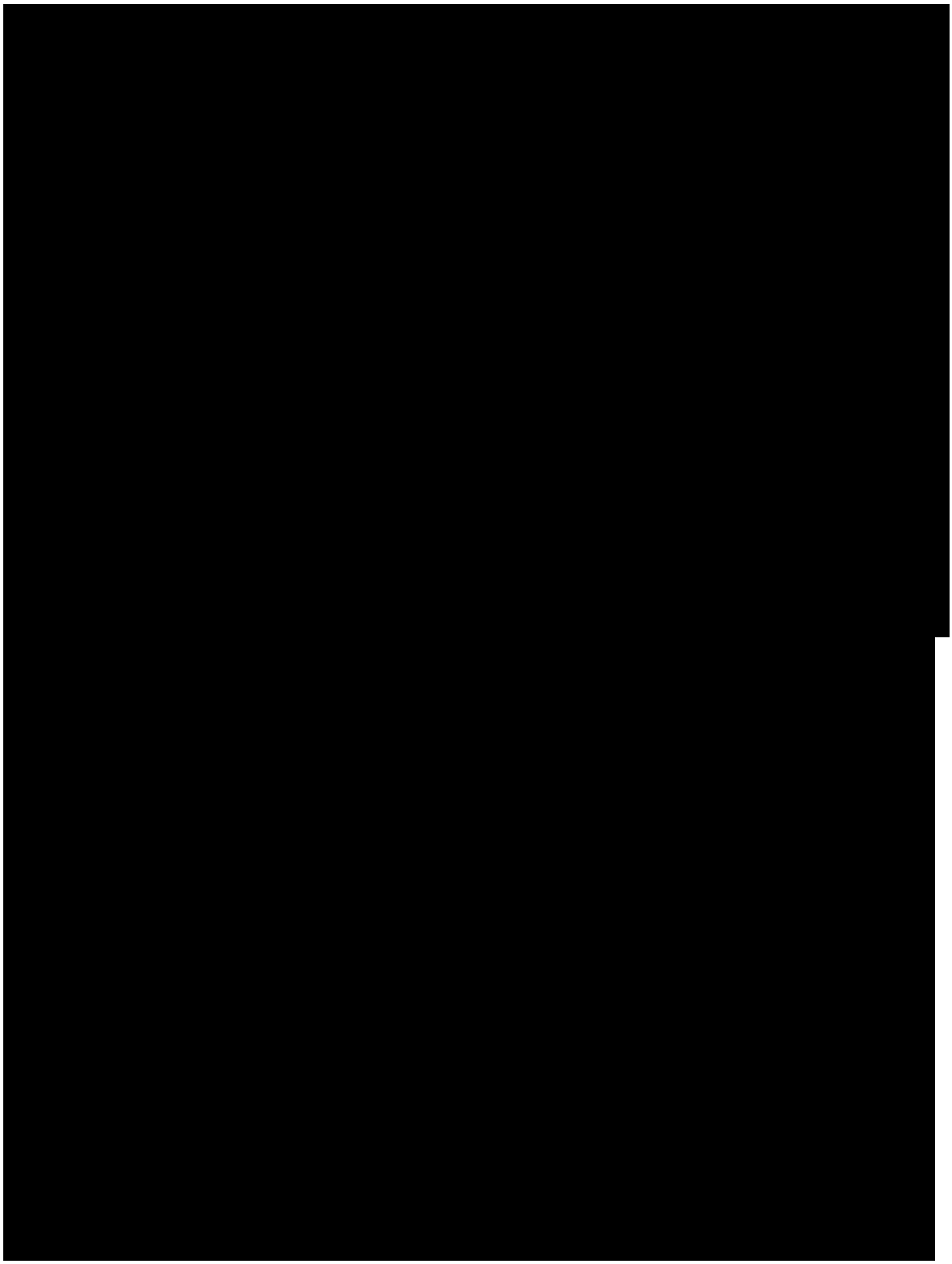


Figure 7: Kaplan Meier curves of overall survival in 2L lenalidomide exposed sub-population

2.7. Technical considerations regarding SACT dataset

- While the OS has been adapted to incorporate SACT data for DVd, all other clinical data (including PFS, TTD) remain aligned to the DREAMM-7 trial data. This is due to only TFS being available from SACT (introducing uncertainty on the validity of using TFS as a proxy for PFS) and TTD SACT data being publicly unavailable.

- Comparators in the adapted economic model (SVd, hKd) are aligned to the NMA using the DREAMM-7 dataset. No further analysis of comparator data from SACT was incorporated.

- Certain functionality in the model has been rendered obsolete by the SACT approach, and so has been stripped out of the model for the Committee's convenience:
    - PFS:OS surrogacy analysis
    - BVd independent extrapolation
    - OS-adjusted analysis for subsequent treatments
    - OS informative prior analysis using CASTOR
    - DVd is fixed as the baseline curve for all clinical inputs (PFS, OS, TTD)
    - KRd has been made unavailable in the model
    - The PSA is not functional in the model, due to lack of covariance matrices derived from the digitised SACT KM data.

2.8. **Results**

Results of the incorporation of SACT data are displayed below in ***Table 9*** - **Table *11***. These demonstrate that in general the use of SACT-informed data as a baseline improves the ICER for BVd relative to DVd. In particular, using SACT-informed data in the manner prescribed by the Committee's preferred base case results in a very substantial improvement in ICER for BVd relative to DVd, adding nearly a full additional QALY regardless of which OS extrapolation curve is selected. This is consistent with the Company's position that **the Company base case was appropriate and conservative** in the use of parametric extrapolation.

Table 9 - Summary table for ICER of BVd versus DVd using SACT ITT data (IA-2)

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) BVd vs comparator
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Table 10 - Summary table for ICER of BVd versus DVd using SACT 2L Len-exposed data

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) BVd vs comparator
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	327

Table 11 - Summary table for ICER of BVd versus DVd using SACT 2L Len-exposed data fitted with an exponential extrapolation

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) BVd vs comparator
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

3. *DREAMM-7 Interim Analysis 2 (IA2)*

3.1. **Background**

GSK notes that subsequent to making their evidence submission, a new datacut of the DREAMM-7 trial has become available. This datacut demonstrates statistically significant OS improvement relative to DVd. GSK has taken the decision to update the original submission with these new data for the following reasons:

- The Committee expressed a preference for more up-to-date data if this was possible to provide (e.g. updating the LEPUS study). Subsequent correspondence with NICE has confirmed that providing these IA2 data would therefore probably also be helpful.
- The Committee expressed dissatisfaction with the preferred OS extrapolation of the Company and EAG. Since the IA2 datacut reports statistically significant OS, this is likely to address Committee concerns on this point.

IA2 is not substantially different – either directionally or in magnitude – from IA1. Consequently, it should not significantly alter the Committee's decision-making, save for reassuring them on the extrapolation of OS.

3.2. **Introduction**

The IA2 data from DREAMM-7 confirmed that the principal strength of the clinical evidence base is the very strong signal that BVd is superior to the existing NHS SoC in a head-to-head clinical trial. At the IA1 data cut-off, BVd had already demonstrated a statistically significant PFS benefit, with a 59% reduction in the risk of progression or death (HR, 0.41; 95% confidence limit (CL) 0.31-0.53; p<0.00001), in patients at first relapse or later. The PFS benefit of BVd over DVd was consistent at the IA2 analysis, with BVd demonstrating a median PFS that was two and a half times compared with DVd ([redacted] vs [redacted] months).

Importantly, the findings are highly consistent across endpoints, with a particular emphasis on the consistent and clinically meaningful survival benefit associated with BVd based on IA2. The updated analysis of DREAMM-7 showed a clear, strong and statistically significant OS superiority of BVd over DVd ([redacted]). This further

showcased the strong and lasting OS benefit for the BVd group compared with the DVd group that was already observed from the less mature IA1 results.

3.3. Primary and selected secondary outcomes of IA2 analysis

3.3.1. Primary outcome – Progression-free survival

The DREAMM-7 trial met its primary endpoint for PFS assessed by IRC at the IA1 analysis. The median PFS in the BVd group was almost three times longer than DVd (36.6 months [95% CI: 28.4, NR] vs. 13.4 months [95% CI: 11.1, 17.5] in the DVd group. This was also supported by a HR of 0.41 (95% CI: 0.31, 0.53; p <0.00001) showing a 59% reduction in the risk of disease progression or death).

The IA2 results were consistent with the primary analysis and further underscored the superior PFS outcomes associated with BVd compared with DVd. The strong and clinically meaningful superiority of BVd was showcased by a consistently prolonged median PFS ([redacted] versus [redacted] for the DVd group) and a hazard ratio (HR) of [redacted](Table **12**). This superior PFS benefit associated with BVd was also demonstrated by the sustained separation of the Kaplan Meier (KM) curves between the treatment groups during the longer IA2 follow-up (Figure **8**).

Overall, the IA2 PFS results were consistent with the IA1 results presented in the CS. The Company notes that this strongly confirms their position that **the Committee already have a suitable base case upon which to confidently make decisions**.

Table 12. IA2 progression-free survival based on independent reviewer-assessed response (ITT population)

	BVd (N=243)	DVd (N=251)
Number of participants, n (%)		
Progressed or died (event)	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%)	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for time variable (months)[a]	[redacted]	[redacted]
1st Quartile	[redacted]	[redacted]

	BVd (N=243)	DVd (N=251)
95% CI	[redacted]	[redacted]
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
3rd Quartile	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Hazard ratio[b]	[redacted]	[redacted]
Number of participants in the model	[redacted]	[redacted]
Estimate	[redacted]	
95% CI	[redacted]	
Progression-free survival rate	[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]
Time-to-event endpoint at 18 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 24 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

a. CIs were estimated using the Brookmeyer Crowley method (Brookmeyer & Crowley, 1982).

b. Hazard ratios were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III), with a covariate of treatment.

Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this table.

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; IA2, second planned interim analysis; ITT, intention-to-treat.

Source: GSK Data on file (GSK, 207503_Table2.0007_Summary of PFS (Data on file), 2025).

Figure 8. Kaplan Meier curves of progression-free survival based on independent reviewer-assessed response (ITT population)

Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They were counted as 4 unique participants in this figure.
Abbreviations: BOR/DEX, bortezomib/dexamethasone; DARA; Daratumumab; GSK, GlaxoSmithKline; ITT, intention-to-treat
Source: GSK Data on file (GSK, 207503_Figure 2.0037 KM curve PFS (Data on file), 2025) .

3.3.2. **Secondary outcome – Overall survival**

An early and clinically meaningful OS benefit favoured the BVd group versus the DVd group at IA1 (HR=0.57; 95% CI: 0.40, 0.80; p = 0.00049). These strong survival signals remained consistently in favour of the BVd arm at a longer follow-up of 39.4 months. The IA2 results clearly demonstrate the OS superiority of the BVd group the OS benefit being declared statistically significant with a nominal p-value of 0.00023 (HR=0.58; 95% CI: 0.43, 0.79). There were 35 more deaths in the DVd group (103 [41%]) compared with the BVd group (68 [28%]) at IA2 (Table 13).

The prolonged separation between the OS KM curves in favour of BVd at IA2, following the clear and early separation observed at IA1, further substantiates the sustained survival benefit with BVd over DVd (Figure 9). At IA2, OS data have reached 34.6% (171/494 participants) overall maturity and Information Fraction equal to [redacted]. Landmark analysis of OS at 36 months showed a higher survival rate in the BVd group compared with the DVd group (74% versus 60%) (Table 13). Even

though median OS was not reached at IA2, a post hoc analysis based on an exponential extrapolation of the IA2 OS data produced a median OS estimate of 84 months with BVd and 51 months with DVd (GSK, DREAMM-7 OS update_presented at ASH_8DEC24_v1 deck [Data on file], 2024).

Overall, the more mature IA2 results demonstrate a consistent, lasting and statistically significant OS benefit in favour of BVd versus DVd.

Table 13. IA2 summary of overall survival (ITT population)

	BVd (N=243)	DVd (N=251)
Number of participants, n (%)		
Died (event)	68 (28)	103 (41)
Censored, follow-up ended	[redacted]	[redacted]
Alive date obtained	[redacted]	[redacted]
No alive date obtained	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
Event summary, n (%)		
Death	68 (28)	103 (41)
Estimates for time variable (months)[a]		
1st quartile	33.9	15.2
95% CI	(21.9, 44.5)	(12.3, 21.1)
Median[b]	-	-
95% CI	(-, -)	(41.0, -)
3rd quartile	-	-
95% CI	(-, -)	(-, -)
Hazard ratio[b]		
Number of participants in the model	243	251
Estimate	0.58	
95% CI	(0.43, 0.79)	
Stratified log-rank[c]		
p-value	0.00023	
Overall survival rate		
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]
Time-to-event endpoint at 18 months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-event endpoint at 24 months	0.79	0.67
95% CI	(0.73, 0.84)	(0.61, 0.73)
Time-to-event endpoint at 36 months	0.74	0.60
95% CI	(0.68, 0.79)	(0.54, 0.66)

a. CIs were estimated using the Brookmeyer Crowley method (Brookmeyer & Crowley, 1982).

b. Hazard ratios were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes), and R-ISS at screening (I vs. II/III), with a covariate of treatment.
c. p-value from 1-sided stratified log-rank test. At 171 actual events (48.2% OS information fraction), OS was declared significant if the P value was <.00112

Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They are counted as 4 unique participants in this table.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; ITT, intention-to-treat; R-ISS, Revised International Staging System.
Source: DREAMM-7 supplementary clinical study report (GSK, 207503_Supplementary clinical study report (Data on file)., 2025).

Figure 9: Kaplan Meier curves of overall survival (ITT population)

Note: There were 2 participants in the ITT Population who were randomised, not treated, re-screened, and re-randomised. They are counted as 4 unique participants in this figure.
Abbreviations: BVd, belantamab mafodotin, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; HR, hazard ratio; ITT, intention to treat; NR, not reached; OS, overall survival;
Source: DREAMM-7 supplementary clinical study report (GSK, 207503_Supplementary clinical study report (Data on file)., 2025).

3.3.3. **Secondary outcome – Time to treatment discontinuation**

Median TTD had already been reached at IA1 for both treatment arms. The IA2 analysis produced consistent results, with the BVd group having a longer median TTD than DVd (months [95% CI:] versus months [95% CI:] in the DVd group (Table 14). In addition, landmark analysis of TTD at 24 and 36 months showed a higher TTD rate in the BVd group compared with the DVd group (and respectively) (Table 14).

Table 14. IA2 summary of time to treatment discontinuation (Safety population)

	BVd (N=242)	DVd (N=246)
Number of participants, n (%)		
Treatment Discontinued or Death (event)	[redacted]	[redacted]
Censored, Treatment not Discontinued	[redacted]	[redacted]
Event Summary		
Treatment Discontinued	[redacted]	[redacted]
Death	[redacted]	[redacted]
Estimates for Time Variable (Months)[a]		
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 Rate		
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]
Time-to-Event Endpoint at 18 Months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-Event Endpoint at 24 Months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Time-to-Event Endpoint at 36 Months	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

a. Intervals for time variables are estimated using the Brookmeyer Crowley method (Brookmeyer & Crowley, 1982).
[redacted]
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab in combination with bortezomib, and dexamethasone; TTD, time to treatment discontinuation.
Source: GSK data on file (GSK, 207503-sSAP-07-Efficacy-IA2 (Data on file), 2024).

The longer TTD associated with the BVd arm was also demonstrated by the sustained separation of the KM curves between the treatment groups during the longer IA2 follow-up (Figure 10).

Figure 10. Kaplan Meier curves of time to treatment discontinuation

(GSK, 207503-sSAP-07-Efficacy-IA2 (Data on file), 2024).

3.4. Results

Table 15 gives summary results for the impact of using the IA2 comparison. Table 16 gives comparable results from the CS submission model (incorporating exponential OS extrapolation curves as per EAG preference). These tables cumulatively show that the impact of switching to the IA2 data is to decrease both incremental costs and QALYs by around 10%, and therefore the net effect is that there is no significant change to overall cost-effectiveness.

Table 15: Summary table for ICER of BVd versus DVd using IA-2 DREAMM-7 data

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) BVd vs comparator
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Table 16: Summary table for ICER of BVd versus DVd using original (IA1) submission assumptions (plus exponential BVd OS extrapolation)

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)

							BVd vs comparator
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

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Single Technology Appraisal (STA)

Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

EAG addendum: review of company's post-ACM1 analyses and implementation of committee preferences

Produced by	York Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Eleonora Uphoff, Research Fellow, CRD, University of York Rojé Layne, Research Fellow, CHE, University of York Claire Rothery, Professor of Health Economics, CHE, University of York Sofia Dias, Professor of Health Technology Assessment, CRD, University of York Ana Duarte, Senior Research Fellow, CHE, University of York
Correspondence to	Ana Duarte, University of York, ana.duarte@york.ac.uk
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None.

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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.

Note on the text

All commercial-in-confidence (CON) data have been [redacted].

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1 OVERVIEW

This addendum to the External Assessment Report (EAR) presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company and implementation of the committee's preferred assumptions after the first appraisal committee meeting (ACM1).

An overview of the committee's preferred assumptions and the company's response to them is provided in Table 1.

In Section 2 the EAG provides a critique of the evidence submitted by the company, focussing on ascertaining whether the committee requests from ACM1 have been appropriately fulfilled and the elements with greater impact on the estimates of cost-effectiveness. Due to the limited time available (2 weeks), the revised economic model was not fully re-checked, and analyses code for the revised network meta-analyses (NMA) and newly presented matching-adjusted indirect comparisons (MAIC) were not reviewed.

Table 1 Summary of committee's preferred assumptions and company implementation

Committee's preferred assumption/ additional evidence request	Company analyses and additional evidence	Alignment with committee's preferences
Population/ positioning of BVd		
As per full Marketing Authorisation (MA): Adults with MM who have had at least one previous treatment (i.e., 2L+) If the full MA population is not possible: Adults with multiple myeloma (MM) who have had either: • only 1 previous treatment (i.e., 2L only), **or** • 1 or 2 previous treatments (i.e., 2L+) and have had previous exposure to lenalidomide.	2L only population as per the company's original base-case, but separate analyses are presented for the following subpopulations: • lenalidomide 'unsuitable' (original CS) • lenalidomide 'suitable' (new subpopulation) These analyses use an updated data cut of DREAMM-7 trial, the interim analysis 2 (IA2) data cut. Company new base case uses independently modelled BVd OS curve from DREAMM-7 ITT (IA2 data cut) with an exponential extrapolation function and an independently modelled DVd OS with Weibull extrapolation (informative prior with CASTOR).	Does not match the committee's preference for the full MA population, as it excludes positioning at 3L and 3L+. Expansion of 2L-only population to include the lenalidomide 'suitable' subpopulation matches one of the alternative committee preferences to consider all 2L patients if full MA population not feasible. The updated IA2 DREAMM-7 data cut was not requested by the committee.
Comparators		
All currently available treatment options for the updated population submitted by the company.	For lenalidomide 'unsuitable' subgroup (original CS), no change in comparators. For new subgroup of lenalidomide 'suitable', only carfilzomib + lenalidomide + dexamethasone (KRd) included.	For lenalidomide 'unsuitable' (original CS), all relevant comparators have been included. For lenalidomide 'suitable' (new subpopulation), KRd is a relevant comparator. Available doublet therapies (i.e., lenalidomide + dexamethasone) for which this subpopulation is eligible were not considered relevant by the company. Parameterisation of treatment effectiveness for the new comparator, KRd, is informed by an unanchored MAIC using data from the ASPIRE and DREAMM-7 trials (ITT, IA2 data cut).
Overall survival data from SACT for baseline DVd		
DVd overall survival (OS) should be informed by SACT data and used as baseline to derive OS curves for remaining treatments under comparison. Relative effects for BVd vs. DVd from DREAMM-7 should be applied to estimate BVd survival.	Data for a subgroup of 2L lenalidomide pretreated patients from SACT was used to estimate OS outcomes for DVd and used in exploratory analyses only. The company presents two analyses using different sources of relative treatment effects for BVd: • subgroup-specific HR from DREAMM-7 (2L lenalidomide pretreated patients, using the same data cut as in the original CS, the IA1 data cut) • ITT population from DREAMM-7 (2L+, , which is not restricted to the 2L-only subgroup of participants and	SACT OS data was not used to inform the new base-case, as the company considers that the request is methodologically flawed, and hence only informs exploratory analyses. The EAG notes that the analysis requested by the committee is in line with NICE methodologic guidance. The company maintains the use of independently modelled OS curves for BVd and DVd but updated with the DREAMM-7 IA2 data cut in their base-case analysis.

	not restricted to lenalidomide refractory or exposed subpopulations).	The company compares OS for DVd from SACT data to DREAMM-7 but with ITT (2L+) data (i.e., not the subpopulation of 2L-only lenalidomide pretreated patients).
Indirect treatment comparisons using later data cut-off from LEPUS study		
Use later data cut-off from LEPUS study	NMA updated with the latest data cut from LEPUS study and DREAMM-7 IA2 data cut.	Updated NMA HRs for PFS and OS for company new base case: • SVd vs DVd • hKd vs DVd • BVd vs DVd modelled with independent curves rather than NMA HR Differences in results from previous analyses are plausible given the inclusion of the IA2 data.
Exposure to belantamab mafodotin		
Committee agreed use of IPD for belamaf to inform dosing may be appropriate. Committee would like to see evidence to support no loss of efficacy in the 8- to 12-week dosing intervals. Analyses using IPD for all treatments where available, to reassure committee that RDI is a decent proxy for DVd.	Company has investigated extended belamaf dose delays in the DREAMM-7 phase III study [1] • Post-hoc analyses show that belamaf efficacy in patients with dose and schedule modifications is similar to that in the ITT IPD for the DVd arm is available from the DREAMM-7 trial but not feasible for other comparators • IPD analysis makes no difference to RDI calculations for daratumumab, and company considers it reasonable to exclude it from the model.	Updated base case does not include IPD analysis of DVd, owing to time constraints. Company expects this to lead to a small improvement in ICER if it had been implemented.
Costs of subsequent treatments		
Analysis should be updated where teclistamab is included as a fourth-line option.	Teclistamab has been included as a treatment option in the fourth-line subsequent treatment.	As per committee request
Baseline age from SACT data		
Baseline age should be reflective of NHS population, preferably using SACT data.	A baseline age of 70 years was used in line with the SACT data source.[2]	Age changed in new company base case from 64 years in DREAMM-7 to 70 years in SACT, but OS curves for BVd and DVd are extrapolated from DREAMM-7 observed data instead of using SACT as the absolute baseline curve.
Health state utility values		
Treatment independent values applied from an appropriate source, e.g. utility values from TA897 for 2L only population, (other alternative sources company could justify using include DREAMM-7 trial or Hatswell et al. (2019))[3]	A baseline utility of 0.767 was applied for PFS state, independent of treatment and elicited directly from the DREAMM-7 trial. For the progressed disease (PD) state, the meta-regression study from Hatswell et al. (2019)[3] was used to elicit a decrement to apply to PFS in like with recommendation from the EAG (0.734).	The new base-case includes a treatment independent utility value for PD derived by applying to PFS utility from DREAMM-7 a decrement based on Hatswell et al. (2019)[3] but reweighted to adjust for patients dying at different lines (rather than a simple average, as per the EAG original base case). Overall, this approach is more conservative towards BVd that the company's and EAG's original base-case assumptions.

Disutility of eye-related adverse events		
Committee would like to see evidence that EQ-5D is sensitive to ocular adverse events (AEs) and that EQ-5D would capture QoL lost through ocular AEs. In cost-effectiveness analysis explore impact of including and excluding ocular AEs disutilities in scenarios	Company considers it inappropriate to include disutility for eye-related AEs in addition to reported utility scores from the trial (eye-related AEs were common in the DREAMM-7 trial and dose adjusted in trial accordingly) but presents a scenario analysis inclusive of these disutilities and excludes them from the new base-case.	Company does not present evidence that validates ocular AEs would be captured by EQ-5D. Company presents analyses with a without ocular AE disutilities.
Updated PAS for belamaf		
New PAS price for belamaf, dated 23rd April 2025.	Company results not updated with new PAS.	This was not requested by the committee; the EAG considers in this document cost-effectiveness results inclusive of the 23rd April 2025 PAS price for belamaf. Results with cPAS prices for all treatments under comparison and subsequent therapies are presented in a separate confidential appendix.

Abbreviations; AE, adverse events; CS, company submission; IA, interim analysis; ITT, intention to treat; KRd, carfilzomib + lenalidomide + dexamethasone; MA, marketing authorisation; MM, multiple myeloma; PAS, patient access scheme; OS, overall survival

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Population

Belantamab mafodotin (belamaf) in combination with bortezomib plus dexamethasone (BVd) received UK marketing authorisation (MA) on 17th April 2025 for the treatment of adults with multiple myeloma (MM) in patients who have received at least one prior therapy. In anticipation of the Medicines and Healthcare products Regulatory Agency (MHRA) license wording, the NICE appraisal committee did not consider the decision problem addressed in the CS that was restricted to a second line (2L) only population and in adults for whom lenalidomide is unsuitable to be sufficient to capture the full MA for BVd. The committee would prefer to evaluate BVd within the full MA, but if this is not possible, it would prefer the decision problem to include a population of adults with MM who have had either:

- only 1 previous treatment (that is, second line only), or
- 1 or 2 previous treatments and have had previous exposure to lenalidomide.

In response, the company's proposed position is adults with MM who have had only 1 previous treatment (that is, second line only). This includes both adults for whom lenalidomide is unsuitable, as per the company's original position, and for whom lenalidomide is suitable, a new subpopulation.

The EAG's response

The cost-effectiveness of BVd is evaluated against treatments recommended by NICE and available in the NHS at 2L-only, i.e., not covering the full MA. The relevant comparators at third line (3L) and 3L+, as listed in the NICE scope for this appraisal, have not been considered in the cost-effectiveness evaluation of BVd, and no formal evidence from a 3L-only or 3L+ subpopulation of DREAMM-7 has been presented.

The evidence informing the cost-effectiveness of BVd in the company's revised base case is informed by the updated data cut (IA2) for the ITT population of DREAMM-7 (2L+) rather than the subgroup-specific evidence for the 2L-only population. The EAG considers the use of data from the ITT population to inform the relative effectiveness of BVd vs. DVd to be a reasonable approximation for the 2L-only population, given this allows inclusion for more data and increases statistical power compared to using a small subgroup (N=[redacted] 2L only, BVd study arm).

The company's expansion of the 2L-only population to include adults for whom lenalidomide is suitable is in line with the committee's preference if the full MA population is not feasible.

The EAG considers this issue resolved for a NICE recommendation in a 2L-only population.

2.2 Comparators

The NICE appraisal committee indicated that the comparators should be updated to include all currently available treatment options for the updated population submitted by the company. For the subpopulation of adults with MM who have had only 1 previous treatment and for whom lenalidomide is unsuitable, the company made no changes to the comparators. The comparators differ by eligibility of DVd, as per the company's original position:

- In the DVd eligible subpopulation, BVd is compared with DVd and hKd.
- In the DVd ineligible subpopulation, BVd is compared with SVd and hKd.

For the new subpopulation of adults with MM who have had only 1 previous treatment and for whom lenalidomide is suitable, a new comparator is included in the company's revised base case. In this subpopulation, the company states that patients cannot receive daratumumab and, therefore, DVd is not a relevant comparator. In this subpopulation, the comparator included by the company is carfilzomib plus lenalidomide and dexamethasone (KRd):

- In the lenalidomide suitable subpopulation, BVd is compared with KRd.

To inform the cost-effectiveness of BVd relative to KRd, the company conducted an unanchored MAIC of BVd and KRd, using data from the DREAMM-7 ITT population for BVd (updated IA2 data cut) and data from the KRd arm of the ASPIRE trial. Hazard ratios (HR) for OS and PFS were applied directly to the unweighted DREAMM-7 BVd arm (reference arm) because the weighted BVd and unweighted BVd arms were closely aligned for OS (see Figure 1 of company's technical appendix).[4] The company indicates that the assumption of proportional hazards (PH) is conservative because BVd crosses over KRd at approximately 12 months and leads to an increasing BVd survival advantage over time (Figure 1 of company's technical appendix).[4]

In the absence of published time to treatment discontinuation (TTD) data, the progression free survival (PFS) HR from the MAIC for KRd vs. BVd (assuming PH) was used as a proxy for the TTD HR for KRd and applied to the BVd TTD extrapolation curve. The extrapolated curve was used to inform time on treatment with KRd. Adverse event incidence for KRd was taken from the ASPIRE trial. All other modelling assumptions coincided with the base case model, with costing data sources updated to align with the new comparator of KRd. The drug acquisition and administration costs for this treatment were also updated in the model.

The EAG's response

The EAG agrees with the company that DVd and SVd are not relevant comparators for the lenalidomide suitable subpopulation at 2L based on recommendations in NICE technology appraisals

TA974 and TA897. The other 2L comparators for a lenalidomide suitable population in the NICE scope are bortezomib monotherapy (TA129), KRd (TA695), carfilzomib plus dexamethasone (TA657), and lenalidomide plus dexamethasone (TA586). The EAG considers bortezomib monotherapy as not relevant as it is rarely used in the NHS for the treatment of relapsed/ refractory MM, while KRd, the triple combination of carfilzomib plus lenalidomide and dexamethasone is likely to supersede the combination therapies of carfilzomib plus dexamethasone and lenalidomide plus dexamethasone. Therefore, the EAG agrees with the company that the most relevant comparator for BVd in the lenalidomide suitable subpopulation at 2L is KRd.

The EAG notes that for the cost-effectiveness results presented in Table 2 of the company's response document[5] the cost of KRd has been overestimated compared to costs in NHS practice, as the unit cost assumed for lenalidomide (£4320 per 21 capsules) was sourced from the British National Formulary, which is considerably higher than the corresponding electronic market information tool (eMIT) cost (£28.27 per 21 capsules). The EAG corrects this in the analyses presented in a separate confidential appendix. Furthermore, the company's modelled treatment duration for KRd does not align with recommendations for the delivery of this treatment in clinical practice or the stopping rule in the ASPIRE trial. TA695[6] recommended that KRd should be commissioned for a maximum of 18 treatment cycles, in line with the stopping rule applied in the ASPIRE trial. Thus, the EAG is concerned that the duration of treatment with KRd may have been overestimated in the model and is not consistent with the effectiveness data used to inform this comparator.

The ASPIRE study was identified from the set of studies in the systematic review presented in the original CS comparing interventions that were not connected to the network of therapies originally presented (CS, Document B, Figure 15). The company noted that ASPIRE was the only RCT identified that included KRd and the suitability of ASPIRE for use in an indirect comparison was assessed.[7, 8] However, it is unclear whether non-randomised studies of KRd were available that could have also been used to conduct an indirect comparison to BVd.

ASPIRE enrolled patients with relapsed MM who had one to three previous treatments. Between 2010 and 2012, 792 patients were recruited and randomised to receive KRd or lenalidomide with dexamethasone (Rd). Similar to DREAMM-7, patients were younger than in the NHS (median age 64 vs 75.6 years in NCRAS). At the time of recruitment for ASPIRE, 19.8% of trial participants had received lenalidomide and 7.3% were refractory to lenalidomide (versus 32.6% in DREAMM-7), reflecting the changes to the standard of care over time.

The company conducted an unanchored MAIC, combining data for the 2L+ DREAMM-7 population (IA2 data cut) and data on patients who received KRd from the ASPIRE trial. This is different from the committee's preferred population. Published data from ASPIRE by subgroups lenalidomide-

exposure and line of treatment are available but these were not used by the company.[9, 10] The company did state that published efficacy data for the 2L subgroup were consistent with the ITT population. In TA695[6] subgroup results were presented to the committee who noted that the effect sizes were similar to the ITT population (results are confidential and therefore redacted in the appraisal documents).

In response to an EAG information request in May 2025, the company argue[11] that ASPIRE participants align with 2L patients currently eligible for KRd in NHS practice. The company note that a significant proportion of patients in the ASPIRE ITT population match the BlueTeq criteria for 2L eligibility for KRd in NHS practice, and baseline characteristics are well matched to the BlueTeq criteria. However, 53.5% were 3L+. In addition, patients who previously received lenalidomide (19.8% in ASPIRE) and patients who had not received bortezomib in a previous line (34.1% ASPIRE) would not currently be eligible to receive KRd in the NHS. It is unclear what proportion of the ASPIRE ITT population would be eligible to receive KRd in NHS practice.

The company selected key prognostic factors and treatment effect modifiers (TEMs) using published literature and clinical expertise.[8] Participants from the DREAMM-7 BVd arm and the ASPIRE KRd arm were matched on those characteristics. Key imbalances include differences in 2/3L, lenalidomide-refractory status, ISS stage III, ECOG, and creatinine clearance. A substantial proportion of data was missing for Revised International Staging System (R-ISS) stage and cytogenic risk in ASPIRE; this was assumed missing-at-random and imputed.

The weights calculated and used for adjustment of the HR in the preferred analysis, gave several patients in DREAMM-7 BVd arm a very small weight (close or equal to zero) and some had large weights (>4).[8] The effective sample size was [redacted] (original sample size 243). Weighting achieved balance in the identified prognostic factors and TEMs, except for R-ISS. This may have introduced bias favouring Bvd, as ASPIRE has a higher proportion of stage III R-ISS patients.

The unanchored MAIC was used to calculate the HR of BVd compared to KRd for the DVd ineligible (lenalidomide suitable) population. However, even assuming all matching assumptions are reasonable and there is no bias, it should be noted that the resulting HRs apply to the ITT population in the ASPIRE study.

Overall, the EAG is satisfied that the limitations in the unanchored MAIC have been adequately described and explored by the company but notes the considerable uncertainty in this type of analysis.

The HR for BVd vs. KRd estimated through the MAIC is applied to the survival extrapolation of the DREAMM-7 BVd arm (IA2, ITT population) in the company's updated base case. Corresponding analyses using SACT data are not presented, as the company only performed analysis for the SACT

lenalidomide exposed subpopulation in Lawton et al. (2024),[2] who would not have been eligible to receive KRd.

Similarly to the modelling of hKd and SVd in the company's original base-case, modelling the treatment effectiveness of KRd implicitly assumes that the hazards between this treatment and the baseline curve are proportional. Hence the company's modelling approach assumes that the relative treatment effectiveness of BVd vs. KRd is constant over the time (at least until logical constraints are imposed on the extrapolation curves [e.g., OS ≤ general population mortality]). The company does not present any data to support the PH assumption between BVd and KRd. Whilst the EAG acknowledges that assuming PH may have been a reasonable simplification to model this comparator, this is another source of uncertainty and one that may overestimate the treatment effect of BVd. Given this and the concerns highlighted above about the potential overestimation of KRd costs, the EAG cannot validate the company's statements that the comparison against KRd is conservative.[4]

2.3 Updated analyses based on the preferred population and using SACT for baseline DVd curve

The committee requested that OS data from the Systemic Anti-Cancer Therapy (SACT) dataset for DVd was used to inform the baseline survival curve and that DREAMM-7 data was used to inform BVd relative effects. The committee also requested a scenario using DREAMM-7 data (to inform BVd and DVd effectiveness) for the preferred population.

The company did not incorporate SACT data in their updated base-case analysis and instead presented exploratory analyses using SACT data. The baseline OS curve in these analyses was informed by survival data in a population of patients receiving DVd at 2L and who had prior lenalidomide exposure. Digitised KM data from Lawton et al. (2024)[2] was used to reconstruct the individual patient data and alternative parametric models fitted to extrapolate the survival data. The company considered the Weibull distribution as the best fitting model to extrapolate OS for DVd. A set of exploratory analyses are presented by the company using the following data:

- DVd OS baseline with Weibull extrapolation and HR for BVd vs. DVd from DREAMM-7:
    - ITT IA2 population (HR=0.58), see results in Table 8 of the company's response to the EAG information request.[11]
    - Lenalidomide exposed, 2L, IA1 subgroup (HR=[redacted]), see results in Table 9 of the company's response to the EAG information request.[11]

- DVd OS baseline with Exponential extrapolation and HR for BVd vs. DVd from DREAMM-7 lenalidomide exposed IA2 subgroup, see results in Table 10 of the company's response to the EAG information request.[11]

The company considers that the cost-effectiveness results of these analyses all favour BVd compared to the company's base-case and suggest the latter is conservative.

The EAG's response

The company argued that the committee's request to use SACT as the absolute baseline for the economic model was "substantially out with NICE's preferred Methods",[5] citing NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2[12] which states that RCTs should be the preferred source for relative treatment effects. However, this represents a misunderstanding of the committee's request which was for SACT data to be used as a reference for the DVd arm (baseline curve) with relative treatment effects being informed by the DREAMM-7 RCT, as recommended by NICE DSU TSD 5.[13]

The company also note that using SACT data as the baseline for DVd means that PH need to be assumed for PFS and OS in DREAMM-7.[5] Whilst a full assessment of the PH assumption using IA2 data has not been provided, in the original company submission and EAR it was noted that PH was likely to hold. Whilst the EAG agrees that using the SACT dataset requires this additional assumption, there is no evidence to indicate that this assumption is unreasonable, and it has the advantage of addressing the committee's preference to use NHS-derived data for the baseline patient assumptions. In addition, if the PH assumption does not hold, alternative methods could be used to obtain relative effects from DREAMM-7.[14, 15]

The EAG notes that only OS data from the SACT dataset is presented. Whilst this is in line with the committee's request, and information on PFS was not available from SACT (although time to treatment-free survival from SACT could be used as a proxy for PFS), the use of different underlying populations to inform absolute PFS and OS outcomes in a partitioned survival analysis can be problematic. This is because this modelling approach assumes independence between PFS and OS, despite PFS generally being prognostic of OS and including death events. The assumption of independence between OS and PFS is a well-known limitation of partitioned survival models, but one that may be exacerbated when using external data to inform only one of the survival endpoints (i.e. OS) as the underlying relationship between PFS and OS that is expected when both endpoints are informed from a single population is no longer reflected in observed data from two distinct sources.[16] Hence, the EAG, considers that a partial implementation of the SACT survival data may result in inconsistent survival outcomes being predicted by the model. Due to time limitations, the EAG has not been able to further investigate this issue and/or consider the appropriateness of alternative approaches to incorporate SACT data in the model but notes this issue as it contributes to the uncertainty in the cost-effectiveness estimates.

The EAG was not able to fully replicate the cost-effectiveness estimates presented in Tables 8-10 of the company's response to the EAG information request.[11] The EAG successfully replicated QALY and life years gained for the three exploratory analyses described above, but not the costs. This was due to the company's analyses not including the costs of subsequent treatment with teclistamab (see Section 2.7). For consistency with the committee's request, the EAG included the teclistamab costs in all analyses presented in the confidential appendix.

Finally, the EAG notes that the cost-effectiveness analyses using SACT data could not be run probabilistically, as the model submitted by the company did not have this functionality. The company justified this as being, due to lack of covariance matrices derived from the digitised SACT Kaplan Meier data. It is unclear why this precludes running the probabilistic analysis for two reasons. First, it would still be possible to obtain covariance matrices for the parametric models fitted to the pseudo-individual participant data (IPD) from SACT (except for the exponential distribution, but one could still characterise the uncertainty surrounding its single survival parameter). Second, this ignores the uncertainty on all other probabilistic parameters in the model.

Overall, the EAG considers that the company partially fulfilled the company's request, but is concerned about the interpretation of the economic evidence due to: (i) use of a baseline from a different population than the one considered in the company's updated base-case, and (ii) incorporation of a single survival endpoint (i.e., OS) when a proxy for PFS could also have been used.

2.4 Use later data cut-off from LEPUS study for ITCs

The company updated their original NMAs comparing BVd, DVd, SVd and hKd to include the updated DREAMM-7 data cut (IA2), as well as aligning with the EAG in using the latest available dataset for the LEPUS study. The company stated that the NMA methods used were as previously described.

The EAG's response

The EAG was unable to re-run the NMA models using the updated DREAMM-7 HRs due to time limitations, however the results provided by the company were inspected. Because the network is star-shaped (i.e. only direct evidence is available for each comparison), differences to the EAG's analyses should only be noticeable in comparisons of SVd and hKd to BVd (and BVd to DVd) as these are the only ones affected by the updated DREAMM-7 data. Small differences in comparisons of SVd and hKd to BVd are noticeable in the company's updated NMA results for PFS (Table 2 in company's additional documentation[5]), although it is plausible that these are expected variations due to simulation error in the parameter estimation process. Results for OS (Table 3 in company's additional documentation[5]) match the EAG's expectations for minimal differences. Overall, the results of the updated NMAs are not very different from results used in the original EAG's base case.

2.5 Provide evidence to support no loss of efficacy in the 8- to 12-week dosing intervals

The EAR described a reduction in exposure to belamaf due to dose reductions ([redacted] of patients in BVd study arm) and delays ([redacted] of patients had a delay over 3 weeks and [redacted] over 6 weeks in BVd study arm). Clinical experts supporting the EAG and the company indicated that dosing may be reduced further in practice to avoid ocular side effects. The clinical consensus appears to suggest dosing will be reduced from every four weeks to every eight weeks in NHS clinical practice.

The committee's preferred assumption is for IPD to be used for belamaf to inform dosing. The committee requested evidence to support no loss of efficacy in the 8- to 12-week dosing intervals.

The company used findings from post-hoc analyses of DREAMM-7 presented in a published oral presentation[1]to illustrate that there was no evidence of loss of efficacy in the longer dosing interval.

The EAG's response

The oral presentation slides shared by the company show that, from 15 months after the first dose with belamaf, patients in the trial had a median of 9 to 12 weeks between doses. The proportion of patients with partial response or better remained relatively constant over this period. [1] The company also cite data indicating a modified PFS (mPFS) in the ITT population of 36.6 months, versus [redacted] months for patients with a dosing schedule extended to 12 weeks or longer ([redacted]) (median follow-up 28.2 months). The EAG could not find these results for the 'extended dosing schedule' subgroup in the presentation slides, nor in other documentation supplied by the company after ACM1.

The EAG concludes that the assumption of no change in efficacy with the longer dosing interval is likely to be reasonable, although the evidence provided is very limited and only applies to PFS.

2.6 Analysis using IPD RDI for DVd

The committee requested that analyses using IPD to inform drug acquisition costs should be used where available (i.e., for DVd), and this would reassure committee that relative dose intensity (RDI) is a reasonable proxy for DVd.

The company did not use IPD for DVd dosing in the model,[5] explaining that the mean RDI of daratumumab was high (97.2%) and stable over time. Therefore, the impact on costs of applying the IPD derived daratumumab dose over time vs. a constant RDI was expected to be minimal. To illustrate this, the company contrasts cumulative mean RDI dose between treatments in DREAMM-7. (see Figure 2 in the company's response documents)[5] If IPD were used, the company expects the ICER to be slightly improved.

The EAG's response

The EAG agrees with the company that dosing of daratumumab is less variable than belamaf and stays relatively constant over the duration of the trial. DREAMM-7 data show a dose delay for [redacted] of participants, with only [redacted] delayed for longer than 6 weeks. The median duration of a dose delay was [redacted] days for daratumumab, compared to [redacted] days for belamaf.

It is therefore likely that RDI is appropriate to model dosing of daratumumab, and that the use of IPD would have only a small impact on the estimates of cost-effectiveness.

2.7 Teclistamab included as a fourth-line option

The committee requested that the analysis is updated to consider the inclusion of teclistamab as a fourth-line treatment option when estimating the costs of subsequent treatments. The company updated the economic version of the model and included the committee's request in their analyses. The implementation of this request relied on the assumption that 40% of patients at 4L would be treated with teclistamab and that it would displace other subsequent treatments which are reweighted accordingly in the model. The proportion of patients on treatment with teclistamab at 4L is not justified by the company. The company concluded that the impact of this change is small and favourable towards the cost-effectiveness of BVd.

The EAG's response

It is unclear why the company assumed a market share of [redacted] for teclistamab at 4L, but the EAG acknowledges that, regardless of the value assumed for this parameter, the impact of this on the estimates of cost-effectiveness is low. The EAG considers this issue resolved.

2.8 Baseline age should be reflective of NHS population

The committee considered that the baseline age in the model should be reflective of NHS population and preferably be informed by SACT data. The company addressed this concern by updating starting age in the model to 70 years from the full population (2L) in Lawton et al. (2024)[2] from which the company extracted survival data of the lenalidomide-exposed (prior lenalidomide) subgroup to inform the company's scenario using SACT data (see Section 2.3). The impact of this change is small and favourable towards BVd.

The EAG's response

The EAG considers that the committee's preference for age to be better aligned with that of the population in NHS clinical practice should be considered alongside the committee preference for the source of survival data informing the baseline DVd curve in the model. As the company did not accept the committee's preference for SACT data to inform baseline survival curves, using instead independently modelled DVd and BVd informed by DREAMM-7 data, it is inconsistent to assume a

starting age from a different source without considering the impact of age on mortality. The OS curves from DREAMM-7 reflect the all-cause mortality risks of a population with a baseline age of 64 years in the trial (as per the company's original base-case analysis). As mortality risk in the general population increases with age, using an older age than that reflected in the observed survival data risks introducing adjustments for the general population mortality at an earlier time point in the extrapolations for both DVd and BVd. The EAG presents results of the company's updated base-case assumptions using a starting age of 64 years consistent with the DREAMM-7 survival data in the confidential appendix.

2.9 Treatment independent utility values applied from an appropriate source

The committee requested that treatment independent utility values from appropriate sources (e.g., TA897 for the 2L subpopulation) were used to inform health state utilities. The company also stated that the alternative sources, such as DREAMM-7 or Hatswell et al. (2019)[3] could be used, if justified.

The company updated base-case applies treatment independent health state utilities:

- Informed directly by DREAMM-7 utility values for the progression free (PF health state) and corresponding to a utility value of 0.765.
- By applying a utility progression related decrement to the PF health state utility value (from DREAMM-7 data) to derive the progressed disease (PD) health state utility value of 0.734.

The PD utility decrement was derived from Hatswell et al. (2019)[3] as in the EAG base-case. However, it differs from the EAG base-case as the decrement was estimated as a weighted average (rather than a simple average) across lines of subsequent treatment, based on information on rates of attrition across lines of treatment. The PD health state utility in the company's updated base-case is higher than (i) the EAG base-case (0.664) and (ii) the treatment independent PD utility derived directly from the DREAMM-7 utility data (0.742). The company's updated base-case utility PF utility also differs from the corresponding values used in the EAG and company's original base-case, which both considered treatment-specific health state utilities.

The EAG's response

The EAG considers that the company's update to health state utility values complies with the committee's request. The method used to estimate the PD utility decrement in relation to the PF health state, may be considered a reasonable approach provided that the study informing patient attrition across treatment lines[17] is a suitable source of information. The company does not describe how the study was identified or why it is an appropriate source. Given the time constraints, the EAG only validated the implementation of this change in the economic model, but it is reassured about the face validity of the health state utilities in PF and PD in the updated base-case. The EAG notes that the

company's original base-case health state utility approach resulted in higher values in PD compared to PF for the comparator treatments, which the EAG did not consider plausible. Given that this inconsistency is resolved in the company's updated base-case, the EAG considers this issue resolved.

2.10 Include eye-related AEs disutilities in scenarios

The committee requested evidence that validates the assumption that EQ-5D would capture the disutility associated with ocular adverse events (AEs), as well as analyses including and excluding ocular AEs.

The company did not present any evidence to validate the appropriateness of using EQ-5D to capture disutility form ocular AEs. In terms of additional analyses, the company clarified that the inclusion of ocular AEs in the company's original base-case had been erroneous and that their preference was for AEs to exclude ocular AE disutilities from the analysis. The company's updated base case results presented in Tables 11 and 12 of the company's response to the EAG request for information include these disutilities.[11]

The EAG's response

The company has partially fulfilled the committee's request by providing analyses with and without ocular AEs, but no evidence has been presented to support the validity of using the EQ-5D instrument to capture disutility related to ocular AEs. The impact of including/excluding disutility associated with ocular AEs on the estimates of cost-effectiveness is marginal.

3 UPDATED MODELLING ASSUMPTIONS

In response to ACM1, the company presents an updated base-case cost-effectiveness analysis which incorporates the following committee-preferred assumptions:

- Population consisting of patients at 2L only. While this does not fully match the committees preferred population (i.e., in line with the MA for belamaf), it was one of the committee's preferred alternatives, if the MA population was not feasible. As part of this change, the company presents cost-effectiveness for an additional subpopulation, lenalidomide suitable, comparing BVd to KRd.
- Use later data cut-off from LEPUS study for ITCs.
- Teclistamab included in the costs of subsequent treatments.
- Baseline age reflective of the population in NHS clinical practice (i.e., 70 years old as per SACT data).

- Treatment independent health state utility values.
- Inclusion of disutility associated with AE ocular events.

In addition, the company also introduced the following changes that were not requested by the committee:

- Updated DREAMM-7 survival data from latest trial data cut (IA2) with the OS extrapolation model for the BVd (exponential) differing from the company's original base-case (Weibull). IA2 DREAMM-7 survival data were also used to inform the updated ITC estimates.
- Updated DREAMM-7 IPD from IA2 data cut informing BVd dosing.

The company maintained their original position on the use of DREAMM-7 data to inform the independently modelled BVd and OS extrapolations.

Results of the company's updated analysis using the most recent PAS price for belamaf (April 2025) are presented in the company's response to the EAG information request.[11] Key analyses were reproduced by the EAG and updated to include cPAS for other treatments in the model; results are presented in a separate confidential appendix alongside further analyses varying treatment stopping rules for KRd (see Section 2.2) and starting age in the model (see Section 2.8).

4 REFERENCES

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