Single Technology Appraisal

Belantamab mafodotin with pomalidomide and dexamethasone for previously treated multiple myeloma [ID6211]

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

4. **Expert personal perspectives from:**
   a. Dr Karthik Ramasamy – clinical expert, nominated by GSK
   b. Dr Rakesh Popat – clinical expert, nominated by GlaxoSmithKline
   c. David Robinson – patient expert nominated by Myeloma UK

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRIG)

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

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

[ID6211]

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments

Document B

Company evidence submission

August 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 with numerous painful and debilitating symptoms. The evolving nature of MM, and the development of resistance to different classes of therapies as the disease progresses necessitates the need for novel therapies to prolong survival, particularly for patients in relapse. The need to frequently reassess treatment pathways as new treatments emerge and the standard of care (SoC) improves can create 'gaps' in the pathways; for instance, if a historic SoC in a later line is used earlier due to innovation in combining it with something new, patients in later lines have fewer treatment options.

Belantamab mafodotin [Blenrep®] (hereafter referred in the submission as 'belamaf') is a first-in-class B-cell maturation antigen-targeted (BCMA) antibody-drug conjugate (ADC). In this submission, GlaxoSmithKline (GSK) considers the clinical and cost-effectiveness of belamaf plus pomalidomide and dexamethasone (BPd) for the treatment of adults with relapsed/refractory multiple myeloma (RRMM) who have had one prior line of therapy (LoT), including a lenalidomide-containing regimen, and for whom lenalidomide is unsuitable.

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 BPd in the treatment pathway (GSK proposes that BPd should be considered for patients for whom lenalidomide is unsuitable in second line [2L]) and thus, only relevant lenalidomide-sparing comparators in 2L are considered for this appraisal. This focus on the subgroup is based on clinical feedback from UK clinicians, who have informed GSK that 2L is an area with increasing unmet need in the current treatment pathway. The comparator within DREAMM-8 (pomalidomide plus bortezomib and dexamethasone [PVd]) is a EU SoC, recommended in 2L by European Haematology Association (EHA) - European Society for Medical Oncology (ESMO) guidelines due to the favourable efficacy and manageable safety profile of pomalidomide-based triplet regimens in patients who are lenalidomide-exposed or refractory.

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 including a lenalidomide-containing regimen	Adults (≥18 years) with RRMM who have had 1 LoT including a lenalidomide-containing regimen (2L patients) and for whom lenalidomide is unsuitable.	There is a considerable unmet need in current NHS practice at 2L for a new, more efficacious triplet regimen for patients who have had a prior lenalidomide containing regimen, and for whom lenalidomide is unsuitable. See sections B.1.3.2.2 and B.1.3.2.3.
Intervention	Belantamab mafodotin (Belamaf, Blenrep®) with pomalidomide and dexamethasone	As per scope	N/A

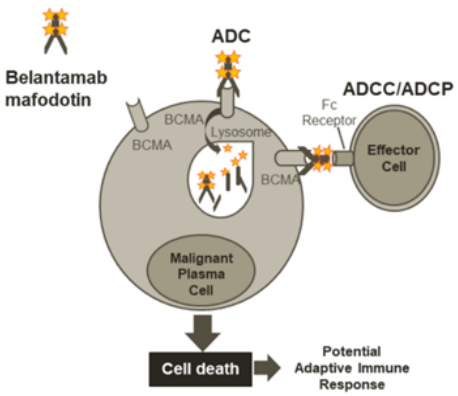
Comparator(s)	For people who have had 1 prior therapy: • bortezomib monotherapy • carfilzomib with dexamethasone • daratumumab with bortezomib and dexamethasone • selinexor with bortezomib and low-dose dexamethasone (only if, their condition is refractory to lenalidomide) For people who have had more than one prior therapy, NICE recommend several treatment options; these are removed from this table for brevity, since they are not relevant to the 2L decision problem.	For people who have had a prior lenalidomide containing regimen, and for whom lenalidomide is unsuitable: • carfilzomib with dexamethasone • daratumumab with bortezomib and dexamethasone • selinexor with bortezomib and low-dose dexamethasone (for a subgroup of patients who are refractory to daratumumab and lenalidomide)	In line with NICE Methods, the decision problem addresses only those comparators with the potential to affect prescribing decisions in England and Wales. As the standard practice in MM is to treat patients with several modalities in combination regimens (1), GSK do not consider bortezomib monotherapy to be a relevant comparator as it is rarely used in clinical practice (2-4).
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: BPd.

Table 2. Technology being evaluated

UK approved name and 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 (5-7). Belamaf provides patients with a unique mechanism of action (MoA) without impacting BCMA expression, leaving this open for future targeting by BCMA-directed agents (7). 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) (8). **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 (7).

Marketing authorisation/CE mark status	The Great Britain conditional 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 (8, 9). The regulatory submission for DREAMM-8 was made in July 2024.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Proposed indication: belamaf in combination with pomalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy including lenalidomide (10).
Method of administration and dosage	Method of administration: belamaf is for intravenous infusion only. Belamaf should be administered by intravenous infusion using an intravenous infusion pump over a minimum of 30 minutes. Belamaf must not be administered as an intravenous push or bolus injection. Posology: Administration of belamaf should be continued according to the recommended schedule until disease progression or unacceptable toxicity. Belamaf is administered plus other treatments (refer to the corresponding SmPC for the combination products) (9). The recommended dosage of belamaf is 2.5 mg/kg administered once in Cycle 1 and 1.9 mg/kg administered every 4 weeks from Cycle 2 (8). For further details see Appendix C.
Additional tests or investigations	Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, must be performed before each of the first 4 doses of belamaf and during treatment as clinically indicated (8). 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 70 mg dose will be priced proportionally per mg.

Abbreviations: ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CE, cost-effectiveness; DREAMM-8, DRiving Excellence in Approaches to Multiple Myeloma; GB, Great Britain; mg, milligram; MM, multiple myeloma; MHRA, Medicines and Healthcare Regulatory Agency; NHS, National Health Service; PAS, Patient Access Scheme; MoA, mechanism of action; 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 (11). Patients with MM typically experience painful and debilitating symptoms, including fatigue, bone pain and peripheral neuropathy.
- Whilst MM is incurable, the main goal of treatment is to avoid or delay progression by achieving a deep and durable response to treatment (12-20).
- A major challenge in MM is the cancer's evolution and the build-up of resistance to different classes of therapies as the disease progresses (21-23). This creates a pressing unmet need for therapies with a novel MoA, as clinicians and patients look for approaches to delay progression of diseases that have become refractory to existing treatment. Therefore, it is crucial to prioritise the most effective treatment at each stage of therapy to maximise patient outcomes.
- 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 salvage patients at first relapse.
- SoC treatment options at first relapse (second line [2L]), following lenalidomide exposure, are associated with poor outcomes, demonstrating the need for an efficacious 2L treatment of choice, with a unique mode of action within the NICE treatment pathway (24).

Treatment pathway in MM

- Although it might appear that patients with 2L MM are well served with six NICE approved treatment options, 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 become unsuitable later due to changes in earlier LoTs.
- 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.
    - According to the NICE treatment pathway, regardless of SCT eligibility, all 1L patients receive lenalidomide until disease progression. Consequently, almost all patients enter their first relapse either refractory or ineligible for lenalidomide (25, 26).
    - In addition, patients who are ineligible for SCT are likely to enter 2L refractory to daratumumab too (27).
    - There are limited treatment options at 2L for patients who are lenalidomide-refractory or are patients for whom lenalidomide is unsuitable, and only one triplet is approved for a subgroup also refractory to daratumumab. Data suggests corresponding outcomes for all these treatment options are suboptimal in these subgroups (28-33).

BPd in MM

- Belamaf has demonstrated superior efficacy to all existing 2L treatment options in patients who have been previously treated with lenalidomide (section B.2.6 and

section B.2.9), which suggest that belamaf combinations has the potential to serve the unmet need of deep and durable remissions at early lines of relapse.

- Pomalidomide, part of the backbone of the BPd triplet, is an oral drug that offers clinical and patient choice and flexibility in dosing and administration. Pomalidomide-based regimens have shown favourable efficacy post lenalidomide use and are a 2L SoC in EU. It works synergistically with belamaf (34), is well tolerated, even in elderly patients, with manageable adverse events. Having pomalidomide in 2L, where most regimens in the current treatment pathway are bortezomib-based offers flexibility and compliments the treatment pathway. UK clinicians have highlighted that early treatment with pomalidomide-based regimens can be beneficial for MM patients (35). This affirms the choice of a Pd backbone with a new therapy for a lenalidomide-exposed population in 2L.

- If approved, belamaf in combination would be the first off-the-shelf, outpatient BCMA-targeted therapy available to NHS patients, serving the acute unmet need for patients who at first relapse were already exposed to or refractory to lenalidomide.

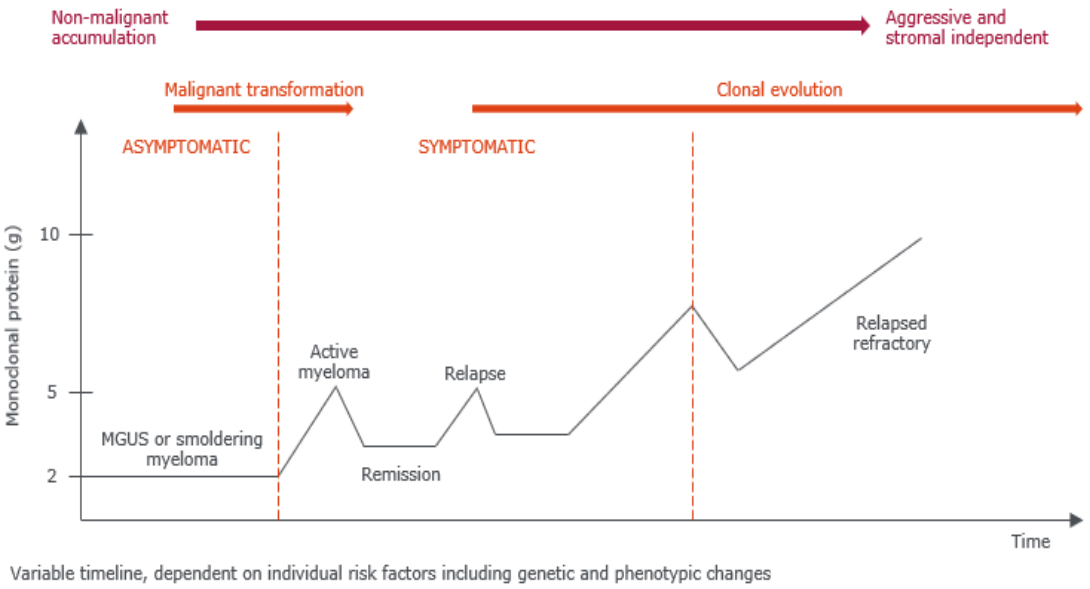
B.1.3.1 Disease overview

B.1.3.1.1 Overview of multiple myeloma

MM is an orphan, incurable, progressive, malignant plasma cell disorder, characterised by abnormal proliferation of clonal B cells in the bone marrow (11). 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 (36). 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 (37, 38).

One of the major challenges in MM is the evolution of the cancer and the development of resistance to different classes of therapies as the disease progresses, i.e., RRMM (21-23). 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 (39, 40). 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 (41).

Figure 2. Clinical course of multiple myeloma



Adapted from Kurtin et al. 2013 (38).
Abbreviations: MGUS, monoclonal gammopathy of undetermined insignificance.

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, median progression-free survival (PFS) decreased from 18 (15–22), 10 (8–13), 8 (7–10), to 6 (4–8) months from 1L to fourth LoT (4L), respectively (42). This demonstrates the progressive and aggressive nature of RRMM, as well as the need for effective treatments with a diverse range of MoAs as early as possible in the treatment pathway (37, 43).

B.1.3.1.2 Epidemiology

MM is a rare disease accounting for approximately 2% of all new cancer cases and 12.4% of haematological malignancies in the UK (44, 45). There are an estimated 4,660 new cases of MM in the UK each year, with an annual incidence rate of 7.2 cases per 100,000 people (46). Five-year prevalence of MM in the UK is estimated to be 23.9 per 100,000 (45). In England, 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 as per 2013-2017 data (47). MM has greater incidence in males, accounting for 58% of cases in the UK (46).

MM contributes to an estimated 3,098 deaths every year in the UK, which equates to more than eight deaths each day (48).

Each year, more than 43% of all new UK MM cases are diagnosed in patients aged 75 and over (46, 49-51). 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 (52).

In Europe, 95% of the patients diagnosed with MM receive 1L treatment (53). Subsequently, 61% of those patients receive 2L treatment, which rises to 64% in the UK (53, 54). This is equivalent to approximately 3,400 patients in the UK who are eligible for 2L treatment (27, 53, 55). 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 stem cell transplantation (SCT) (54).

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 (56). At diagnosis, the clinical manifestations of symptomatic MM are present in about 70% of patients and are commonly defined using the term “CRAB”: hypercalcaemia, renal insufficiency, anaemia, and bone lesions (43, 57).

Vascular, metabolism and nutrition, and musculoskeletal and connective tissue comorbidities are common among patients with RRMM (12). 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 (43). In a meta-analysis of 34 clinical studies in MM patients (N=3,023), which included 12 studies of patients with advanced stages of MM, fatigue (98.8%), pain (73%), constipation (65.2%), and tingling sensation in the hands and feet (53.4%) were the most prevalent symptoms (58). Furthermore, patients with RRMM have a higher Charlson Comorbidity Index compared to those with newly diagnosed MM (52, 59-62).

As the disease progresses, symptoms and complications from previous treatments may persist. 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) (58, 63).

Although new targeted treatment options for MM have extended survival for patients while maintaining HRQoL, i.e., help maintain HRQoL by delaying disease progression, there remains a significant adverse event (AE) burden. An interview conducted among 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%) (64). 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 (18, 65).

B.1.3.1.4 Life expectancy

Although there is currently no cure for myeloma, it is highly treatable in most patients. With an increasing number of new and effective treatment options, the prognosis and life expectancy of myeloma patients has greatly improved over recent years. 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 will live for at least 10 years (44). With improvements in treatments and life expectancy, myeloma has the potential to become a cancer that is treatable over a very long period.

However, the outlook is less favourable for lenalidomide-pre-treated patients, as real-world evidence suggests that lenalidomide-refractoriness independently predicts lower life expectancy. This is evident from the real-world retrospective analysis of National Cancer Registration and Analysis Service (NCRAS) data, where median overall survival (OS) with the current 2L SoC (daratumumab plus bortezomib and dexamethasone [DVd]) was [redacted], whereas for the lenalidomide refractory group it was only [redacted] While a 6-month difference in OS may seem modest, it is clinically significant for patients facing an aggressive disease with limited options, underscoring the urgent need for better therapies. Thus, an improving OS remains a necessity for both patients and clinicians in the 2L setting, where lenalidomide refractoriness is very high in the UK.

B.1.3.1.5 Humanistic burden

The high symptom burden experienced by MM patients often results in detrimental impact on HRQoL, with the impairment found to be increasing with increased symptoms severity, which can be either disease or treatment-related (13).

As patients transition from a treatment free interval (TFI) at 1L to 2L and subsequent treatments, it has been observed that HRQoL deteriorates (66). A UK based study, conducted in 370 MM patients, demonstrated that 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), patients in later phases had worse HRQoL profile than their first TFI. This deterioration in HRQoL is an indicator of the increasing symptom burden and cumulative toxicities as patients progress through treatment lines. (66).

A RW study conducted in Europe across ten countries, characterised the psychological burden of relapse on patients with RRMM (67). The study charted the evolution of negative emotional outcomes in patients during relapse of the disease, especially during the first relapse (67). Patients reported worsened energy levels, increased tiredness, impaired concentration, ability to perform daily activities, decreased participation in social activities, and worsening overall QoL, upon progression from stable disease to disease relapse (67). 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 (67). Thus, longer remission in earlier lines of treatment (i.e., 2L) is essential for improving patients' quality of life (QoL).

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 (15). 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 (15). The same pattern was reported with the EORTC QLQ-MY20 scores, demonstrating a worse HRQoL with more relapse cycles (15).

The symptoms of MM also may 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 can lead to frequent fractures; additionally, fatigue is also a challenge that impacts patients' ability to work (68). However, it is not only the physical symptoms that pose challenges; mental difficulties in accepting their diagnosis and/or relapse can lead patients to have a low mood and lack motivation (68, 69).

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 (16, 70). 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+) (16). The main reasons for hospitalisations among patients on active treatment were drug administration and management of AEs (16). 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%) (16).

Effective treatments that induce long remission can potentially save the NHS significant costs, particularly if treatments can be administered in earlier LoTs, for instance, at first relapse.

B.1.3.2 Clinical management of RRMM and place of belamaf in the treatment pathway

B.1.3.2.1 Anticipated positioning of belamaf plus pomalidomide and dexamethasone in the treatment pathway

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

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 clinicians may use for treating that patient.

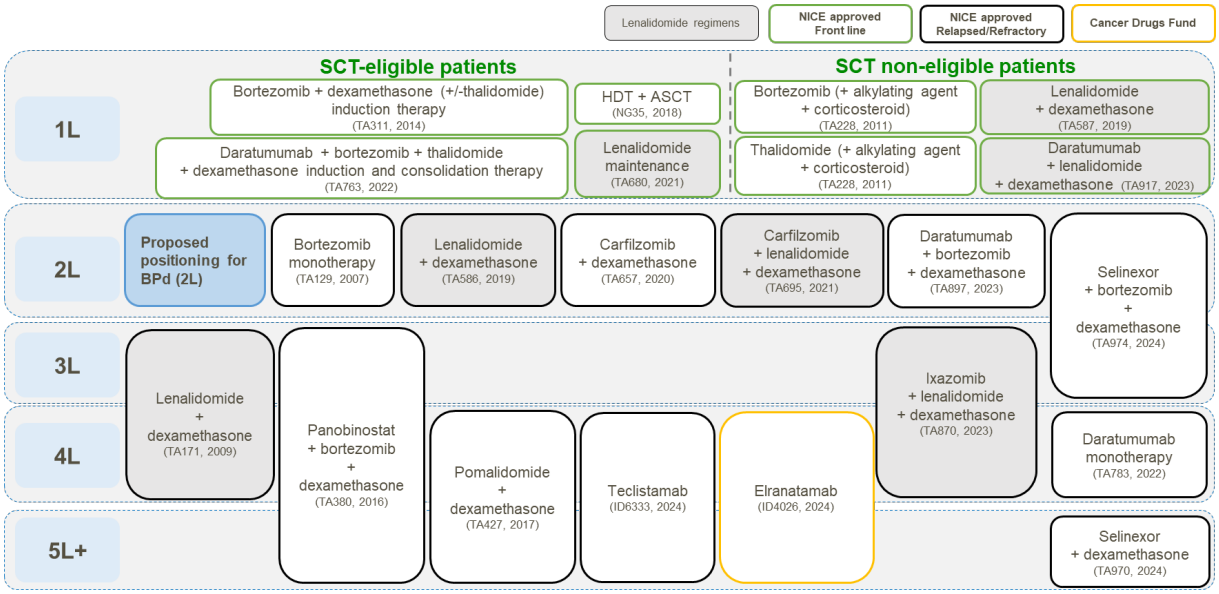
Although it might appear that patients with 2L MM are well served with six NICE approved treatment options, patients for whom a lenalidomide-containing regimen is unsuitable are notably underserved (25, 26). In fact, the complexity of MM as a disease hides the acute burden of unmet need in this population. Prior exposure to MM drugs in patients with RRMM affects the treatment outcomes with subsequent therapies. Thus, the efficacy of a given MM therapy largely depends on previous therapy, particularly those from within the same class, implying that medications which may have been a good choice at 1L may now be unsuitable as patients progressed to 2L treatment.

Selinexor plus bortezomib and dexamethasone (SVd) was recently approved for both 2L and third line (3L). The eligibility for SVd is dependent on patients being refractory to both lenalidomide and daratumumab at 2L. Treating a patient with SVd in 2L means patients will not be eligible to receive SVd again at 3L, which limits the number of treatment options available for patients in 3L, another area in the treatment pathway with a recognised gap. Hence, a lenalidomide-sparing regimen which is nominally available in 2L might actually be reserved for 3L, increasing the burden of unmet need on patients at 2L.

GSK notes that NICE are currently assessing another belamaf-based triplet regimen, belamaf plus bortezomib and dexamethasone (BVd [NICE ID6212]). If approved, BVd would go some way to addressing the urgent unmet need in the 2L population. However, GSK proposes that BVd and BPd would have a synergistic effect if both approved together, and provide clinical and patient choice in a therapy area where flexibility to tailor treatment according to the specific patient and disease characteristics can provide the best outcomes. When compared to bortezomib, pomalidomide is orally administered, offering patients and physicians convenience and flexibility where required (4). Additionally, the different side effect profile of the two medicines allows patients that may not be suitable for one to use the other, further advocating for synergistic usage of two different backbones. Post-lenalidomide treatment, pomalidomide-based triplet regimens have demonstrated favourable efficacy, and thus, UK clinicians have highlighted its use in early lines of therapy where almost all patients are lenalidomide-exposed can be advantageous for MM population (4).

For these reasons GSK proposes to position BPd in 2L as outlined in Figure 3.

Figure 3. Anticipated positioning of belamaf plus pomalidomide and dexamethasone in the NICE treatment pathway



Notes: The subpopulation of patients for whom lenalidomide is unsuitable shows the greatest unmet need (71). The proposed positioning for DREAMM-8 has been shaded in blue. Treatment regimens in the pathway containing lenalidomide have been shaded in grey.
Selinexor plus bortezomib and dexamethasone (SVd) is recommended only for patients with RRMM that are refractory to both lenalidomide and daratumumab at 2L and for patients who are refractory to lenalidomide at 3L (NICE TA974) (3).
For elranatamab, NICE will withdraw the final draft guidance and instead issue draft guidance for consultation. The draft guidance will make the same recommendation seen in the final draft guidance, namely that elranatamab is recommended for managed access only if pomalidomide plus dexamethasone would otherwise be offered. As there will continue to be a positive draft recommendation for managed access in the relevant population, interim funding will remain available for patients eligible for elranatamab under this recommendation (NICE ID4026) (72).
Teclistamab for treating RRMM after 3 or more treatments is under consultation with draft guidance (NICE ID6333) (73).
Abbreviations: 1L–5L+, first- to fifth-line and onwards; ASCT, autologous stem cell transplant; 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 belamaf in combination as the new SoC for patients for whom lenalidomide is unsuitable at 2L, and this submission presents the cost-effectiveness of BPd in the same population. The number of patients eligible for a lenalidomide-containing regimen in 2L is small (and it might in fact be zero based on clinical feedback (4, 74)), and therefore the majority of the impact on the NHS of approving BPd will be due to patients for whom lenalidomide is unsuitable, which this submission focusses on.

The most common reason for unsuitability of lenalidomide-containing regimens in RRMM patients is attributed to the acquired refractoriness 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 (75). However, lenalidomide refractoriness is not the only reason a lenalidomide-containing therapy might be considered unsuitable for a patient; contraindications to lenalidomide may also lead to unsuitability. For instance, patients with fluctuating renal function or those requiring haemodialysis require lenalidomide

dose-adjustments, which can be cumbersome and difficult to manage. Additionally, severe skin reactions and allergies to lenalidomide can limit its suitability. In such cases, pomalidomide may be a viable alternative, as it does not require dose adjustments for renal function and may be better tolerated by patients who experience adverse reactions to lenalidomide. (76-80).

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 MM

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 patients (37, 43, 81). 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 1L setting. However, in general, clinicians consider two main treatment pathways at 1L:

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.

Treatment for those who are eligible for a SCT

The first-choice treatment for patients with MM is autologous SCT (ASCT), where eligible (1). 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) (1, 82). 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 bortezomib, thalidomide and dexamethasone (VTd) 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 also likely to 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 SCT

As with the SCT-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 that lenalidomide remains an unsuitable choice of therapy in 2L as well. In addition, almost all patients who started treatment prior to 2024 and are still on 1L treatment will eventually become refractory to lenalidomide (but not daratumumab).

For SCT-ineligible patients starting treatment in 2024, the new SoC is DRd (83). As this is a very recent addition to the MM treatment pathway in the NHS, many patients will still be prescribed more established 1L treatment regimen like lenalidomide and dexamethasone (Rd) (84). Patients who cannot tolerate Rd may be offered a thalidomide- or bortezomib-based regimen (85). Therefore, almost all new starters of 1L treatment who are not eligible for an ASCT will receive DRd and eventually become refractory to both lenalidomide and daratumumab. UK-based clinicians believe increasing daratumumab refractoriness will lead to the wider usage of currently available daratumumab-sparing alternatives in 2L (4).

It is relevant for assessing the cost-effectiveness of BPd that the proportion of patients who are daratumumab-refractory in 2L is approximately 10%; however, this is expected to grow by 10% each year (4). Therefore, the cost-effectiveness estimates presented in this dossier are an extreme lower bound of how cost-effective BPd 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 RRMM

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

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) (86), or DVd (86). Unfortunately, both have limited efficacy in lenalidomide-refractory population as seen in Table 3 (87). DVd is typically preferred over Kd, as ESMO guidelines generally recommend the use of triplet regimens, although doublet therapies may be prescribed for patients who are too frail to receive triplets (1).

SVd is the third lenalidomide-sparing option for RRMM, which has recently gained NICE approval at both 2L and 3L. SVd is also associated with poor treatment outcomes in 2L. The use of SVd in earlier LoTs, i.e. 2L, precludes its use in 3L, leaving patients without any NICE-approved options at 3L (88).

The limitations of the existing 2L treatment armamentarium are summarised in Table 3, which highlights the unmet need for effective 2L treatments.

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) (24). • The poor outcomes for DVd in the lenalidomide-refractory subgroup from CASTOR are also aligned with a recent UK RW 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) (31).
Kd	• Notably, median PFS for the lenalidomide-refractory subgroup in ENDEAVOR was substantially lower than that in the 2L subgroup (8.6 months versus 22.2 months (89)). • ESMO guidelines recommend against the use of doublet regimens when triplets are available (1). • Undesirable cardiac side-effect profile (29).
SVd	• Overall poor clinical outcomes in lenalidomide-refractory patients (median PFS of 10.2 months reported in the BOSTON trial) (90). • Not available to patients unless they are also refractory to daratumumab (3). • 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; BPd, Belamaf plus pomalidomide, and dexamethasone; CI, confidence interval; DRd, daratumumab plus lenalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; DREAMM-8, 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; RW, real-world; SVd, Selinexor plus bortezomib, and dexamethasone; TTNTD, time to next treatment or death.

Therefore, there is a pressing need for effective lenalidomide-sparing 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. 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) (4, 74). Following the positive NICE recommendation for DRd in 1L, patients at first relapse are expected to be daratumumab refractory, which will further increase the need for a daratumumab-sparing regimen (83).

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 (2). 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) (3). 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.

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). As described in section B.1.3.2.2, the majority of MM patients eligible for 2L treatment are anticipated to be a population for whom a lenalidomide-containing regimen would be unsuitable, aligning with the DREAMM-8 clinical trial patient population.

A treatment with a novel MoA, such as belamaf, offers a valuable and clinically important treatment option for patients for whom a lenalidomide-containing regimen is unsuitable. The combination of pomalidomide and dexamethasone (Pd) with belamaf provides complementary advantages. The MoA of pomalidomide (immunomodulatory agent) synergises and enhances the efficacy of belamaf (34). Notably, pomalidomide-based doublet and triplet regimens have demonstrated favourable efficacy in lenalidomide-exposed or refractory population, further affirming the advantages of a Pd backbone with belamaf for patients for whom lenalidomide regimens are unsuitable (35, 91).

AEs associated with pomalidomide, such as thrombocytopenia and neutropenia, can be managed with dose modifications, which clinicians are confident in dealing with in their routine practice (78). Considering pomalidomide is administered orally, it provides clinical and patient choice and flexibility in terms of dosing schedule and treatment administration for patients and clinicians (92). Thus, the manageable safety profile of pomalidomide, alongside its convenience which may be preferred by older patients, further advocating the usage of Pd backbone (91).

Additionally, PVd, a 2L EU SoC, is recommended by EHA and ESMO guidelines for both lenalidomide-refractory and lenalidomide-sensitive patients, following bortezomib plus lenalidomide and dexamethasone (VRd) and DRd (93). Currently, Pd is recommended by the NHS after three or more lines of therapy (94). Based on its demonstrated efficacy and safety benefits, an early use of Pd backbone plus belamaf is advocated by clinicians to offer additional treatment option for MM patients for whom lenalidomide is unsuitable and potentially lessen the burden of disease progression (4, 92).

B.1.4 Equality considerations

No equality considerations of relevance were identified for DREAMM-8.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- DREAMM-8, a multicentre phase III randomised trial, compared the technology being evaluated (BPd) to a EU 2L SoC and EHA-ESMO recommended 2L regimen (PVd). The trial included 155 patients (BPd arm) / 147 patients (PVd arm) in the intention-to-treat (ITT) population and 150 patients (BPd arm) / 145 patients (PVd arm) in the safety population. At the point of the primary analysis (data cut-off: 29 January 2024), the median study follow-up was 21.8 months.
- The primary endpoint of this trial was PFS based on independent review committee (IRC) assessment of response, and the secondary endpoints were OS, DoR, minimum residual disease (MRD), overall response rate (ORR), complete response rate (CRR), very good partial response (VGPR), time to best response (TTBR), time to response (TTR), TTP, PFS-2, sustained MRD, and HRQoL.
- The proposed positioning of BPd is for patients for whom lenalidomide is unsuitable in 2L, due to the high unmet need identified in this patient subgroup (as outlined in section B.1.3.2). As noted in Section B.1.3.2.3, GSK believes that lenalidomide will effectively be unsuitable for every patient at 2L in the NHS, and so therefore the ITT population is used to capture this. This population demonstrates the strongest evidence base and represents the largest sample size of RRMM participants across both arms (N=302) randomised to either BPd or PVd. Furthermore, it facilitates use of the most appropriate data in the NMA, to closely align with the populations of the other included comparator studies (detailed in section B.2.9).
- The DREAMM-8 study results provides further supportive evidence that belamaf in combination 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 profile, and ease of administration.
    - BPd demonstrated a statistically significant and clinically meaningful IRC-assessed PFS benefit in the ITT population (95% confidence interval (CI): 0.37, 0.73; hazard ratio (HR), 0.52; p<0.001; showing a 48% reduction in risk of disease progression or death) with median PFS not yet reached compared with PVd (NR vs 12.7 months).
        - PFS benefit consistently favoured BPd vs PVd across prespecified subgroups, including patients with lenalidomide-refractory or high-risk cytogenetic MM. In the lenalidomide-refractory subgroup, median PFS (95% CI) was [redacted] with BPd versus [redacted] with PVd [redacted]. In the high-risk cytogenetic subgroup, median PFS (95% CI) was [redacted] with BPd versus [redacted] with PVd [redacted].
    - OS showed a positive trend favouring the BPd arm in the ITT population
        - Median OS was NR in both groups. The 12 months OS survival rate was higher in the BPd group compared with the PVd group (83% vs. 76%).
    - BPd was associated with greater depth of response in the ITT population with a CRR that was more than double that reported in the PVd (40% vs 16%). MRD negativity rate (10^{-5}) in patients treated with BPd was five times more than that in patients treated with PVd (24% vs 5%).
        - 64% and 38% of responders in the BPd and PVd 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) in the BPd group was longer than PVd ([redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]].
- The safety and tolerability of BPd was consistent with those previously described for belamaf, despite the longer time on treatment compared to previous monotherapy studies (95, 96).
  - 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 BPd arm, overall HRQoL did not differ between arms over time.
  - The rates of infections were higher in the BPd group compared with the PVd group in the DREAMM-8 trial; however, after adjusting for time on treatment, the EAIRs were lower in the BPd group than in the PVd group.

- Network meta-analysis (NMA) results suggest that BPd is more efficacious compared to all lenalidomide-sparing comparators (PVd, DVd, SVd, Kd), for all populations in terms of PFS and OS.
  - In terms of PFS, BPd (DREAMM-8 ITT population used) demonstrated statistically significant improvements over comparator treatments in the lenalidomide-exposed population including PVd [redacted], high-dose carfilzomib plus dexamethasone (hKd) [redacted], and SVd [redacted], while numerical improvement was observed over DVd [redacted], with consistency across populations of interest: lenalidomide-exposed, lenalidomide-refractory, lenalidomide-exposed and ITT, and lenalidomide-refractory and ITT patients.
  - All the HR results indicated an OS benefit for BPd over hKd ([redacted]) and PVd [redacted] in the lenalidomide-exposed 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 (97).

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 (97-99) and is considered suitable to inform single technology appraisals that are submitted to NICE (97, 100).

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 plus pomalidomide and dexamethasone

DREAMM-8 is a multicentre phase III, randomised, open-label trial evaluating the efficacy and safety of BPd compared with a EU SoC, EHA-ESMO recommended regimen, pomalidomide plus bortezomib and dexamethasone (PVd) for the treatment of adult RRMM patients. Key inclusion criteria for DREAMM-8 included previous treatment with at least one prior LoT, including a lenalidomide-containing regimen (lenalidomide must have been administered for at least 2 consecutive cycles) (101-103). This is the only trial directly comparing BPd to PVd, and therefore the clinical data and cost-effectiveness analyses presented in this submission are based on this trial.

The DREAMM-8 trial evaluated the efficacy and safety of belamaf at a dose of 2.5 mg/kg (intravenous [IV]) on day 1 of cycle 1 and 1.9 mg/kg on day 1 of cycle 2 onwards, once every 4 weeks (Q4W) plus pomalidomide, and dexamethasone in intent to treat (ITT) population. The proposed positioning of BPd is for all patients for whom lenalidomide is unsuitable at 2L due to the increasing unmet need identified in this patient population. Given that the most common reason for unsuitability is due to lenalidomide refractoriness, the most appropriate population to inform cost-effectiveness is the DREAMM-8 ITT population, which was 100% lenalidomide-exposed. The ITT population of DREAMM-8 aligns closely with the proposed positioning of BPd in the treatment pathway, and also includes a large sample size across both the treatment arms in RRMM patients (n=302) randomised to either BPd or PVd, which reduces uncertainty around the cost-effectiveness results. In addition, the use of the ITT population from DREAMM-8 is supported by: validation from external experts, the NMA conducted (for both PFS and OS) (see section B.2.9.3), adjustment of OS for NHS aligned subsequent treatment and use of the PFS:OS surrogacy relationships identified in other RRMM trials. The subsequent sections summarise evidence for the ITT population, defined as all randomised participants, irrespective of whether randomised treatment was administered.

The clinical effectiveness evidence summary for DREAMM-8 is presented in Table 4. (101-103).

Table 4. Clinical effectiveness evidence

Trial name	DREAMM-8 trial (28, 101-103)		
Trial design	Phase III, multicentre, randomised, open-label trial comparing BPd with PVd		
Population	Adults (≥18 years) with RRMM who have had at least 1 prior LoT, including a lenalidomide-containing regimen		
Intervention(s)	BPd: Belamaf was administered IV at the dose of 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2 onwards in each 28-day cycle. Pomalidomide was administered orally 4 mg per day on Days 1 to 21 of each 28-day cycle. Dexamethasone was administered orally at a dose of 40 mg per day on Days 1, 8, 15, and 22 of each 28-day cycle. For participants who were >75 years old or had comorbidities or were intolerant to 40 mg, dexamethasone could be administered at the lower dose of 20 mg.		
Comparator(s)	PVd: Pomalidomide was administered orally at 4 mg daily on Days 1 to 14 of each 21-day cycle Bortezomib was injected SC at 1.3 mg/m^2 on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1 through 8, and on Days 1 and 8 of each 21-day cycle for Cycles 9+. Dexamethasone was administered orally at a dose of 20 mg on the day of and day after bortezomib of each 21-day cycle or on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for Cycles 1 through 8, and then on Days 1, 2, 8, 9, and once every 3 weeks for Cycles 9+. For participants who were >75 years old or had comorbidities or were intolerant to 20 mg, dexamethasone could be administered at the lower dose of 10 mg on the day of and day after bortezomib		
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	• PFS • OS • 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 • PFS-2 • Sustained MRD*

Abbreviations: AE, adverse event; BPd, belamaf plus pomalidomide, and dexamethasone; DoR, duration of response; DREAMM-8, 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; PVd, pomalidomide plus bortezomib and dexamethasone; RRMM, relapsed refractory multiple myeloma; SC, subcutaneous; TTBR, time to best response; 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 5.1.2.3 of DREAMM-8 primary analysis report for additional details on sustained MRD

B.2.2.2 Comparators

Section B.1.3.2.2 identifies three potential comparators approved by NICE for patients who have previously received a lenalidomide-containing regimen and for whom lenalidomide is unsuitable. The relevant comparators are: DVd, SVd, and Kd. Please note that PVd was not considered a relevant comparator for this appraisal as it is not a NICE approved treatment. The clinical SLR 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 (24, 27, 104, 105). In both 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 (106).

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 (107, 108). 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 (107, 108). 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-8 trial (first patient in [FPI- 13 October 2020] to database lock date [19 February 2024], the efficacy and safety of the intervention BPd was compared to PVd in the population of interest (2L RRMM).
- 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, including a lenalidomide-containing regimen, and must have a documented disease progression during or after their most recent therapy. Key exclusion criteria included intolerance to pomalidomide and bortezomib; refractoriness to bortezomib, and prior treatment with anti-BCMA therapy.
- Participants were stratified based on the number of prior LoTs (1 vs. 2/3 vs. ≥4), prior bortezomib (yes vs. no), and prior anti-CD38 treatment (yes vs. no), 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.
- In the current submission, GSK reports results for efficacy outcomes (PFS, OS, DoR, ORR, and other efficacy outcomes) & HRQoL for the intention-to-treat (ITT) population (N=155 for BPd and N=147 for PVd). Safety results are presented for the safety analysis population (N=150 for BPd and N=145 for PVd).
- Results presented are based on the primary analysis for DREAMM-8 (Data cut-off: 29 January 2024) with the median study follow-up was 21.8 months.

B.2.3.1 Belamaf plus pomalidomide and dexamethasone (DREAMM-8)

Summary of trial methodology

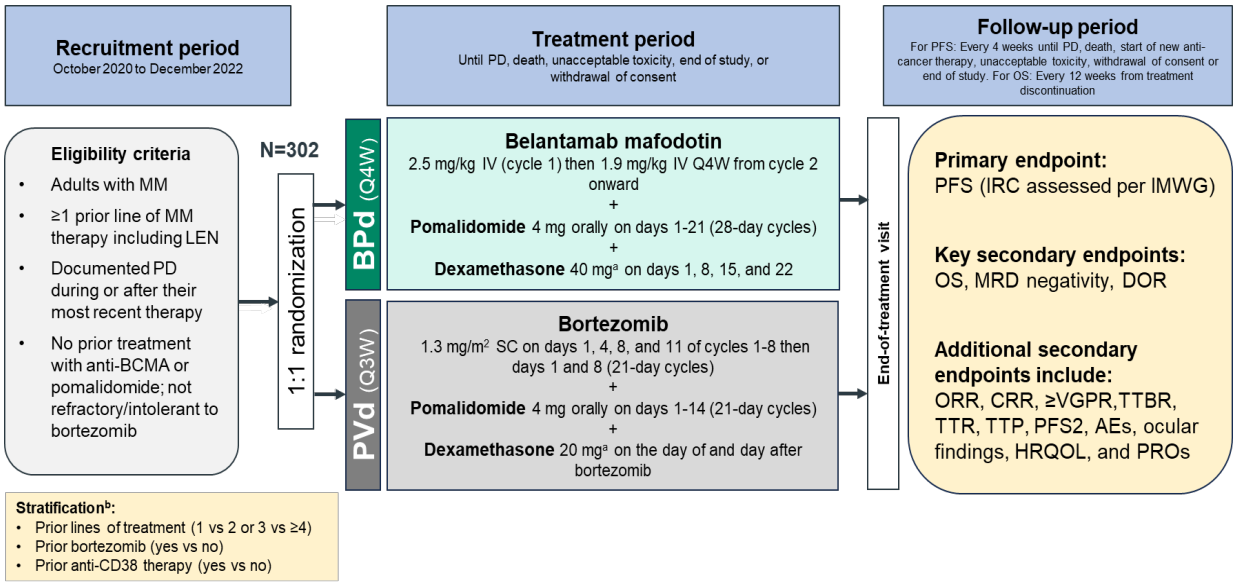
DREAMM-8 is a phase 3, open-label, randomised trial investigating the efficacy and safety of BPd compared with the combination of PVd in adults (≥18 years) with RRMM. This study was conducted at 95 centers in 18 countries (Australia, Brazil, Canada, China, Czech Republic, France, Germany, Israel, Italy, Japan, South Korea, New Zealand, Poland, Russian Federation, Spain, Turkey, the UK, and the US), including five centres in the UK (103).

The trial included a Screening Period, a Treatment Period, and a Follow-up Period (Figure 4). Participants were centrally randomised in a 1:1 ratio to either of the two treatment arms: belamaf 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2 onwards Q4W plus pomalidomide and dexamethasone and pomalidomide plus bortezomib and dexamethasone. Stratification factors included number of prior lines of therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib treatment (yes vs. no). In the original protocol, patients were stratified based on ISS status (I vs. II/III). After Protocol Amendment 1, this randomisation was replaced by prior anti-CD38 treatment (yes vs. no). No cross-over was allowed and no more than 50% of participants with ≥2 prior lines of treatment were enrolled (101, 102).

Treatment was continued in both arms until PD per IMWG criteria, death, unacceptable toxicity, start of a new anti-myeloma therapy, 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 Q4W (±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, PFS2, and survival status Q12W (±14 days) until withdrawal of consent, loss to follow-up, death, or the end of the study (101, 102).

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

Figure 4. Overview of the DREAMM-8 trial design



a. The dose level of dexamethasone was reduced by half if participant age >75 years or had comorbidities or were intolerant to 40 mg dose in Arm A or 20 mg dose in Arm B, respectively.
b. Prior lines of treatment (1 vs. 2 / 3 vs. ≥4), prior bortezomib treatment (yes or no) and prior anti-CD38 treatment (yes or no). No more than 50% of participants with 2 or more prior lines of treatment were enrolled. It was anticipated that no more than 15% of participants with 4 or more prior lines of treatment would be enrolled. No cross-over was allowed. Prior to Protocol Amendment 1, stratification included ISS status (I vs. II/III) instead of anti-CD38 treatment.

Abbreviations: AE, adverse event; BCMA, B-cell maturation antigen; BPd, belamaf, pomalidomide, and dexamethasone; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; HRQOL, health-related quality of life; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; IV, intravenous; LEN, lenalidomide; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival on subsequent line of therapy; PRO, patient reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous; TTBR, time to best response; TTP, time to progression; TTR, time to response; VGPR, very good partial response.
Source: DREAMM-8 trial protocol; DREAMM-8 primary analysis clinical study report (101, 102)

The primary endpoint of the DREAMM-8 trial was PFS, defined as the time from randomisation until the earliest date of PD, determined by an Independent Review Committee (IRC), according to IMWG criteria or death due to any cause (102).

Other outcomes included:

- Key secondary outcomes: OS, DoR, MRD negative status (102).
- Other secondary outcomes: ORR, CRR, VGPR rate, TTBR, TTR, TTP, PFS-2, AEs, Eye-related findings, HRQoL (102).
- Exploratory outcomes: HRQoL, sustained MRD (102).
- Additional outcomes: TTD, TTNT

B.2.3.2 Comparative summary of the methodology of the DREAMM-8 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-8 trial methodology

Trial name	DREAMM-8 trial (101-103).
Location	Global, multicentre study(including the UK)
Trial design	Multicentre, phase III, randomised, open-label trial comparing BPd with PVd.
Key dates	First patient dosed: [redacted] Data cut-off dates: 29 January 2024 (primary analysis)
Patient disposition & follow-up	A total of 302 participants with RRMM were randomised to either BPd or PVd. Per protocol no more than 50% of participants with ≥2 prior lines of treatment could be enrolled. Enrollment of maximum allowed participants with ≥2 lines of prior therapy was completed just over half way through global study enrollment, with the latter half of enrollment period enrolling only participants with 1 prior LoT. [redacted] participants ([redacted]) withdrew from the study ([redacted] in the BPd group and [redacted] in the PVd group). The primary reason for early withdrawal from the study was withdrawal of consent by the participant. There were fewer deaths in the BPd group (31%) compared with the PVd group (37%). More participants were ongoing in study in the BPd group ([redacted]) compared with the PVd group ([redacted]) at the data cut-off. At the data cut-off, 42% of participants in the BPd vs. 22% of participants in the PVd 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 by the IMWG criteria (109).
	• Previously treated with at least 1 prior line of MM therapy including a lenalidomide-containing regimen (lenalidomide must have been administered for at least 2 consecutive cycles) and must have documented disease progression during or after their most recent therapy (110).
	• Has measurable disease with at least one of the following:
	  o Serum M-protein ≥0.5 g/dL (≥5 g/L)
	  o Urine M-protein ≥200 mg/24h
	  o Serum FLC assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
	• Patients who have undergone ASCT or are considered transplant ineligible. Patients with a history of ASCT were eligible for study participation provided the following eligibility criteria were met:
	  o ASCT was >100 days prior to the first dose of study medication
	  o No active bacterial, viral, or fungal infection(s) present
	• 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: • Received prior treatment with or intolerant to pomalidomide • Received prior BCMA-targeted therapy • Intolerant to bortezomib or refractory to bortezomib[1] • Systemic anti-myeloma therapy or use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug • Plasmapheresis within seven days prior to the first dose of study drug • Symptomatic amyloidosis, active POEMS syndrome or active plasma cell leukaemia at the time of screening • Participants after prior allogeneic SCT • Patients with evidence of cardiovascular risk including current clinically significant untreated arrhythmias, history of myocardial infarction, acute coronary syndromes, coronary angioplasty, or stenting or bypass grafting within 3 months of screening, Class III or IV heart failure as defined by New York Heart Association (NYHA), and uncontrolled hypertension • Current corneal epithelial disease except mild punctate keratopathy • 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 Patients with a history of invasive malignancy other than multiple myeloma (except if the disease has been stable for at least 2 years or if they are not undergoing active treatment, other than hormonal therapy) Detailed inclusion and exclusion criteria is provided in DREAMM-8 trial protocol section 5.1 and 5.2 (101).
Settings and where data were collected	95 MM specialty centres in 18 countries, including five centres in the UK (103).
Trial drugs and concomitant medications	The only trial drug included was belamaf, at 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2 onwards Q4W plus pomalidomide and dexamethasone. Patients received full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

	While the participants were receiving treatment with pomalidomide in either arm of the study, thromboprophylaxis was recommended, and the choice of regimen was based on an assessment of the participant's underlying risks, in accordance with local prescribing information. Antiviral prophylaxis was recommended in accordance with local prescribing information for participants being treated with bortezomib. Concomitant therapy with bisphosphonates was recommended. Concomitant prophylactic treatment for tumour lysis syndrome in participants with a high tumour load was considered. 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:
	  ○ OS
	  ○ DoR
	  ○ MRD
	• Other secondary efficacy endpoints:
	  ○ ORR
	  ○ CRR
	  ○ VGPR
	  ○ TTBR
	  ○ TTR
	  ○ TTP
	  ○ PFS-2
	• Exploratory efficacy endpoints:
	  ○ 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
	• Adverse events of special interest (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 (110), 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 sample collection either on the same day, or within 14 days of the original date of suspected disease progression, preferably before institution of any new anti-myeloma therapy. The assessments to be performed during the End of Treatment Visit are described in the SoA (101). 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 was the only site of progression.
Pre-planned subgroups	PFS analysed by age group; sex; race; ethnicity; race groups; region; number of prior lines of therapy; time to relapse after initiation of first LoT; cytogenetic risk; prior anti-CD38 treatment; prior bortezomib use; baseline ECOG; prior stem cell transplant; refractory to lenalidomide therapy; refractory to anti-CD38 treatment; EMD at baseline; triple-exposed (PI, Immunomodulator, anti-CD38); prior exposure to lenalidomide and anti-CD38 mAb.

1. Participants who experienced a PD during treatment, or within 60 days of completing treatment, with a bortezomib-containing regimen of 1.3 mg/m^2 twice weekly

Abbreviations: AE, adverse event; AESI, adverse events of special interest; BCMA, B-cell maturation antigen; BPd, belamaf plus pomalidomide, and dexamethasone; CR, complete response; CRR, complete response rate; DREAMM-8, DRiving Excellence in Approaches to Multiple Myeloma; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; 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; Q4W, once every 4 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-8 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 or death due to any cause (110)
Secondary	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.
	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
	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 (110)
	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 (110)
	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 (110)
	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 (110)
	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 (110)
	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 (110)
	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 (110) or death due to PD

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 (110)
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)	Defined as the time from randomization until the date of start of follow-up of anti-cancer treatment or death due to any cause

Abbreviations: CR, complete response; CRR, complete response rate; DoR, duration of response; IMWG, International Myeloma Working Group; IRC, independent review committee; MRD, minimal residual disease; NGS, next generation sequencing; ORR, overall response rate; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PR, partial response; 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-8 trial protocol (101); DREAMM-8 primary analysis clinical study report (102).

B.2.3.2.1 Patient disposition

A total of 302 participants with RRMM were randomised to either BPd or PVd. Per protocol no more than 50% of participants with greater than or equal to two prior lines of treatment could be enrolled. Enrolment of maximum allowed participants with greater than or equal to two lines of prior therapy was completed just over halfway through global study enrolment, with the latter half of enrolment period enrolling only participants with one line of prior therapy.

[redacted] participants ([redacted]) withdrew from the study ([redacted] in the BPd group and [redacted] in the PVd group). The primary reason for early withdrawal from the study was withdrawal of consent by the participant. There were fewer deaths in the BPd group ([redacted]) compared with the PVd group ([redacted]). More participants were ongoing in study in the BPd group (61%) compared with the PVd group (57%) at the data cut-off. At the data cut-off, 42% of participants in the BPd vs. 22% of participants in the PVd group were on study treatment.

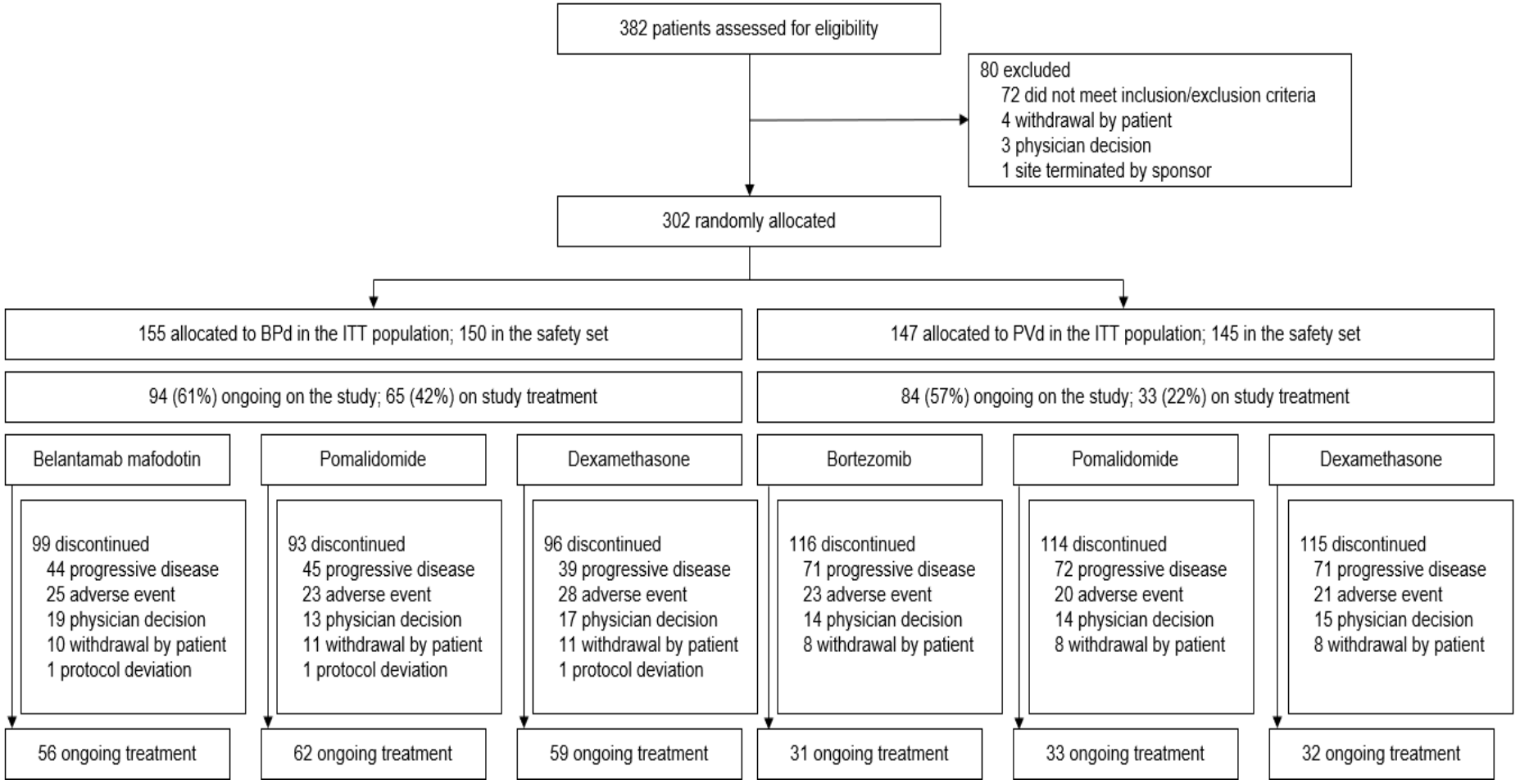
The flow of participants through the DREAMM-8 trial is summarised in a CONSORT diagram in Figure 5 (28).

In the BPd vs. PVd groups, the median duration of follow-up was comparable (22.4 months [range: [redacted]] vs. 20.5 months [range: [redacted]]).

At the data cut-off, the percentage of participants who discontinued belantamab mafodotin ([redacted]) was [redacted] compared with the percentage of participants who

discontinued bortezomib ([redacted]). The percentage of participants who discontinued due to disease progression was [redacted] for belantamab mafodotin ([redacted]) than for bortezomib ([redacted]). The other main reasons for discontinuation were AEs ([redacted]) and physician's decision ([redacted]) which were reported for a similar percentage of participants for belantamab mafodotin and bortezomib. At the data cut-off, the percentage of participants who discontinued pomalidomide in the BPd group ([redacted]) was lower compared with the PVd group ([redacted]). The percentage of participants who discontinued pomalidomide due to disease progression in the BPd group was [redacted] compared with [redacted] in the PVd group. The other main reasons for discontinuation were AEs ([redacted]) and physician's decision ([redacted]) which were reported for a similar percentage of participants for each treatment group. Treatment discontinuation of belantamab mafodotin or bortezomib related to study treatment was reported as [redacted] and [redacted] of participants in the BPd and PVd groups, respectively (102).

Figure 5. DREAMM-8 CONSORT FLOW diagram



B.2.3.2.2 Patient demographics and baseline characteristics

Baseline characteristics and prior treatments were well balanced between arms (Table 7). Participants were predominantly white (86% and 87%) with a median age of 67.0 years and 68.0 years in the BPd and PVd groups, respectively. Participants ≥75 years of age accounted for 12% and 24% of study participants in the BPd and PVd groups, respectively. All patients had previously received lenalidomide, and 236 patients (78%) had lenalidomide-refractory disease (125 [81%] patients in the BPd group while 111 [76%] patients in PVd group). Additionally, the proportion of patients with high-risk cytogenetics is balanced between the two treatment arms (34% in the BPd group versus 32% in PVd group).

Table 7. Baseline demographics, clinical characteristics, and prior therapies (ITT population)

Characteristics	**BPd (N=155)**	**PVd (N=147)**
Age, median (range), years[a]	67.0 (40 - 82)	68.0 (34 - 86)
Age category, n (%)		
19 to <65 years	64 (41)	53 (36)
65 to <75 years	72 (46)	59 (40)
≥75 years	19 (12)	35 (24)
Sex, n (%)		
Male	99 (64)	82 (56)
Female	56 (36)	65 (44)
Race, n (%)		
White	133 (86)	127 (87)
Black	0	0
Asian	20 (13)	17 (12)
Native Hawaiian or other Pacific Islander	1(1)	2 (1)
Mixed race	1 (1)	0
ECOG PS ≤1, n/N (%)[b]	146/150 (98)	140/145 (97)
R-ISS stage at screening, n (%)		
I	93 (60)	85 (58)
II	39 (25)	40 (27)
III	22 (14)	22 (15)
Unknown	1 (<1)	0
Time since diagnosis, median (range), years	4.04 (0.4 - 16.7)	3.43 (0.4 - 17.7)
Cytogenetic risk, n (%)[c]		

Characteristics	BPd (N=155)	PVd (N=147)
Standard[d]	72 (46)	75 (51)
High[e]	52 (34)	47 (32)
t(4;14)	23 (15)	20 (14)
t(14;16)	7 (5)	11 (7)
del(17p13)	32 (21)	26 (18)
Missing or not evaluable	31 (20)	25 (17)
Extramedullary disease, n (%)		
Yes	20 (13)	11 (7)
No	135 (87%)	136 (93)
Myeloma immunoglobulin, n (%)		
IgG	86 (55)	102 (69)
Prior lines of therapy, n (%)		
1	82 (53)	77 (52)
2 or 3	54 (35)	48 (32)
4+	19 (12)	22 (15)
Time to relapse on latest prior line of therapy, n (%)[g]		
≤12 months	22 (14)	20 (14)
>12 months	133 (86)	127 (86)
Prior proteasome inhibitor, n (%)		
Any	140 (90)	136 (93)
Bortezomib	134 (86)	130 (88)
Carfilzomib	34 (22)	37 (25)
Ixazomib	11 (7)	15 (10)
Prior immunomodulatory drugs, n (%)		
Any	155 (100)	147 (100)
Lenalidomide	155 (100)	147 (100)
Thalidomide	49 (32)	48 (33)
Pomalidomide	0	1 (<1)
Prior daratumumab, n (%)	36 (23)	39 (27)
Prior ASCT, n (%)	99 (64)	82 (56)
Chemotherapy, n (%)	108 (70)	87 (59)
Steroids, n (%)	152 (98)	146 (99)
Positive refractory status by agent, n (%)		

Characteristics	BPd (N=155)	PVd (N=147)
Proteasome inhibitor	**40 (26)**	**35 (24)**
Bortezomib	16 (10)	8 (5)
Carfilzomib	18 (12)	23 (16)
Ixazomib	8 (5)	11 (7)
Immunomodulatory drugs	**127 (82)**	**111 (76)**
Lenalidomide	125 (81)	111 (76)
Thalidomide	9 (6)	6 (4)
Pomalidomide	-	-
Chemotherapy	**15 (10%)**	**11 (7%)**
Steroids	**74 (48%)**	**62 (42%)**

[a] Age was imputed when full date of birth was not provided.

[b] Analyzed in the safety population.

[c] Participants may have been included in more than 1 category. Only positive results were summarized.

[d] If the participant had negative results for all high-risk abnormalities: t(4;14), t(14;16), or 17p13del.

[e] If the participant had at least 1 high-risk abnormality: t(4;14), t(14;16), or 17p13del.

[f] Results may not have been collected or reported for all participants.

[g] Time to relapse was defined as the time from the start date of the first prior line of the therapy to the date of randomization for participants with 1 prior line or to the start date of the second prior line of the therapy for participants with >1 prior line.

Abbreviations: ASCT, autologous stem cell transplant; BPd, belamaf plus pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; IgG, immunoglobulin; PD, progressive disease; PVd, pomalidomide plus bortezomib, and dexamethasone; R-ISS, Revised International Staging System.

Source: DREAMM-8 primary analysis clinical study report (102)

B.2.3.2.3 Follow-up anti-myeloma therapy

At the data cut-off, 58% of participants in the BPd group and 78% in the PVd group had discontinued all components of study treatment; this includes participants who died, were never dosed, or had withdrawn from study. Follow-up anti-myeloma therapy was initiated in 27% and 52% of participants in the BPd and PVd groups, respectively (section 4.5.3 of Clinical study report [CSR]) (102).

The median time from study treatment discontinuation to start of subsequent anti-myeloma therapy was longer in the BPd group compared with the PVd group ([redacted] days vs. [redacted] days) (section 4.5.3 of CSR) (102).

For any line of subsequent therapy, a higher percentage of participants in the PVd group versus the BPd group, calculated as the percentage of all participants in the specific treatment group, initiated the following treatments as follow-up therapy: steroids (24% in the BPd group vs. 40% in the PVd group), mAbs (15% vs. 35%), PIs (17% vs. 24%), immunomodulators (9% vs. 20%), bispecific antibodies ([BsAb] 4% vs. 11%), and ADCs (0 vs. 7%) (Table 8 and section 4.5.3 of CSR) (102).

Post BPd treatment, <1% of participants received BCMA-targeted therapy (teclistamab, a BsAb). Post PVd treatment, approximately 14% of participants received BCMA-targeted therapy: <7% of participants received BCMA-targeted BsAbs (teclistamab, Regn5458, EMB-06, elranatamab) and 7% received BCMA-targeted ADC (belantamab or belantamab mafodotin). Not all of these treatments are NHS approved and thus, inverse-probability of censoring weighting (IPCW) analysis has been performed to understand the true OS benefits of each treatment arm (Appendix O).

Table 8. Follow-up anti-myeloma therapy (ITT population)

	Any Subsequent Anti-Myeloma Therapy	
Drug Class, n (%)	**BPd (N=155)**	**PVd (N=147)**
Steroids	37 (24%)	59 (40%)
mAb	24 (15%)	51 (35%)
Anti-CD38 antibodies	23 (15%)	49 (33%)
Other mAb	4 (3%)	2 (1%)
Proteasome inhibitor	26 (17%)	36 (24%)
Immunomodulator	14 (9%)	29 (20%)
Chemotherapy	16 (10%)	25 (17%)
BsAb	6 (4%)	16 (11%)
Other	5 (3%)	7 (5%)
Antibody-drug conjugate	0	10 (7%)
Stem cell transplant	1 (<1%)	5 (3%)

Note: Multiple categories per participant were possible, total may add to more than 100%.
Abbreviations: BsAb, Bispecific antibody; BPd, belamaf plus pomalidomide, and dexamethasone; ITT, intention-to-treat; mAb, monoclonal antibody; PVd, pomalidomide plus bortezomib, and dexamethasone.
Source: DREAMM-8 primary analysis clinical study report. (102)

B.2.3.3 Methods used for expert elicitation or expert opinion

GSK conducted six 1:1 Advice Seeking Consultancy Meetings with three UK Multiple Myeloma clinical experts prior to submission. Three consultant haematologists practicing in England were engaged to validate the following components of the NICE submission: DREAMM-8 data and its reflection of real-world practice in England/Wales, treatment pathway and unmet need in earlier LoTs for RRMM, positioning of BPd in the treatment pathway, OS adjustment for therapies not used in the UK, HCRU, survival curve extrapolations, OS adjustments for subsequent treatments and budget impact estimates. A 1:1 advisory format was chosen for the expert elicitation meetings, with individual 2-hour meetings held for each of the three experts. Clinical experts were selected based on:

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

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 (101, 102, 111).

1) ITT Population included all randomised patients: 155 patients (BPd arm) / 147 patients (PVd arm), whether or not randomised treatment was administered.
2) The Safety Population included all randomised patients: 150 patients (BPd arm)/145 patients (PVd arm) who received at least one dose of study treatment.

The primary analysis based on the data cut-off date of 29 January 2024 was conducted per Committee for Medicinal Products for Human Use request (102). Four interim analyses (IA) were planned for the study (101):

- IA1 was planned at the time of approximately 35 PFS events (25% information fraction) (101).
- IA2 was planned at the time of approximately 145 PFS events (~84% information fraction).
- IA3 was planned at the time of approximately [redacted].
- IA4 was planned at approximately [redacted] (101)

The statistical analysis undertaken in the DREAMM-8 trial is presented in Table 9.

Table 9. DREAMM-8 statistical analysis

Trial number (acronym)	DREAMM-8 trial, NCT04484623 (101-103, 111)
Hypothesis objective	The overall study objective was to evaluate the clinical efficacy and safety of BPd in patients with RRMM who had received at least 1 prior LoT, including a lenalidomide-containing regimen. The primary efficacy analysis was the comparison of the distribution of PFS between the 2 treatment groups. H_O: $\theta \geq 1$ VS. H_1: $\theta < 1$ where, θ is the PFS HR (belamaf/ pomalidomide/ dexamethasone vs. pomalidomide/ bortezomib/ dexamethasone arm).
Sample size, power calculation	To ensure >90% power to test the null hypothesis: PFS HR = 1, versus the specific alternative hypothesis: PFS HR = 0.6, a total of approximately 173 PFS events are needed. The calculation assumes a comparison of PFS by log-rank test at overall 1-sided alpha level of 2.5% with 1:1 randomization ratio, and two interim analyses: an interim analysis for harm using gamma spending function with parameter of -3 when observing ~25% PFS events and an early efficacy analysis using Lan De Mets O'Brien Fleming alpha spending function (112). The calculation further assumes approximately 302 participants to be randomized in a 1:1 ratio to receive BPd or PVd, with a uniform enrolment rate of 11.2 participants per month and enrolment period of approximately 27 months. It is estimated that the targeted 173 PFS events will be observed approximately 35 months from the time when the first participant is randomized under H1, assuming an annual dropout rate of 5%. These calculations were conducted using the software package EAST v6.5. If the number of participants required by local regulatory agencies are not recruited within the planned recruitment target, enrolment may continue in separate cohorts until the country enrolment requirements, as required by local regulatory bodies, have been reached. Additional participants that are enrolled in separate cohorts will not be included in the analysis portion of the study planned for the marketing application. However, these additional participants will be included in country-specific supplemental analyses, requested by the applicable regulatory authorities concerned, as detailed in the country-specific SAP.

Trial number (acronym)	DREAMM-8 trial, NCT04484623 (101-103, 111)
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 B.2.6.1.1 - B.2.6.1.7 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 prior anti-CD38 treatment. 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 (White, Black or African American, Other), region (North America, Europe, North East Asia [Japan, China and Republic of Korea], Rest of World [ROW]), 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 173 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 (113). 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 two randomisation factors: number prior lines of therapy and prior bortezomib use. 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** OS, DoR, MRD, ORR, CRR, VGPR, TTBR, TTR, TTP, and PFS-2 were assessed using the ITT Population (section B.2.6) Analyses conducted are as follows: • **OS**– OS was conducted at planned analyses using similar approach as for the PFS analysis (i.e., KM estimates, stratified log-rank test, Cox P model stratified by randomisation factors, and examination of non-PH effect). • **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 (110). • **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 two randomisation factors: number of prior lines of therapy and prior bortezomib use. A one-sided p-value was produced. • **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 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 and the associated 95% CI for the difference was also calculated. • **CRR**– summaries of CRR (sCR, CR) by treatment arms were provided in the same way as ORR • **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.

	• **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. • **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. **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 **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 70 days after the last dose of study treatment, until the patient withdraws consent for study participation, or until the patient starts subsequent anti-myeloma therapy, whichever occurred first. AEs were recorded using the 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 (114) 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.

Trial number (acronym)	DREAMM-8 trial, NCT04484623 (101-103, 111)
	To ensure a comprehensive understanding of corneal events, data were collected in the following way during DREAMM-8: • Eye-related AEs were collected and coded using MedDRA coding dictionary and events were graded for intensity/severity using CTCAE 5.0 (114). **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 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 (115).
Data management and patient withdrawals	• As of the data cut-off (29 January 2024), [redacted] withdrew from the study ([redacted] in the BPd group and [redacted] in the PVd group). The primary reason for early withdrawal from the study was withdrawal of consent by the participant. There were more deaths in the PVd group ([redacted] compared with the BPd group ([redacted]. More participants were ongoing in study in the BPd group ([redacted]) compared with the PVd group ([redacted]) at the data cut-off. At the data cut-off, 42% participants in the BPd vs. 22% participants in the PVd group were on study treatment.

Abbreviations: AE, adverse event; BoR, best overall response; BPd, belamaf plus pomalidomide, and dexamethasone; CI, confidence interval; CR, complete response; CRR, complete response rate; CTCAE, Common Terminology Criteria for Adverse Events; DREAMM-8, DRiving Excellence in Approaches to Multiple Myeloma; DoR, duration of response; 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; PVd, pomalidomide plus bortezomib, and dexamethasone; QoL, Quality of life; 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 10 presents a summary of quality assessment for the DREAMM-8 trial. Further details for complete quality assessment can be found in Appendix D.

Table 10. Quality assessment for DREAMM-8 trial

Was randomisation carried out appropriately?	**Yes** - All participants were centrally randomised using an IRT system. Before the study was initiated, log-in directions for the IRT system were provided to each site to be used to for study drug supply. Randomisation list was done centrally using a randomisation schedule generated by the GSK Clinical Statistics Department in RandALL NG or by the Contract Research Organisation, which assigned participants in a 1:1 ratio to Treatment Arm A (BPd) and Treatment Arm B (PVd).
Was the concealment of treatment allocation adequate?	**Yes** - DREAMM-8 is an open-label study; therefore, no blinding of treatment identity was needed for either treatment Arm A (BPd) or treatment Arm B (PVd). 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. 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 (BPd) or Treatment Arm B (PVd). 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 prior anti-CD38 treatment (yes or no). No more than 50% of participants with 2 or more prior lines of treatment were enrolled. No cross-over was allowed.
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 ≥12% (Table 7)

Were the care providers, patients and outcome assessors blind to treatment allocation?	**No** - as DREAMM-8 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 302 patients randomised (155 in BPd and 147 in the PVd group), 295 received study treatment: 150 patients received BPd and 145 patients received PVd (see section 4.6.1 of CSR) (102).
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: BPd, belamaf plus pomalidomide, and dexamethasone; CSR, clinical study report; DREAMM-8, DRiving Excellence in Approaches to Multiple Myeloma; PVd, pomalidomide plus bortezomib, and dexamethasone; GSK, GlaxoSmithKline; IRC, Independent Review Committee; IRT, Interactive Response Technology; ITT intention-to-treat; OS, overall survival
Source**:** DREAMM-8 trial protocol (101); DREAMM-8 primary analysis clinical study report (102).

B.2.6 Clinical effectiveness results of the relevant studies

As described above, DREAMM-8 is the pivotal trial providing evidence of the efficacy of BPd in the relevant population. DREAMM-8 was designed as a head-to-head study versus PVd, 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 in combination represents a 'step change' for the MM community and gives clinicians flexibility of choice for patients who are unsuitable for lenalidomide.

DREAMM-8 was powered to detect differences in multiple outcomes of relevant clinical interest, of which six are presented below in Table 11 and the remainder are presented in Appendix N. The results presented in this document are for all primary and key secondary endpoints, plus secondary and exploratory endpoints of high relevance to cost-effectiveness modelling.

All results in this section are presented for the ITT Population (n = 302). At the time of primary analysis (data cut-off: 29 January 2024), the median study follow-up was 21.8 months, the data for which is presented in this document.

Table 11. Summary of clinical effectiveness

Endpoint	BPd (N=155)	PVd (N=147)	Reference
Progression free survival, median months (95% CI)	NR (20.6, NR)	12.7 (9.1, 18.5)	B.2.6.1.1
Overall survival, median months (95% CI)	NR (33.0, NR)	NR (25.2, NR)	B.2.6.1.2
Duration of response, median months (95% CI)	NR (24.9, NR)	17.5 (12.1, 26.4)	B.2.6.1.3
Minimal residual disease, sCR/CR % (95% CI)	23.9 (17.4, 31.4)	4.8 (1.9, 9.6)	B.2.6.1.4
Overall response rate sCR+CR+VGPR+PR % (95% CI)	77.0 (70.0, 83.7)	72.0 (64.1, 79.2)	B.2.6.1.5
TTD, median months (95% CI)	[redacted] ([redacted])	[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: BPd, belamaf plus pomalidomide and dexamethasone; CI; confidence interval; CR, Complete Response; PR, Partial Response; PVd, pomalidomide plus bortezomib and dexamethasone; sCR, Stringent Complete Response; TTD, Time to treatment discontinuation; VGPR, Very Good Partial Response.
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.6.1 Primary and key secondary results of the DREAMM-8 trial

B.2.6.1.1 Primary outcome - Progression-free survival

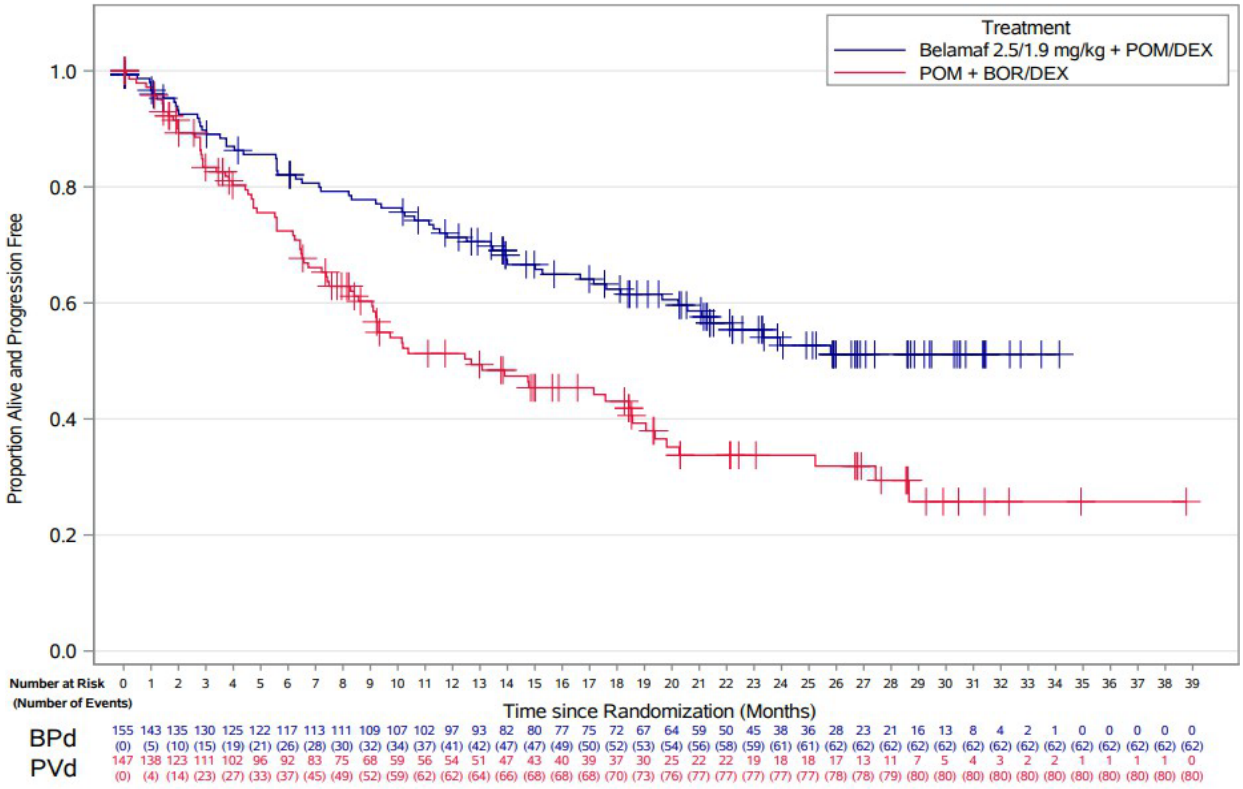
The DREAMM-8 trial met its primary endpoint of PFS assessed by IRC. It showed a statistically significant and clinically meaningful PFS benefit for BPd compared with PVd. The median PFS was not reached in the BPd group (95% CI: 20.6, NR). Median PFS was 12.7 months (95% CI: 9.1, 18.5) in the PVd group (28).

The KM curves for PFS showed a clear and early separation between the treatment groups in favour of the BPd group (Figure 6). This is supported by a HR of 0.52 (95% CI: 0.37, 0.73; p-value <0.001) showing a 48% reduction in the risk of disease progression or death (Table 12).

Milestone analysis of PFS at 12 months showed a higher PFS rate in the BPd group compared with the PVd group (71% vs. 51%). Follow-up for PFS is ongoing for [redacted] of participants in the BPd group and [redacted] of participants in the PVd group.

PFS analysis based on investigator-assessed responses was consistent with IRC results (section 5.1.1.1 of the DREAMM-8 CSR (102)).

Figure 6. Kaplan Meier curves of PFS based on independent reviewer-assessed response (ITT population)



Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; ITT, intention-to-treat; POM/DEX, pomalidomide/dexamethasone; PVd, pomalidomide plus bortezomib, and dexamethasone.
Source: DREAMM-8 primary analysis clinical study report (102); DREAMM-8 publication (28).

Table 12. Progression-free survival based on independent reviewer-assessed response (ITT population)

	BPd (N=155)	PVd (N=147)
Number of participants, n (%)		
Progressed or died (event)	62 (40%)	80 (54%)
Censored, follow-up ended	25 (16%)	34 (23%)
Censored, follow-up ongoing	68 (44%)	33 (22%)
Event summary, n (%)		
Disease progression	46 (30%)	66 (45%)
Death	16 (10%)	14 (10%)
Estimates for time variable (months)[a]		
1st Quartile (95% CI)	10.3 (5.6, 14.0)	5.5 (3.7, 6.5)
Median (95% CI)	NR (20.6, NR)	12.7 (9.1, 18.5)
3rd Quartile (95% CI)	[redacted]	[redacted]

	BPd (N=155)	PVd (N=147)
Hazard ratio[b]		
Estimate[d] (95% CI)	0.52 (0.37, 0.73)	
Estimate[e] (95% CI)	[redacted]	
Estimate[f] (95% CI)	[redacted]	
Estimate[g] (95% CI)	[redacted]	
Stratified log-rank[c]		
p-value	<0.001	
Progression-free survival rate		
Time-to-event endpoint at 6 months (95% CI)	[redacted]	[redacted]
Time-to-event endpoint at 12 months (95% CI)	[redacted]	[redacted]
Time-to-event endpoint at 18 months (95% CI)	[redacted]	[redacted]

a. CIs for time variable estimated using the Brookmeyer Crowley method (113).
b. Hazard ratios were estimated using a Cox Proportional Hazards model with stratification factors and covariates according to the corresponding footnote.
c. p-value from 1-sided stratified log-rank test. with stratification factors according to the corresponding footnote. Nominal p-values are provided for sensitivity analyses.
d. Stratification factors: A and B assessed according to the IVRS strata; Covariate: Treatment.
e. Stratification factors based on pooling stratification in SAP using A, B, C, and D; Covariate: Treatment.
f. Stratification factors: A and B assessed according to the IVRS strata; Covariate: Treatment, C and D according to eCRF data.
g. Stratification factors: A and B according to eCRF data; Covariate: Treatment.

All grey highlighted rows represent key results of PFS in DREAMM-8.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; CI, confidence interval; ITT, intention-to-treat; PVd, pomalidomide plus bortezomib, and dexamethasone.
Source: DREAMM-8 primary analysis clinical study report (111)

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

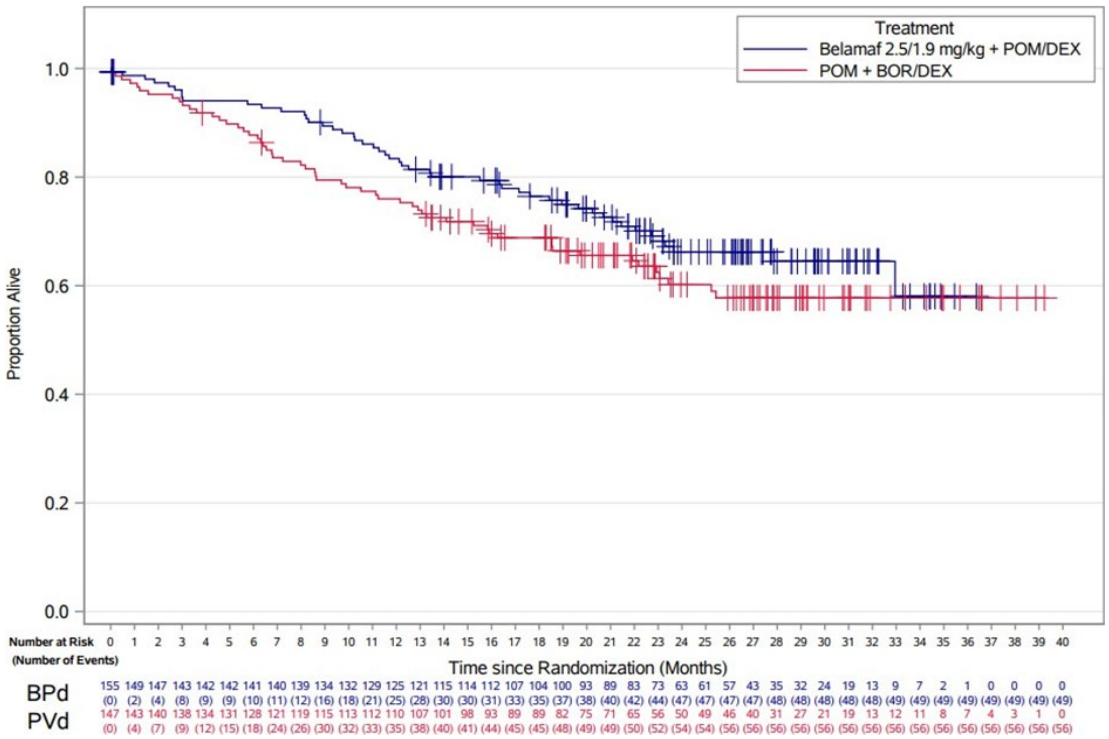
B.2.6.1.2 Secondary outcome – Overall survival

At the data cut-off, there was a positive OS trend in favour of the BPd group. The KM curves for OS showed an early separation between the treatment groups in favour of BPd (Figure 7). The 12 months OS survival rate was higher in the BPd group compared with the PVd group (83% vs. 76%) (102). Most censoring occurred after approximately 12 months, which is in alignment with the minimum follow-up for ongoing participants.

Median OS was not reached in either treatment group (Table 13). OS data have reached 34.7% [redacted] overall maturity and information fraction equal to [redacted], where 217 were the planned deaths for OS analysis according to the SAP. The OS p-value (0.095) did not cross the pre-defined OS boundary adjusting for the observed number of events at the time of analysis. [redacted]

[redacted]

Figure 7. Kaplan Meier curves of OS (ITT population)



Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; ITT, intention-to-treat; POM/DEX, pomalidomide/dexamethasone; PVd, pomalidomide plus bortezomib, and dexamethasone.
Source: DREAMM-8 primary analysis clinical study report (102); DREAMM-8 publication (28).

Table 13. Summary of overall survival (ITT population)

	BPd (N=155)	**PVd (N=147)**
Number of participants, n (%)		
Died (event)	49 (32%)	56 (38%)
Censored, follow-up ended	12 (8%)	7 (5%)
Censored, follow-up ongoing	94 (61%)	84 (57%)
Event summary, n (%)		
Death	[redacted]	[redacted]
Estimates for time variable (months)[a]		
1st quartile (95% CI)	19.0 (12.2, 23.3)	12.7 (8.0, 18.5)
Median (95% CI)	NR (33.0, NR)	NR (25.2, NR)
3rd quartile (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio[b]		
Estimate[d] (95% CI)	0.77 (0.53, 1.14)	

	BPd (N=155)	PVd (N=147)
Estimate[e] (95% CI)	[redacted]	
Stratified log-rank[c]		
p-value[d]	0.095	
p-value[e]	0.102	
Overall survival rate		
Time-to-event endpoint at 6 months (95% CI)	[redacted]	[redacted]
Time-to-event endpoint at 12 months (95% CI)	[redacted]	[redacted]
Time-to-event endpoint at 18 months (95% CI)	[redacted]	[redacted]

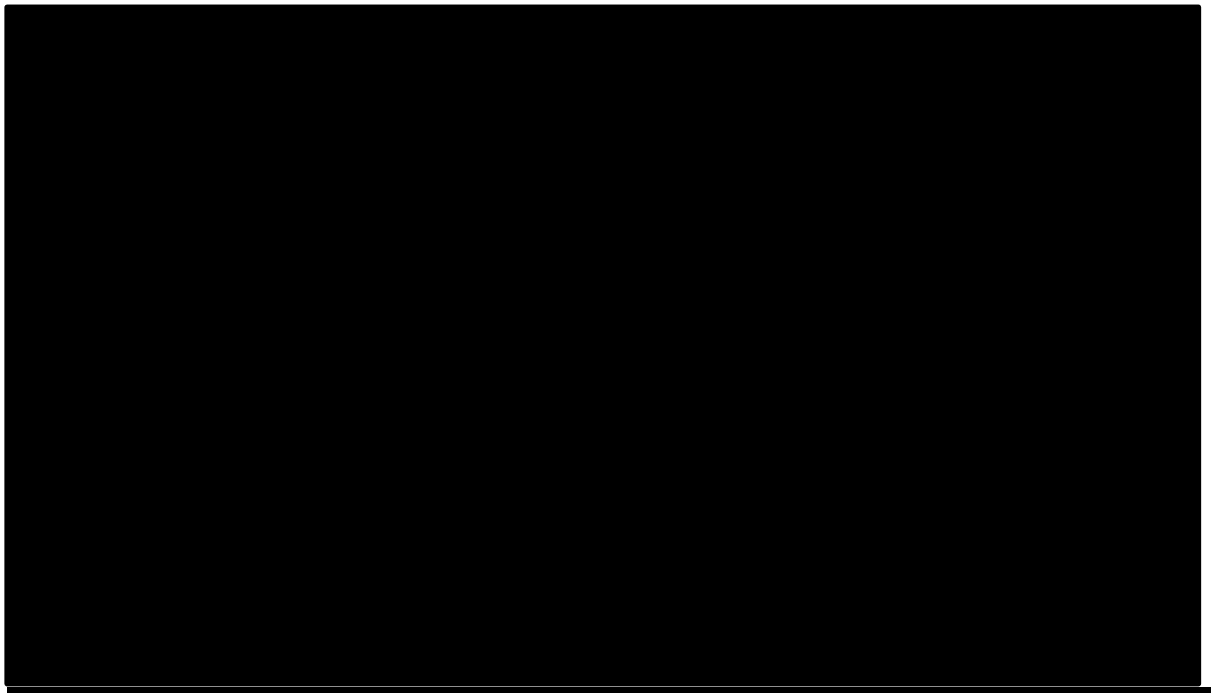
a. CIs were estimated using the Brookmeyer Crowley method (113).
b. Hazard ratios were estimated using a Cox Proportional Hazards model according to the corresponding footnotes.
c. p-value from 1-sided stratified log-rank test according to the corresponding footnotes.
d. Stratification factors: Number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no) assessed according to IVRS strata; Covariate: Treatment.
e. Stratification factors: Number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no) assessed according to eCRF strata; Covariate: Treatment. Nominal p-value is provided.

All grey highlighted rows represent key results of DoR in DREAMM-8.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; CI, confidence interval; ITT, intention-to-treat; PVd, pomalidomide plus bortezomib, and dexamethasone.
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.6.1.3 Secondary outcome – Duration of response

At the data cut-off, median DoR was not reached in the BPd group, while the median DoR was 17.5 months in the PVd group ([redacted]). The KM curves for DoR showed a clear and early separation between the treatment groups in favour of BPd ([redacted]). In the BPd group, 55% of participants with response had not progressed or died and had follow-up for PFS ongoing at the data cut compared with 31% of participants in the PVd group.

[redacted]



[redacted]

[redacted]

	BPd (N=155)	PVd (N=147)
Number of participants, n (%)		
n	120	106
Progressed or died (event)	39 (33%)	49 (46%)
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 (95% CI)	[redacted]	[redacted]
Median (95% CI)	NR (24.9, NR)	17.5 (12.1, 26.4)
3rd Quartile (95% CI)	[redacted]	[redacted]
Duration of response rate		
Time-to-event endpoint at 6 months (95% CI)	[redacted]	[redacted]

	BPd (N=155)	PVd (N=147)
Time-to-event endpoint at 12 months (95% CI)	[redacted]	[redacted]
Time-to-event endpoint at 18 months (95% CI)	[redacted]	[redacted]

a. CIs for time variables were estimated using the Brookmeyer Crowley method (113).
All grey highlighted rows represent key results of DoR in DREAMM-8.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; CI, confidence interval; ITT, intention-to-treat; PVd, pomalidomide plus bortezomib, and dexamethasone.
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.6.1.4 Secondary outcome – Minimal residual disease

At the time of primary PFS analysis, the proportion of all participants (ITT population) who achieved MRD negativity was higher in the BPd group compared with the PVd group (23.9% vs. 4.8%) (Table 15). MRD negativity rate was defined as the percentage of participants who achieved MRD negative status (as assessed by NGS at 10^{-5} threshold) at least once during the time of confirmed CR or better response based on IRC assessment per IMWG. Detail on these alternative definitions is given in Appendix N. Results of MRD negativity analysis using investigator-confirmed response or in participants with VGPR or better were consistent with the primary MRD analysis. MRD negativity by best response based on IRC assessment showed higher MRD negativity rate in the BPd group compared with the PVd group in all response categories.

Table 15. Summary of MRD negativity based on independent reviewer-assessed responses (ITT population)

Best Response		BPd (N=155)	PVd (N=147)
sCR/CR	MRD negativity rate[a]	37 (23.9%)	7 (4.8%)
	95% CI	(17.4%, 31.4%)	(1.9%, 9.6%)
	p-value[b,c,d,e]	<0.001	

a. The percentage of participants achieving MRD negative status (assessed by NGS at 10^{-5} threshold) during confirmed CR+ according to IRC-assessed response based on IMWG. Rates were calculated out of N per treatment group. P-values are 1-sided.
b. Nominal p-value based on CMH test, adjusting for A and B assessed according to IVRS strata.
c. Unadjusted nominal p-value based on Fisher's exact test.
d. Nominal p-value based on CMH test, adjusting for pooling stratification using A, B, C and D.
e. Nominal p-value based on CMH test, adjusting for A and B as per eCRF.
Note: A: Number of lines of prior therapy, B: Prior bortezomib use, C: ISS status, D: Prior Anti-CD38.
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.6.1.5 Secondary outcome – Overall response rate

At the PFS data cut-off, ORR was comparable between the BPd and PVd groups (77% vs. 72%) (Table 16). Alternative definitions of response such as VGPR+ Rate, CRR and CBR show a similar trend (Appendix N).

Table 16. Summary of independent reviewer-assessed best response with confirmation (IMWG Criteria) (ITT population)

	BPd (N=155)	PVd (N=147)
Best response, n (%)		
Stringent complete response (sCR)	14 (9%)	4 (3%)
Complete response (CR)	48 (31%)	20 (14%)
Very good partial response (VGPR)	37 (24%)	32 (22%)
Partial response (PR)	21 (14%)	50 (34%)
Overall response rate, n, %		
sCR+CR+VGPR+PR (95% CI)	120, 77% (70.0%, 83.7%)	106, 72% (64.1%, 79.2%)
Difference in overall response rate		
Difference (95% CI for difference)	[redacted]	

Note 1: CIs are based on the exact method.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; CI, confidence interval; CR, complete response; IMWG, International Myeloma Working Group; IRC, independent review committee; ITT, intention-to-treat; PR, partial response; PVd, pomalidomide plus bortezomib, and dexamethasone; sCR, stringent complete response; VGPR, very good partial response.
All grey highlighted rows represent key results of ORR in DREAMM-8.
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.6.1.6 Secondary outcome – Time to treatment discontinuation

The median TTD in the BPd group was longer than PVd ([redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]] (Table 17).

Landmark analysis of TTD at 18 months showed a higher TTD rate in the BPd group compared with the PVd group ([redacted]) (Table 17). The KM curves for TTD showed a clear and early separation between the treatment groups in favour of the BPd group ([redacted]).

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	BPd (N=150)	PVd (N=145)
Number of Subjects		
Treatment Discontinued or Death (event)		
Censored, Treatment not Discontinued		
Event Summary		
Treatment Discontinued		
Death		
Estimates for Time Variable (Months)[a]		
1st Quartile (95% CI)		
Median (95% CI)		
3rd Quartile (95% CI)		
Time to Treatment Discontinuation Rate		
Time-to-Event Endpoint at 6 Months (95% CI)		
Time-to-Event Endpoint at 12 Months (95% CI)		
Time-to-Event Endpoint at 18 Months (95% CI)		

a. intervals for time variables are estimated using the Brookmeyer Crowley method (113).

Note: TTD is derived as the time from treatment initiation until the date of treatment discontinuation or death due to any cause. Treatment discontinuation is defined as when Belamaf/BOR have discontinued and POM/DEX has either discontinued or completed. Patients who did not discontinue treatment will be censored at the last treatment end date or last contact date.
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; CI, confidence interval; PVd, pomalidomide plus bortezomib, and dexamethasone; TTD, time to treatment discontinuation.
Source: GSK data on file (116).

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 (117).

The mean utility scores, based on EQ-5D-3L, were broadly similar between the two treatment arms across the study visits (Figure 10). 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).

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Pre-progression, there was gradual increase in the utility scores (change from baseline) from Week 13 which became very noticeable from around week 37 onwards (Figure 11). For the time period where most of the recorded EQ-5D-3L data lies, the mean utility scores are similar between BPd and PVd arms.

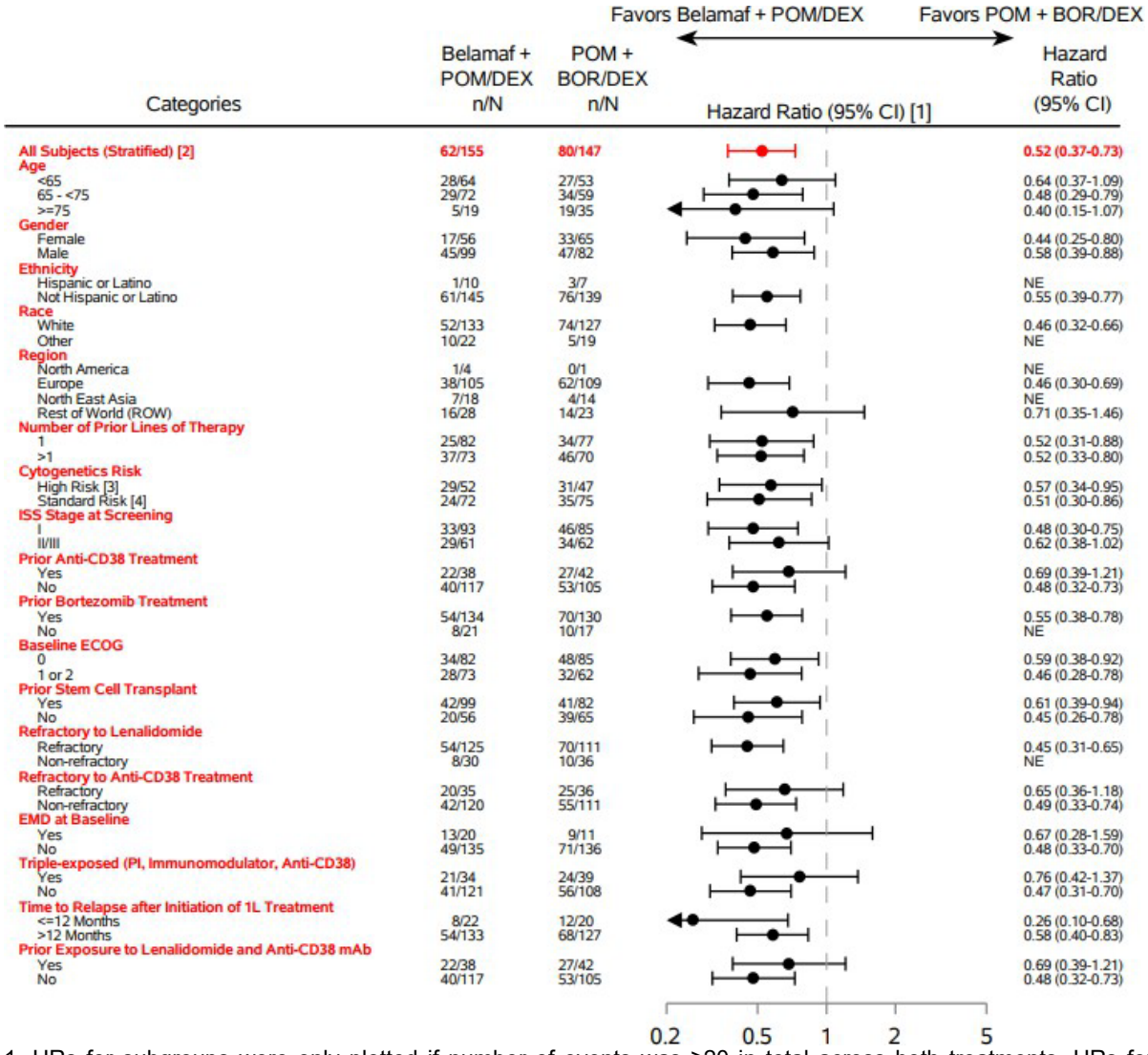
11

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 BPd over PVd.

B.2.7 Subgroup analysis

The PFS benefit favoured BPd and was consistent across all subgroups, including those refractory to lenalidomide and those with high-risk cytogenetics with HR point estimates ranging from 0.26 to 0.76 (Figure 12). Of particular relevance to this submission, post-hoc analysis of the lenalidomide-refractory and high-risk cytogenetic unstratified subgroups also favoured BPd.

Figure 12. Forest plot – Progression-free survival based on independent reviewer-assessed response (ITT population, unstratified)



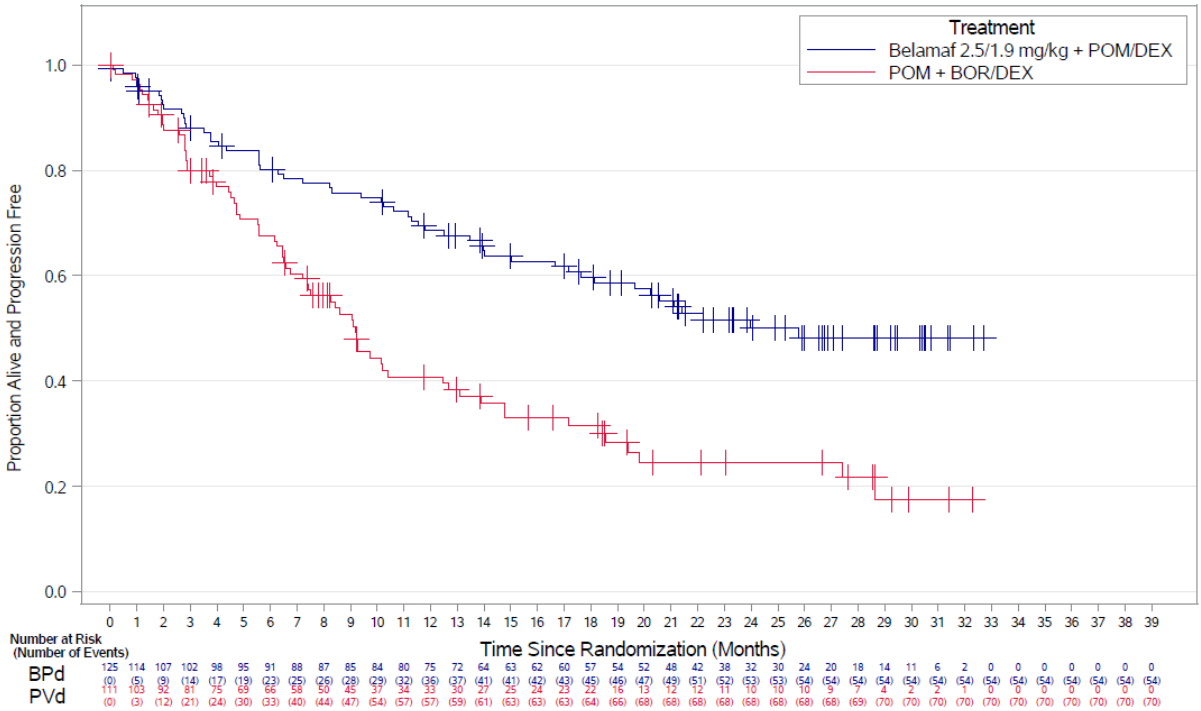
1. HRs for subgroups were only plotted if number of events was ≥20 in total across both treatments. HRs for subgroups were estimated using Cox Proportional Hazard models, without adjustment for stratification variables.
2. Stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≤4), prior bortezomib (no, yes), and according to IVRS strata with a covariate of treatment.
3. A participant was considered as high-risk if the participant had any of the following cytogenetics: t(4;14), t(14;16), or 17p13del.
4. A participant was considered standard risk if the participant had negative results for all high-risk abnormalities: t(4;14), t(14;16), and 17p13del.
Abbreviations: 1L, first line; BPd, belamaf plus pomalidomide, and dexamethasone; CI, Confidence Interval; HR, hazard ratio; ITT, intention-to- treat; LoT, line of therapy; PVd, pomalidomide plus bortezomib, and dexamethasone; R-ISS, Revised International Staging System.
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.7.1 Key subgroup – Lenalidomide-refractory

In the lenalidomide-refractory subgroup (BPd, n=125; PVd, n=111), median PFS (95% CI) was 24.0 months (17.6-NR) with BPd versus 9.2 months (7.2-12.5) with PVd (HR, 0.45; 95% CI, 0.31-0.65), demonstrating favourable treatment response with BPd. 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 PFS based on independent reviewer - assessed response by refractory status (lenalidomide-refractory)



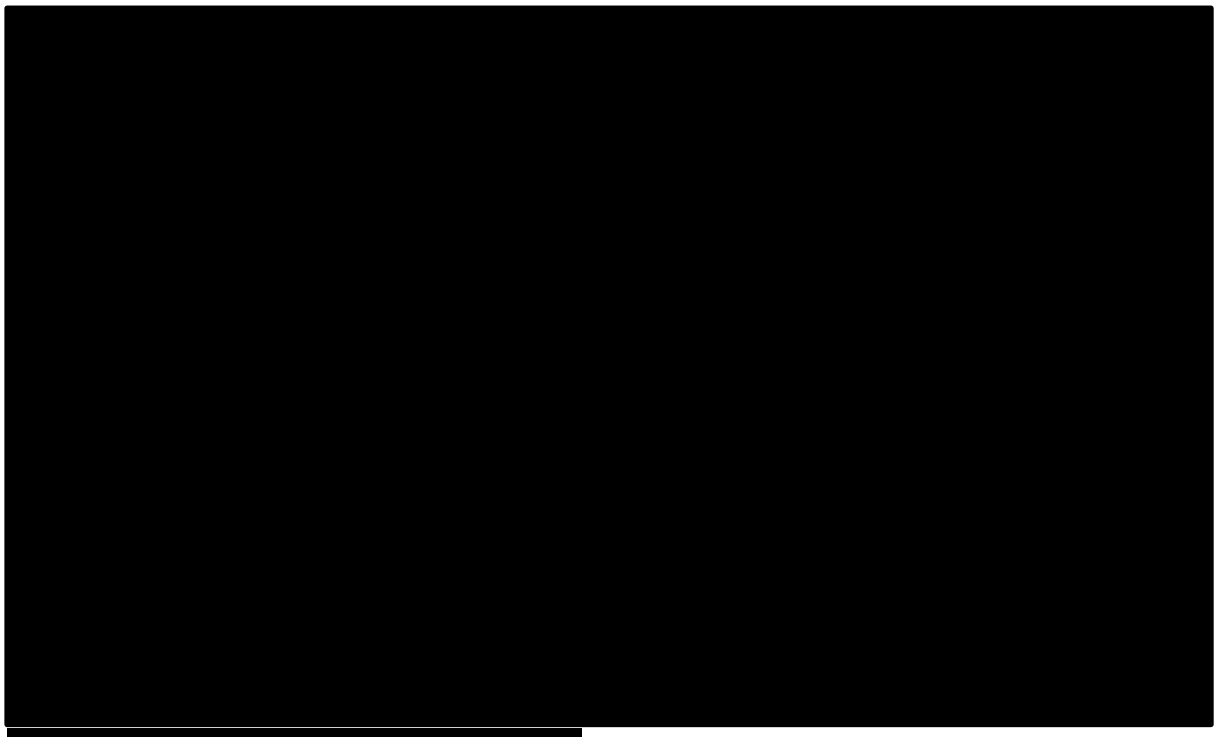
Abbreviations: POM/DEX, pomalidomide/dexamethasone.
Source: GSK data on file (118)

B.2.7.2 Key subgroup – High-risk cytogenetics

In the high-risk cytogenetic subgroup (BPd, n=52; PVd, n=47), the median PFS (95% CI) was [redacted] with BPd versus [redacted] with PVd [redacted], demonstrating similar treatment response with BPd as standard risk patients (HR, 0.51; 95% CI, 0.30-0.86). KM curves for this subgroup are reproduced in [redacted]. For details on non-Primary endpoints in this subpopulation, please see Appendix E.

14

[redacted]



[redacted]

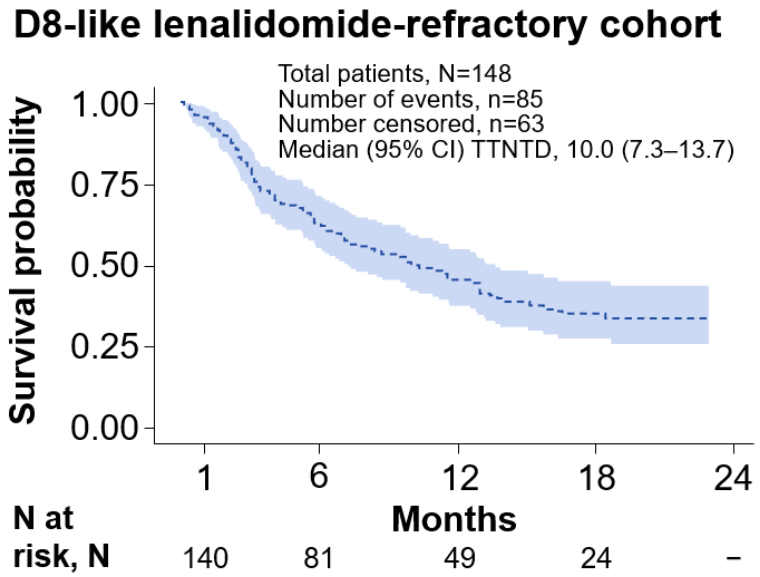
B.2.7.3 Real-world evidence – National Cancer Registration and Analysis Service (NCRAS) study

In accordance with DREAMM-8 study findings, the results from the NCRAS study (Section B.1.3.1.4) were also considered. One aim of the NCRAS study was to describe real-world outcomes for lenalidomide-refractory patients with MM receiving DVd at 2L in England, to identify unmet needs for this patient population, and to contextualise the findings of key clinical trials (CASTOR and DREAMM-8) (28, 119).

This descriptive, retrospective, non-interventional study utilised data collated by the National Cancer Registration and Analysis Service (NCRAS) of the National Health Service in England. The study identified adult patients diagnosed with MM from 1 January 2013 until 31 December 2020 in England (patient survival data follow-up until 31 October 2022). Characteristics and outcomes of lenalidomide-refractory patients treated with DVd at 2L were evaluated for a population broadly aligned to the DREAMM-8 eligibility criteria (DREAMM-8-like cohort). The investigated clinical outcomes were time from start of 2L to next treatment or death (TTNTD; used as an alternative to PFS), time to treatment discontinuation or death (TTDD), and OS, reporting the median and 95% confidence interval for each cohort. Statistical hypothesis tests were not performed.

The DREAMM-8-like cohort included 730 patients. Among these, 371 (50.8%) patients were lenalidomide-refractory. Among lenalidomide-refractory patients, 148 (39.9%) patients in the were treated with DVd at 2L. A summary of baseline characteristics and outcomes of lenalidomide-refractory patients treated with DVd at 2L can be found in the Company's e-poster that was presented at EHA 2024 (31). The median TTNTD, TTDD, and OS for the D8-like cohort were 10.0, 6.8, and 21.1 months, respectively (Figure 15).

Figure 15. TTNTD from initiation of DVd at 2L (D8-like lenalidomide-refractory cohort)



Abbreviations: 2L, second line; CI: confidence interval; DaraVd: daratumumab plus bortezomib, and dexamethasone; n/a: not applicable; NCRAS: National Cancer Registration and Analysis Service; OS: overall survival; TTNTD: time to next treatment or death
Source: EHA abstract (31)

In summary, lenalidomide-refractory patients with MM treated with DVd at 2L in England showed a relatively short TTNTD, further highlighting the unmet need for novel triplet regimen options for patients who are lenalidomide-refractory at first relapse. This 2L only data show a numerically similar median TTNTD to the median PFS of the lenalidomide-refractory population in the multiline CASTOR trial (7.8 months) (24).

B.2.8 Meta-analysis

A pairwise meta-analysis was not conducted as the only identified clinical trial of BPd in RRMM was the DREAMM-8 trial (103).

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 January 2024, to identify all relevant efficacy and safety data for therapies used in the management of patients with 2L+ RRMM (Appendix D). No direct evidence comparing BPd with the regimens defined in the final scope was identified; therefore, a network meta-analysis (NMA) was conducted to assess the relative efficacy of BPd 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 and secondary objective was to evaluate the comparative efficacy of BPd relative to other treatments in achieving PFS and OS, respectively, in patients similar to the DREAMM-8 ITT (lenalidomide-exposed) population. The endpoints of interest were selected based on their importance for clinical practice, and they are also expected to be used in economic modelling. ORR was not available at the time of this submission. Both fixed- and random-effects NMA analyses were conducted, and to account for heterogeneity in outcomes, the fixed-effects model was selected to be the base-case analysis using normal distribution. 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-8) were considered in the NMA feasibility assessment. 12 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 (3). The global NMA conducted was further restricted to include regimens approved by the FDA or EMA and any treatments likely to be a future health technology assessment (HTA) comparator to the DREAMM-8 regimen, BPd (120). 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 eight studies, summarised in Table 18 along with the assessed intervention and comparator treatments. The network of evidence presenting all available, non-outcome specific, evidence is shown in Figure 16. Results relevant to the decision problem will be discussed. Finally, in the NMA hKd was used to specify high dose carfilzomib plus

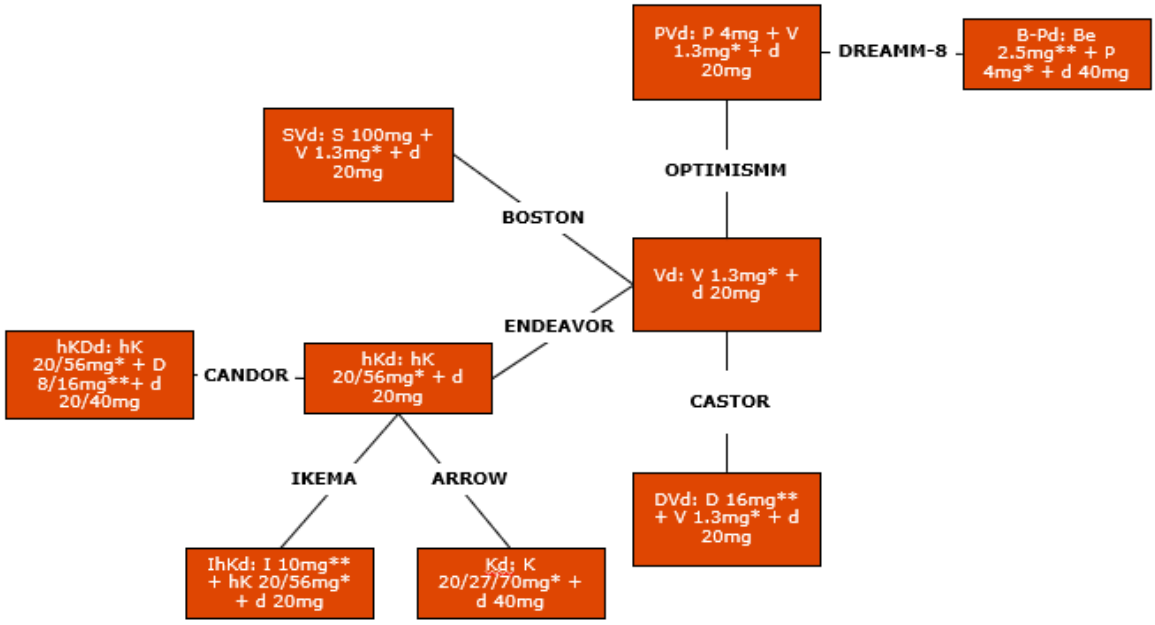
dexamethasone instead of Kd, to distinguish between the different trials used to connect the network. hKd was the used in the Table 18 to align the terminology to the terms used in the different studies.

Table 18. Summary of studies considered eligible for the network meta-analyses

Study, author, year	Intervention	Comparator
DREAMM-8 (101, 103)	BPd	PVd
ARROW Mateos, 2019 (121)	Kd	hKd
BOSTON Grosicki, 2020 (107)	SVd	Vd
CANDOR Dimopoulos, 2020 (122); Usmani, 2022 (123); Usmani, 2023 (124)	hKDd	hKd
CASTOR Spencer, 2018 (125) Sonneveld, 2023 (125)	DVd	Vd
ENDEAVOR Dimopoulos, 2016 (108)	hKd	Vd
IKEMA Moreau, 2021 (126) Joseph, 2022 (127); Martin, 2023 (128)	IhKd	hKd
OPTIMISMM Richardson, 2019 (129)	PVd	Vd

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hK, high dose carfilzomib; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib plus daratumumab and dexamethasone; IhKd, isatuximab plus high dose carfilzomib and daratumumab; ITT, intent to treat; len, lenalidomide; Kd, carfilzomib and dexamethasone; LoT, line of treatment; PVd, pomalidomide plus bortezomib, and dexamethasone; SVd, selinexor plus bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone.
Note: hKd was used to specify high dose carfilzomib plus dexamethasone within the different trials used to connect in the network.

Figure 16. Overall (non-outcome specific) network of evidence



* mg/m^2. ** mg/kg.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hK, high dose carfilzomib; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib plus daratumumab, and dexamethasone; IhKd, isatuximab plus high dose carfilzomib and daratumumab; ITT, intent to treat; Kd, carfilzomib and dexamethasone; LOT, line of treatment; PVd, pomalidomide plus bortezomib, and dexamethasone; SVd, selinexor plus 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 factors are

TEMs in this population, ideally efficacy results by subgroup for the most important potential TEMs and prognostic variables would be explored for the lenalidomide-exposed population. However, only the OPTIMISMM study reported subgroup results in the lenalidomide-exposed population. PFS results by subgroup were used to evaluate whether a variable was a TEM or not, because PFS is the primary endpoint of DREAMM-8. 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 bortezomib 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.

For this NMA, the ITT population from the DREAMM-8 trial was used, which was 100% lenalidomide-exposed and 53% 2L, with the rest of the patients being 3L+ patients. Using the ITT population from DREAMM-8 was the most suitable approach, as it ensures the inclusion of a large population (i.e., about 80% patients in DREAMM-8 are lenalidomide refractory), and this approach (i.e., using ITT) was aligned with the populations of the other included comparator studies.

In particular, some of the included studies in this NMA reported results for lenalidomide-exposed patients, but most studies included more mixed populations in terms of prior lenalidomide use and LoT. The reporting of results in the included studies was adequate for the lenalidomide-exposed population (i.e., a sufficient number of studies reported outcomes for those patients for comparators of interest), but it was not adequate for 2L patients (i.e., none of the eligible studies provided information on 2L patients) (Table 19). In addition, for the lenalidomide-refractory population there was information for one comparator of interest (i.e., SVd), but not for the other two comparators (i.e., DVd and Kd) for PFS, and no information for OS. Thus, the information from the literature for lenalidomide-refractory and/or 2L population was very limited (Table 19). For this reason, the ITT population from DREAMM-8 and the lenalidomide-exposed populations from the comparator studies were used as the primary analysis.

In summary, in the current NMA, the primary analysis is referred to as “lenalidomide-exposed”. Additionally, secondary analysis using the lenalidomide-exposed population from primary analysis plus some studies that reported outcomes for their ITT populations (i.e., not specifically lenalidomide-exposed) was performed. This allowed for more studies to be included in the main network compared to the primary analysis, however additional heterogeneity in the compared populations should be expected. Finally, another secondary analysis was performed where studies that reported outcomes for lenalidomide-refractory populations were included. An overview of the conducted NMAs is provided in Table 20.

Table 19. Overview of possible comparisons in the NMA for PFS and OS for BPd vs relevant comparators

Outcome and population	BPd vs DVd	BPd vs SVd	BPd vs hKd
PFS: Len-exposed	✓	✓	✓
OS: Len-exposed	X	X	✓
PFS: Len-refractory	✓	X	✓
OS: Len-refractory	X	X	X
PFS: 2L	X	X	X
OS: 2L	X	X	X

Notes: ✓: Comparison possible in the NMA for this population; X: Comparison not available for this specific population in the NMA
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, high dose carfilzomib and dexamethasone; Len, Lenalidomide; OS, overall survival; PFS, progression-free survival; SVd, selinexor plus bortezomib, and dexamethasone

Table 20. Overview of conducted analyses

Analysis	Population	Endpoint	Treatment effect type
Primary	Lenalidomide-exposed	PFS	Fixed-effects Random-effects
	Lenalidomide-exposed	OS	Fixed-effects Random-effects
Secondary	Lenalidomide-refractory	PFS	Fixed-effects Random-effects
	Lenalidomide-exposed plus ITT	OS	Fixed-effects Random-effects
	Lenalidomide-refractory plus ITT	OS	Fixed-effects Random-effects

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

As comparisons for BPd against all relevant comparators were necessary to be included in the economic model (see section B.3), the primary PFS and OS NMA analysis was not sufficient to inform all the economic model inputs needed. For this reason, secondary NMA analysis was also used to populate the economic model. An overview of the populations from comparator studies used in the secondary analysis is provided below (Table 21).

Table 21. Overview of populations included in the NMA for the secondary analyses

Secondary analysis	DVd population	SVd population	hKd population
PFS: Lenalidomide-refractory	Lenalidomide-refractory	ITT	Lenalidomide-refractory
OS: Lenalidomide-exposed plus ITT	ITT	ITT	Lenalidomide-exposed
OS: Lenalidomide-refractory plus ITT	ITT	ITT	ITT

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

B.2.9.4 Results

B.2.9.4.1 Interpretation

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

B.2.9.4.2 Goodness of fit

Goodness of fit summary statistics for the primary analyses are provided in [redacted]. The Deviance Information Criterion (DIC) and the total residual deviance were observed to be similar for the FE and RE models for all endpoints. Goodness of fit summary statistics for the secondary and subgroup analyses are provided in Appendix D.

[redacted]22

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

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

B.2.9.4.3 Primary analysis results

The primary analysis included lenalidomide-exposed population from the included studies. The fixed-effect model was preferred for the base-case. This was justified for three main reasons:

Fixed-effects models are more parsimonious than random-effect models, and therefore more suitable for inference.

Random-effect 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.

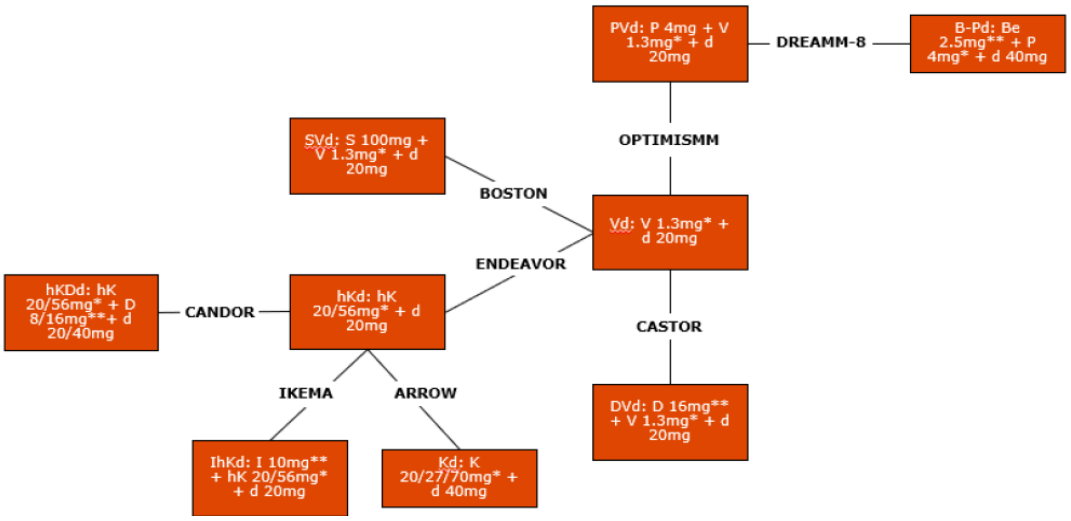
Regardless of the above, Table 22 indicates that there is almost no difference between the fit of the two models, so the choice does not drive decision making.

NMA results are interpreted using forest plots for fixed-effect models in the following sections, whereas additional NMA outputs for fixed-effect and random effect models, league tables, treatment rankings, surface under the cumulative ranking curve (SUCRA) values and rankograms, are presented in Appendix D.

PFS for lenalidomide-exposed

The network for PFS, shown in Figure 17 comprised eight studies [BOSTON (107), OPTIMISMM (129), DREAMM-8 (101, 103), CASTOR (125), ENDEAVOR (108), ARROW (121), IKEMA (126-128) and CANDOR (122-124)] and nine treatment nodes.

Figure 17. Primary analysis - PFS network of evidence for lenalidomide-exposed population

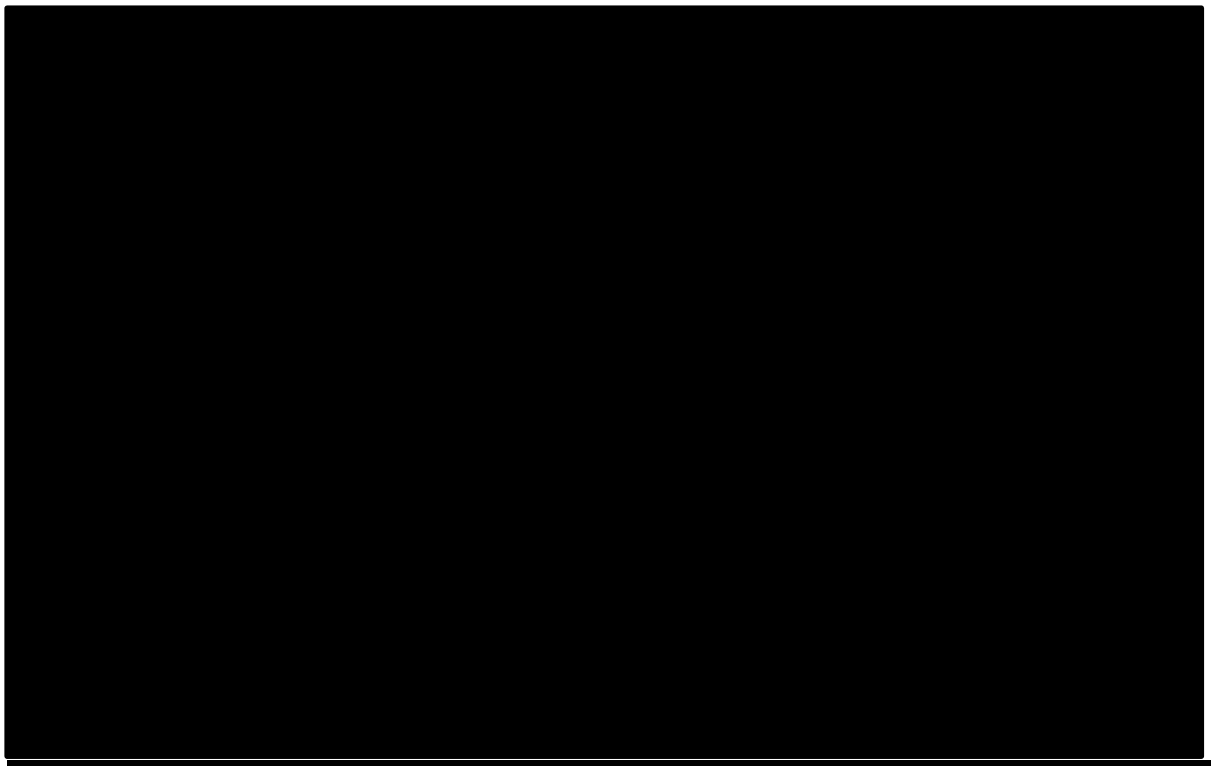


* mg/m^2. ** mg/kg.
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hK, high dose carfilzomib; hKD, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib plus daratumumab, and dexamethasone; IhKd, isatuximab plus high dose carfilzomib and daratumumab; ITT, intent to treat; len, lenalidomide; Kd, carfilzomib and dexamethasone; LOT, line of treatment; PVd, pomalidomide plus bortezomib, and dexamethasone; SVd, selinexor plus bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone

The posterior estimates of the fixed-effect model are graphically illustrated in [redacted]. As discussed previously in section B.2.9.2, 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 BPd over hKd [redacted], and SVd [redacted], while numerical improvement was observed over DVd [redacted]. NMA results for the comparison of BPd over PVd are

aligned with the DREAMM-8 efficacy results in terms of PFS, see section B.2.6.1.1. Insofar as it is relevant as indirect evidence, BPd was superior even to comparators not approved for use in the NHS.

[redacted]

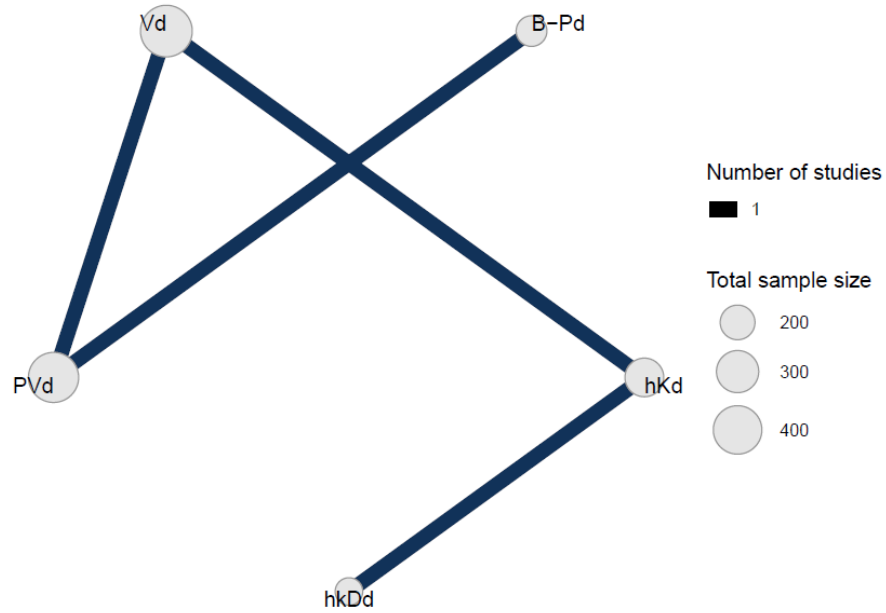


[redacted]

OS for lenalidomide-exposed

The network for OS, shown in Figure 19, consisted of four studies, OPTIMISMM (129), CANDOR (119, 125), ENDEAVOR (108), and DREAMM-8 (101, 103) and five treatment nodes.

Figure 19. Primary analysis – OS network of evidence for lenalidomide-exposed



* mg/m^2. ** mg/kg.
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib plus daratumumab, and dexamethasone; PVd, pomalidomide plus bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone.

The posterior estimates of the fixed-effect model are graphically illustrated in [redacted]. Results suggest numerical improvement in OS for BPd compared to hKd ([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 BPd. NMA results for the comparison of BPd over PVd are aligned with the DREAMM-8 efficacy results for OS (102).

[redacted]

[redacted]

[redacted]

B.2.9.4.4 Secondary analysis results

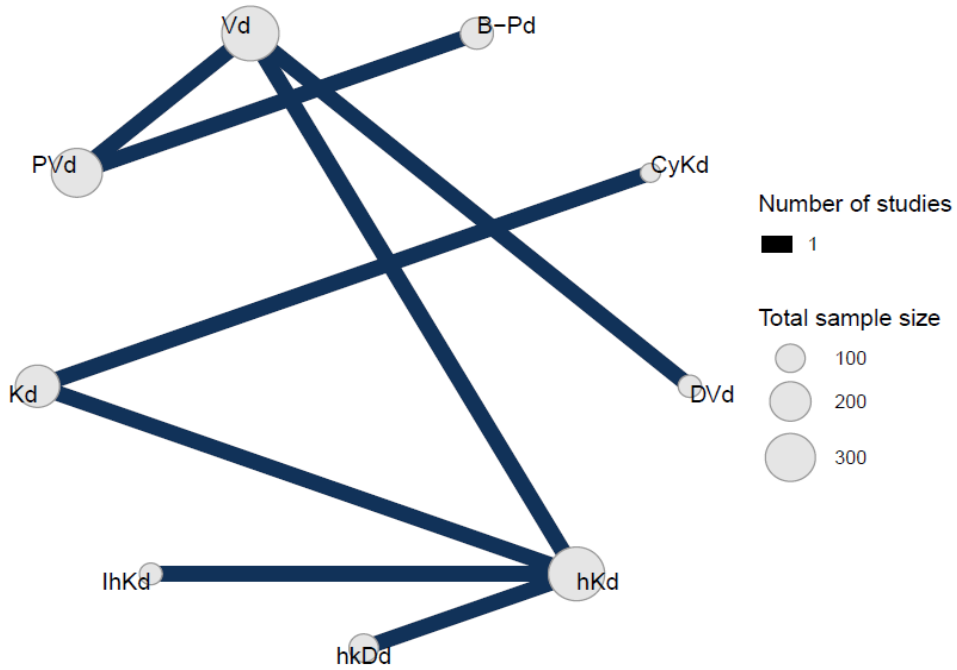
The secondary analyses considered lenalidomide-refractory patients, lenalidomide-exposed and ITT patients, and lenalidomide-refractory and ITT patients restricting the networks to studies reporting efficacy data for these populations. Secondary analyses were conducted for PFS in lenalidomide-refractory patients, and OS in lenalidomide-exposed and ITT patients, and lenalidomide-refractory and ITT patients across the comparator studies.

Lenalidomide-refractory patients

PFS

The network of evidence for PFS, shown in Figure 21Figure 21, consisted of eight studies (DREAMM-8 (101, 103), CASTOR (119, 125), OPTIMISMM (129), ARROW (121), IKEMA (126-128), CANDOR (122-124), ENDEAVOR (108), and GEM_KyCyDex (133)), which reported subgroup-specific data.

Figure 21. Secondary analysis progression-free survival network of evidence – Lenalidomide-refractory population



Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib plus daratumumab, and dexamethasone; IhKd, isatuximab plus high dose carfilzomib and daratumumab; ITT, intent to treat; Kd, carfilzomib and dexamethasone; NMA, network meta-analysis; PFS, progression-free survival; PVd, pomalidomide plus bortezomib, and dexamethasone; Vd, bortezomib and dexamethasone

The posterior estimates of the fixed-effect model are graphically illustrated in [redacted]. Results indicated superiority of BPd over hKd [redacted], while numerical improvement was observed for BPd versus DVd [redacted] in terms of PFS. Results for all relevant comparators were statistically significant to a 95% CrI.

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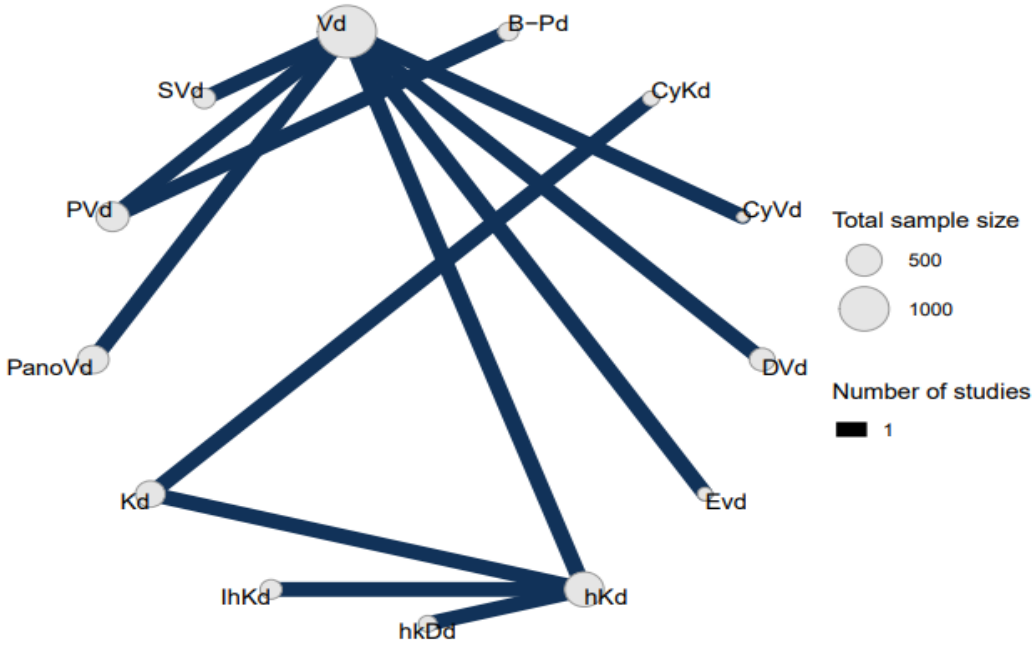
Lenalidomide-exposed plus ITT

OS

The network of evidence for OS shown in Figure 23, consisted of 12 studies (DREAMM-8 (101, 103), CASTOR (119, 125), OPTIMISMM (129), ARROW (121), IKEMA (126-128), CANDOR (122-124), ENDEAVOR (108), BOSTON (90), NCT00813150 (134), NCT1478048 (135), PANORAMA-1 (136), and GEM_KyCyDex (133)), which reported subgroup-specific data.

Figure 23. Secondary analysis OS network of evidence – lenalidomide-exposed plus ITT population



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

The posterior estimates of the fixed-effect model are graphically illustrated in Figure 24. Results indicated numerical improvement of BPd over DVd [redacted] SVd [redacted] and hKd [redacted], and all other non-relevant comparator treatments for the appraisal in terms of OS. Results for all relevant comparators were statistically significant to a 95% CrI.

[redacted]

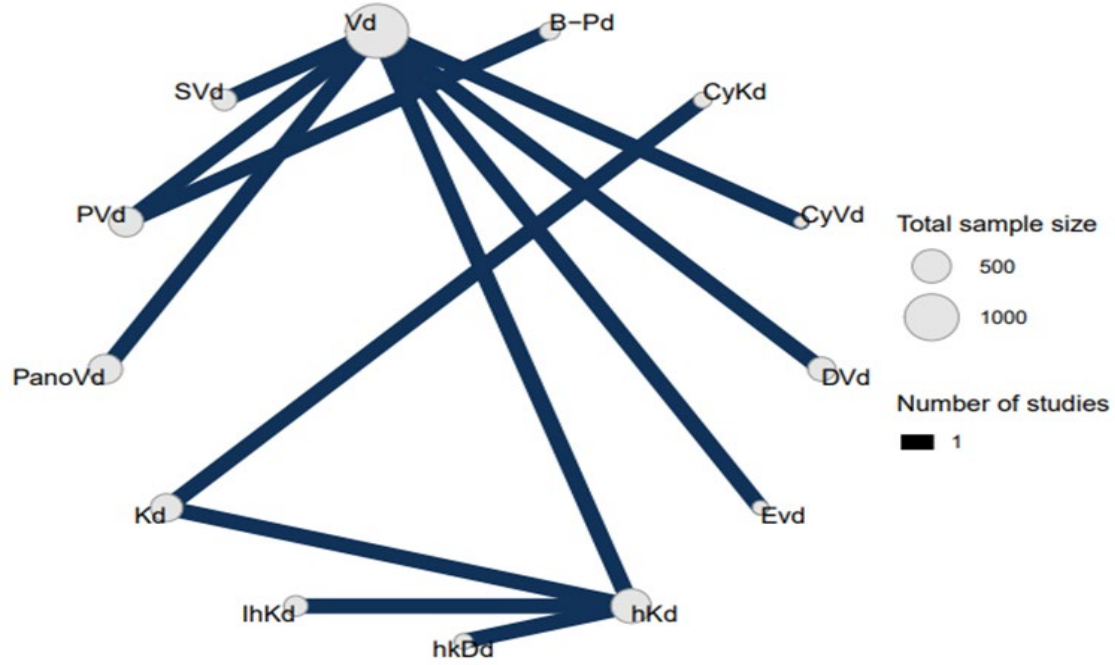
[redacted]

Lenalidomide-refractory plus ITT

OS

The network of evidence for OS is shown in Figure 23, consisted of 12 studies (DREAMM-8 (101, 103), CASTOR (119, 125), OPTIMISMM (129), ARROW (121), IKEMA (126-128), CANDOR (122-124), ENDEAVOR (108), BOSTON (90), NCT00813150 (134), NCT1478048 (135), PANORAMA-1 (136), and GEM_KyCyDex (133)), which reported subgroup-specific data.

Figure 25. Secondary analysis OS network of evidence – lenalidomide-refractory plus ITT population



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

The posterior estimates of the fixed-effect model are graphically illustrated in Figure 26. Results indicated numerical improvement of BPd over DVd [redacted] and hKd [redacted], and all other non-relevant comparator treatments for the appraisal in terms of OS. Results for all relevant comparators were statistically significant to a 95% CrI.

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B.2.9.5 Strengths and limitations

In this NMA, the comparative efficacy of the treatments for patients with at least one prior LoT, including lenalidomide-containing regimen for RRMM was examined, using PFS and OS 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-8. More broadly, PH NMAs have been used in the appraisals of relevant comparators in 2L RRMM (SVd and DVd) (3, 27). In addition, previously published ITCs in RRMM adopted a conventional NMA approach (26, 137-141). 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 random-effect 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 attest 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-8 study had not been reached at the data cut-off point of the analysis. Additionally, median PFS was not reached in the BPd group (95% CI: 20.6, NR), while median PFS was 12.7 months (95% CI: 9.1, 18.5) in the PVd group. An update to the NMA at a later data cut-off, when mature data will be available, 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 BPd in DREAMM-8 was consistent with those previously described for belamaf (95, 96). The safety population included 295 patients (BPd, n=150; PVd, n=145) who received at least one dose of BPd or PVd. Nearly all patients in the BPd group (>99%) and 96% patients in the PVd groups experienced AEs of any grade. Table 23 shows summary statistics for AEs experienced by this population, and further detail on adverse reactions is given in Appendix F.

The BPd arm had higher overall rates of grade 3 or 4 AEs versus PVd (91% vs 73%), any SAEs (63% vs 45%), and AEs leading to dose interruption/delay (91% vs 75%). The incidence of AEs leading to permanent discontinuation of any study treatment, AEs leading to dose reduction, and fatal SAEs were similar in the BPd and PVd groups. Participants in the BPd group stayed on treatment for almost twice as long as the PVd group (median duration of [redacted]). Consequently, AEs were collected for a longer period in the BPd group. Therefore, GSK conducted a post-

hoc analysis to summarize the risk of an AE of interest using exposure-adjusted incidence rates (EAIRs), allowing for meaningful comparisons of key safety endpoints by adjusting for the time on study treatment. In the BPd and PVd arms, when adjusting for total treatment exposure (per 100 person-years), rates of grade 3 or 4 AEs were 66 and 78, and rate of SAEs were 46 and 48, respectively. In total, 19 patients (13%) in the BPd arm versus 9 (6%) in the PVd arm discontinued any trial treatment due to treatment-related AEs. Deaths from serious AEs were reported in 17 patients (11%) in the BPd arm and 16 (11%) in the PVd arm, with 3 (2%) considered related to BPd.

The incidence of AEs in the infections and infestations by System Organ Class (SOC) including opportunistic infections, a known risk with chimeric antigen receptor T-cell and bispecific T-cell engager BCMA-targeting agents was higher (82%) in the BPd group than in the PVd group (68%); however, after adjusting for time on study treatment, the EAIRs were lower in the BPd group than in the PVd group, 59 compared to 73, respectively (102).

Eye-related side effects, a known risk with belamaf, were manageable and resolved with dose modifications (including delays and reductions). A significantly higher rate of dose interruptions and reductions in the BPd arm led 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 BPd arm, overall HRQoL remained stable in the BPd and PVd arms over time (see section B.2.6.1.7 and Appendix N) (102).

Table 23. Summary of adverse events experienced during DREAMM-8 trial (safety population)

	BPd (N=150)	**PVd (N=145)**
Any AE, n (%)	149 (>99)	139 (96)
AE related to any study treatment [a]	143 (95)	118 (81)
Grade 3/4 AE	136 (91)	106 (73)
EAIR[b], per 100 person-years	66	78
Related to any study treatment[a]	120 (80)	85 (59)
AEs leading to permanent discontinuation of any study treatment	22 (15)	18 (12)
EAIR[b], per 100 person-years	11	13
AEs related to any study treatment leading to permanent discontinuation of any study treatment[a,c]	19 (13)	9 (6)
Belamaf discontinuation due to eye-related event	14 (9)	-
AEs leading to dose reduction	92 (61)	88 (61)
EAIR[b], per 100 person-years	44	65

	BPd (N=150)	PVd (N=145)
Belamaf dose reduction due to eye-related event	88 (59)	-
AEs leading to dose interruption/delay	136 (91)	109 (75)
EAIR[b], per 100 person-years	66	80
Belamaf dose interruption / delay due to eye-related event	124 (83)	-
Any SAE	95 (63)	65 (45)
EAIR[b], per 100 person-years	46	48
Related to any study treatment[a]	45 (30%)	21 (14%)
Fatal SAEs	17 (11)	16 (11)
Related to any study treatment[a]	3 (2)	0

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 event rates are calculated as the total number of participants with an event divided by the total person-years (per 100 PY). Total person-years is the sum of all participant exposure calculated as (last dose – first dose + 1) / 365.25.
c. If a fatal SAE occurred but no active decision to discontinue study treatment before death occurred, then the fatal SAE was not reported as leading to study treatment discontinuation. If an AE led to decision to discontinue treatment prior to a fatal outcome, then the AE was reported as leading to study treatment discontinuation.

Abbreviations: AE, adverse events; BPd, belamaf plus pomalidomide, and dexamethasone; EAIR, exposure-adjusted incidence rates; PVd, pomalidomide plus bortezomib, and dexamethasone; SAE, serious adverse event
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.10.2 Adverse reactions by system organ class (SOC)

The overall incidence of AEs by SOC was generally similar across treatment groups and as expected for each drug class. The incidence in the BPd group was higher than in the PVd group for the SOCs of eye disorders (91% vs 37%; grade ≥3, 48% vs 6%), followed by infections and infestations (82% vs 68%), and blood and lymphatic system disorders (64% vs 57%). In the BPd arm, the most frequently occurring grade ≥3 eye-related side effects included blurred vision, reduced visual acuity, and visual impairment (102).

Table 24 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 ≥20% of patients in either 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 BPd versus PVd (55% vs 41%), the incidence of thrombocytopenia AESIs was comparable between the two treatment arms after adjusting for time on study treatment (EAIR: 39.6 and 44.2 per 100 person-years). Similarly, grade 3 and 4 thrombocytopenia AESIs were reported more in patients in the BPd group (38%) versus PVd group (29%) but after adjusting for time

on study, comparable number of patients in the BPd and PVd groups experienced grade ≥3 thrombocytopenia AESI (EAIR: 27.5 and 30.9 per 100 person-years).

The incidence of anaemia was comparable in both the treatment arms of DREAMM-8 trial (23% vs 26% in BPd vs PVd, respectively). The incidence of AEs in the infections and infestations SOC (including Grade ≥3 AEs in this SOC) was higher in the BPd group (82%) compared with the PVd group (68%). When adjusting for time on treatment, the incidence of AEs in this SOC was lower in the BPd group compared with the PVd group (59.3 vs 72.9), while the incidence of Grade ≥3 AEs remained higher in the BPd group compared with the PVd group (35.2 vs 27.9). Other non-eye-related AEs occurring in ≥20% of patients in either arm included diarrhoea and fatigue.

Table 24. Adverse reactions by system organ class (safety population)

	BPd (n=150)		**PVd (n=145)**	
	All	**Grade ≥3**	**All**	**Grade ≥3**
Any adverse event, n (%)	149 (>99)	141 (94)	139 (96)	110 (76)
Blood and lymphatic system disorders, n (%)	96 (64)	77 (51)	83 (57)	61 (42)
Neutropenia	72 (48)	63 (42)	50 (34)	41 (28)
Thrombocytopenia	54 (36)	36 (24)	44 (30)	29 (20)
Anemia	35 (23)	15 (10)	38 (26)	19 (13)
Infections and infestations, n (%)	123 (82)	73 (49)	99 (68)	38 (26)
Pneumonia	36 (24)	26 (17)	17 (12)	11 (8)
COVID-19	56 (37)	10 (7)	31 (21)	3 (2)
Upper respiratory tract infection	40 (27)	2 (1)	25 (17)	0
Eye-related event, n (%)	136 (91)	72 (48)	54 (37)	9 (6)
Vision blurred	119 (79)	26 (17)	22 (15)	0
Visual acuity reduced	34 (23)	20 (13)	8 (6)	1 (1)
Dry eye	91 (61)	12 (8)	14 (10)	0
Photophobia	66 (44)	5 (3)	6 (4)	0
Eye irritation	75 (50)	6 (4)	13 (9)	0
Foreign body sensation in eye	91 (61)	9 (6)	9 (6)	0
Eye pain	49 (33)	3 (2)	7 (5)	0
Cataract	40 (27)	9 (6)	15 (10)	6 (4)
Corneal epithelial microcysts	34 (23)	12 (8)	0	0
Punctate keratitis	34 (23)	9 (6)	1 (1)	1 (1)
Other, n (%)				

	BPd (n=150)		PVd (n=145)	
	All	Grade ≥3	All	Grade ≥3
Diarrhoea	35 (23)	2 (1)	33 (23)	10 (7)
Neuropathy peripheral	11 (7)	1 (1)	34 (23)	4 (3)
Constipation	23 (15)	2 (1)	33 (23)	2 (1)
Fatigue	40 (27)	9 (6)	32 (22)	7 (5)

Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; COVID-19, coronavirus disease 2019; PVd, pomalidomide plus bortezomib, and dexamethasone.
Source: DREAMM-8 primary analysis clinical study report (28, 102)

Treatment-related fatal SAEs were 11% in both arms. In total in the BPd arm 17 patients experienced a fatal AE (of which 3 were considered treatment-related) and in the PVd arm 16 patients experienced a fatal AE (of which none were considered treatment-related). Table 25 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 25. Fatal and treatment-related fatal adverse events (safety population)

	BPd (n=150)		PVd (n=145)	
	Fatal SAE	Fatal TRSAE	Fatal SAE	Fatal TRSAE
Any event	17 (11)	3 (2)	16 (11)	0
COVID-19 pneumonia	5 (3)	-	2 (1)	-
COVID-19	2 (1)	-	2 (1)	-
Pneumonia	2 (1)	1 (1)	1 (<1)	-
Acute kidney injury	1 (<1)	-	0	-
Cerebral infarction	1 (<1)	-	0	-
Chest pain	1 (<1)	-	0	-
Gastrointestinal cancer metastatic	1 (<1)	1 (1)	0	-
Meningoencephalitis herpetic	1 (<1)	1 (1)	0	-
Myocardial infarction	1 (<1)	-	0	-
Pulmonary embolism	1 (<1)	-	0	-
Septic shock	1 (<1)	-	0	-
Acute pulmonary oedema	0	-	1 (<1)	-
Cerebrovascular accident	0	-	1 (<1)	-

Colon cancer metastatic	0	-	1 (<1)	-
Death	0	-	3 (2)	-
General physical health deterioration	0	-	1 (<1)	-
Lower respiratory tract infection	0	-	1 (<1)	-
Pneumonia aspiration	0	-	1 (<1)	-
Sepsis	0	-	2 (1)	-

Note: Preferred terms are presented by descending order by the number of participants in the BPd group.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; COVID-19, coronavirus disease 2019; PVd, pomalidomide plus bortezomib, and dexamethasone; SAE, serious adverse event; TRSAE, treatment-related serious adverse event.
Source: DREAMM-8 primary analysis clinical study report (102)

Eye-related side effects

As described in section B.2.10.2, eye-related side effects were the most characteristic safety profile difference between the BPd and PVd arm. Although most eye-related side effects could be resolved with dose interruption, this led to a significantly lower RDI for BPd than PVd, which has implications for the cost-effectiveness of BPd in UK clinical practice (please see section B.3.5.2.1). 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 26 summarises eye-related side effects that occurred in the BPd arm of the DREAMM-8 trial (eye-related events that occurred on the PVd arm would not usually lead to dose modification, so they are less relevant to the decision problem). At data cut-off, 89% of patients who received BPd had had CTCAE-graded eye-related AEs, as compared with 30% of those who received PVd. 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 27 provides a reference image for the impact of BCVA at different levels on the patient.

Figure 27. Reference images for impact of best corrected visual acuity on patient

Abbreviation: BCVA, Best Corrected Visual Acuity

Among patients in the BPd 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 51 patients and a worsening to bilateral 20/200 was reported in 2 patients. For the first occurrence, 92% patients with worsening to bilateral 20/50 and all patients with worsening to bilateral 20/200 resolved to better either prior to or post the end of treatment exposure, respectively. The remaining 4 (8%) patients with ongoing events at data cut-off, 2 patients continued to be on study treatment, while the remaining 2 patients were no longer on study before the resolution could be documented. The median duration of the first occurrence was approximately four weeks regardless of how severe the initial impact on BCVA was.

Table 26. Summary of eye-related side effects (safety population)

	BPd (N=150)	
	Bilateral worsening of BCVA in patients with normal baseline (20/25 or better in ≥ 1 eye)	
	20/50	**20/200**
Patients, n/N (%)	51/150 (34)	2/150 (1)
Time to onset of first event, median (range), days	112.0 (28 - 761)	351.0 (29 - 673)
Duration of first event, median (range), days[a,b]	29.0 (7 - 196)	25.5 (22 - 29)
First event resolved, n (%)[a]	47.0 (92)	2.0 (100)
Duration of last event, median (range), days	[redacted]	[redacted]
Last event resolved, n (%)[a]	[redacted]	[redacted]

a. Duration is the time from onset of any worsening of BCVA Score to 20/50 until the event is resolved.
b. Snellen acuity response of 'no equivalent value' is considered a worsening event.
Note: Resolution was defined as no longer having BCVA 20/50 or worse in both eyes, i.e., at least 1 eye is missing or better than 20/50.
Abbreviations: BCVA, Best Corrected Visual Acuity; BPd, belamaf plus pomalidomide, and dexamethasone
Source: DREAMM-8 primary analysis clinical study report (102)

Dose modifications of belamaf were based on overall Keratopathy Visual Acuity (KVA) grade. KVA events were reported in [redacted] patients, with majority of patients ([redacted]) experiencing grade ≥3 events. These are summarised in [redacted]. For the first occurrence of grade ≥2 KVA events, median time to onset was [redacted], and median duration of the first occurrence was [redacted]; at data cut-off, [redacted] of those participants had 3 or more occurrences and [redacted] of those patients had their first event resolved prior to or post end of treatment exposure. Eye-related events in the BPd arm led to belamaf dose reductions (encompassing both the decrease in dose and the extension of dosing intervals), interruptions/delays, and discontinuations in [redacted], 86%, and 9% of patients, respectively. Patient reported HRQoL was similar between the two treatment arms over time, as demonstrated by global health status and QoL domains of EORTC QLQ-C30, 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).

[redacted] 27

	BPd (n=150)
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]
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]

	BPd (n=150)
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. Duration is the time from onset of any KVA scale event (Grade 2 or above) until the event is resolved (Grade 1 or better). The proportion of participants whose first occurrence resolved prior to, or post end of treatment is 89% for overall KVA grade, 91% for corneal exam findings, and 93% for BCVA.

Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; KVA, Keratopathy Visual Acuity

Source: DREAMM-8 primary analysis clinical study report (102)

B.2.10.3 Relative dose intensity

In DREAMM-8, eye-related side effects, which are a known risk with belamaf, were managed with dose modifications, including delays and reductions. The efficacy of BPd was maintained even with delays and reductions of the belamaf dose, which resulted in the lower relative dose intensity (RDI) reported for belamaf (versus all PVd components). The median RDI of belamaf was [redacted] for the full treatment duration. The median RDI was [redacted] for [redacted], [redacted] for [redacted], and [redacted] for [redacted]. The overall median RDI of bortezomib was [redacted], with [redacted] relative dose intensity during [redacted], [redacted] during [redacted], and [redacted] for [redacted]. Median dose intensities of pomalidomide and dexamethasone were 84.3% and 81.7%, respectively for participants in the BPd group versus 91.7% and 90.3% in the PVd group. Table 28 summarises the impact that AEs have on median RDI.

This is likely to be reflected in NHS clinical practice considering (see section B.3.5.1.2): 1) RDI from the UK [redacted] dataset; and 2) UK clinical expert advice.

1) <u>RDI from the UK NPP dataset</u>

[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 (143) and International Myeloma Society 2023 (144). 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 37/74 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 54.9%, 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-8 is likely to be reflected in NHS clinical practice.

2) <u>UK clinical expert advice</u>

Feedback from these meetings suggests that in NHS clinical practice BPd will be utilised on a 28-day cycle as employed in DREAMM-8. 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 potentially 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 as in DREAMM-8. Based on the BPd arm in the DREAMM-8 study, 86% of patients achieved a partial response or better and the median time to partial response or better was 1.07 months (range: 0.9 – 9.3 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-8 (median: 52.5%) is likely to be reflected in NHS clinical practice.

[redacted] 28 [redacted]

	BPd (N=150)			PVd (N=145)		
Total duration of exposure, Median (range) months[a]	[redacted]			[redacted]		
	Bela	**Pom**	**Dex**	**Pom**	**Bor**	**Dex**
Number of cycles, Median (range)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average daily dose, Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity, Measure, Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity[d,e], Median (%) (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. Treatment duration=([last date of the study drug] – [first dose date of the study drug]) + 1. See SAP Section 4.5.1 for further details.
b. Dose intensity was the cumulative actual dose/(treatment duration/4 weeks).
c. Dose intensity was the cumulative actual dose/(treatment duration/3 weeks).
d. Relative dose intensity=(dose intensity/planned dose intensity)*100.
e. Planned dose intensity=(cumulative planned dose in actual dosing cycles)/(number of actual dosing cycles) - only actual dosing cycles up to last dose of component were considered.

Note 1: Belantamab mafodotin dose measured in mg/kg; dose intensity measured in mg/kg/cycle; average daily dose in mg/kg/day.
Note 2: Bortezomib dose measured in mg/m^2; dose intensity measured in mg/m^2/cycle; average daily dose in mg/m^2/day.
Note 3: Pomalidomide dose measured in mg; dose intensity measured in mg/cycle; average daily dose in mg/day.
Note 4: Dexamethasone dose measured in mg; dose intensity measured in mg/cycle; average daily dose in mg/day.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; Bela, belantamab mafodotin; Bor, bortezomib; Dex, dexamethasone; Pom, pomalidomide; PVd, pomalidomide plus bortezomib, and dexamethasone; SD, standard deviation
Source: DREAMM-8 primary analysis clinical study report (102).

B.2.11 Ongoing studies

DREAMM-8 (NCT04484623) is an ongoing phase III, open-label, randomised, multicentre clinical trial to evaluate the efficacy and safety of BPd compared with PVd in patients with RRMM who received at least 1 prior LoT, including a lenalidomide-containing regimen. The study is being conducted in 18 countries across 95 centres, including 5 UK sites (103).

DREAMM-7 (NCT04246047) is a phase III, multicentre, open-label, randomised head-to-head trial evaluating the efficacy and safety of belamaf plus bortezomib and dexamethasone (BorDex) versus the daratumumab plus BorDex in patients with RRMM previously treated with a least one prior LoT, and who have documented disease progression during or after their most recent therapy. On 27 November 2023, GSK announced positive headline results from a planned interim analysis of this study. The trial met its primary endpoint of PFS at a prespecified interim analysis and was unblinded early (145).

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-8 trial met its primary endpoint of PFS. BPd demonstrated a statistically significant and clinically meaningful PFS benefit (95% CI: 0.37, 0.73; HR, 0.52; p<0.001; showing nearly 50% reduction in risk of disease progression or death). At 21.8 months median follow-up, median PFS was not yet reached (95% CI: 20.6 - NR) with belamaf combination compared to 12.7 months (95% CI: 9.1 - 18.5) in the PVd arm in the ITT population. PFS benefit consistently favoured BPd versus PVd across prespecified subgroups, including patients who are lenalidomide-refractory and have high-risk cytogenetics. These results were validated by UK clinical experts, who confirmed that the DREAMM-8 PFS for PVd generally aligns to UK clinical private practice and noted that the PFS benefit was favourable for BPd (4).

The median PFS of [redacted] for BPd 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 (24), ENDEAVOR (89) and BOSTON (90)] and the TTNTD (proxy-PFS) reported in emerging UK RWE for lenalidomide-refractory patients treated with DVd at 2L (10.3 months) (31, 32). As described in section B.1.3.2.1, there is a high unmet need for patients for whom lenalidomide is unsuitable at first relapse in the UK, as current treatment options are limited, and corresponding outcomes are poor. Overall, this data suggests improved efficacy in the lenalidomide-refractory group with BPd over other options.

Treatment with BPd resulted in a deeper response, with ≥CR rate 2.5 times higher than that of PVd (40% vs 16%). MRD negativity rate (10^{-5}) in patients treated with BPd was nearly five times higher compared to patients treated with PVd (24% vs 5%). Additionally, it was noted that 64% of responders in BPd group and 38% of responders in PVd group achieved deep responses of VGPR or better with a short and comparable median TTR between the treatment arms ([redacted]).

The median DoR was longer with BPd with median DoR not yet reached (24.9 – NR) versus 17.5 months (12.1 – 26.4) with PVd. Furthermore, a positive OS trend was observed favouring the BPd arm versus PVd arm, although not statistically significant (HR, 0.77; 95% CI: 0.53, 1.14). The 12 months OS survival rate was higher in the BPd group compared with the PVd group (83% vs. 76%). These results were validated by clinical experts, who noted that the OS data was immature, but that they expected to see a benefit in additional follow-ups (4). Furthermore, UK clinicians noted that it was surprising to observe a relatively higher than expected OS at the end of the follow up for patients in the PVd arm, given that a substantial proportion of patients have discontinued treatment in this group. This was attributed to the fact that a large proportion of patients surviving at the end of follow up were already on subsequent therapies outlined in B.2.3.2.3 which are not available in the NHS treatment pathway and were potentially driving the OS for this group (4).

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 13 which became very noticeable from around week 37 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 BPd arm (0.737) indicated higher improvement in utility scores compared to the PVd arm (0.698) patients.

The NMA suggest that BPd is more efficacious compared to the comparators (hKd, DVd, and SVd) when assessing PFS in both lenalidomide-exposed and lenalidomide-refractory analyses. Results were statistically significant for the fixed-effect comparisons, highlighting the clinical benefit of BPd in RRMM. BPd showed favorable results for OS, although not statistically significant, compared to hKd, DVd, and SVd. All results from the lenalidomide-exposed plus ITT, and lenalidomide-refractory plus ITT analyses were in favour of BPd extending OS over comparators.

B.2.12.1.2 Safety

The safety and tolerability of BPd in the DREAMM-8 trial was consistent with those previously described for belamaf (95, 96). 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 89% of the patients who received BPd and 30% of those who received PVd. Despite the higher incidence of eye-related AEs in the BPd arm, overall HRQoL remained stable in the BPd and PVd arms over time. Finally, the rates of infections

were higher in the BPd group compared with the PVd group in the DREAMM-8 trial (82% vs. 68%). However, after adjusting for time on treatment, the EAIRs were lower in the BPd group than in the PVd group (59.4 vs. 72.2).

B.2.12.2 Strengths and limitations of the clinical evidence base

B.2.12.2.1 Strengths of the clinical evidence base

- A key strength of the clinical evidence base of the DREAMM-8 trial is that the results unequivocally favour BPd under all reasonable data cuts. The positive benefit–risk profile was consistent regardless of prior treatments, high-risk status, and frailty. The trial also included patients exposed to and refractory to anti-CD38, reflecting its increased use in frontline NHS settings (4, 146). This strongly implies the results will generalise to the NHS.
- Clinical experts validated PVd as a suitable comparator in DREAMM-8 based on their private clinical practice experience and knowledge of the regimen as a 2L EU SoC. Experts indicated that although it is not routinely used in NHS clinical practice, it is a leading combination in the private setting, and safety results from the DREAMM-8 clinical trial for PVd are comparable with real-world results (4).
- The eye-related side effects associated with belamaf are manageable and reversible, as evidenced by the DREAMM-8 study, which shows effective control through dose delays and reducing the frequency of administration to every 8 weeks, or a combination of both. Despite the incidence of AEs, patients on BPd had a maintained HRQoL.
- The NMA study selection was based on a global SLR. No significant imbalances in disease characteristics were observed across the included studies. The inclusion of both fixed- and random-effect models in the NMA models were aligned with NICE DSU TSD guidance (132). Consistent model fit and treatment effect estimates across models confirm the robustness of the Bayesian NMA approach. The results of the NMA were favourable for belamaf in combination against all relevant comparators for PFS and OS.

B.2.12.2.2 Limitations of the clinical evidence base

- A limitation of the DREAMM-8 trial includes the relatively short follow-up among patients whose participation is ongoing, which limits the interpretation of survival outcomes. Follow-up for survival is ongoing, and further deepening of responses is possible for patients who are still in the trial.
- The trial population included mostly white patients because of the demographic makeup of the countries in which it was conducted, and black patients were not represented. Given the prevalence of myeloma among black patients, the lack of data in this key patient group is a limitation of this trial.

- Although PVd is a 2L EU SoC and globally recommended by EHA-ESMO guidelines, it does not align with the NHS treatment pathway, posing a limitation for the DREAMM-8 trial in this region Given that PVd is not recommended by the NHS, a robust NMA was conducted to indirectly compare it with NHS-recommended treatments like DVd, hKd, and SVd.
- The limited reporting of baseline characteristics in the primary analysis population in the included NMA studies made it challenging to fully assess between-study heterogeneity. This limitation underscores the need for cautious interpretation of the NMA results, particularly concerning the potential impact of underlying trial differences on treatment effect estimates. NMAs do not account for imbalances in population characteristics, which could influence treatment effects across studies. Additionally, a limitation of the NMA results is the immaturity of survival data in DREAMM-8.

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 who have been previously treated with lenalidomide, as treatment options are limited, and efficacy is suboptimal. Therefore, a new and effective therapy with a unique MoA is needed, and if approved, belamaf in combination would be the first BCMA-targeted option within the NICE pathway.

BPd has been evaluated in the DREAMM-8 phase III trial and this trial provides the most robust source of evidence generalisable to the UK population. Belamaf has demonstrated significant superiority to the comparator arm in the DREAMM-8 RCT and existing 2L treatment options where the NMA results suggest that BPd has a favourable efficacy compared to its comparators (hKd, DVd and SVd), for all populations in terms of PFS and OS. Finally, the results from the comparison of BPd vs PVd were aligned between the DREAMM-8 analyses and the NMA.

Belamaf has a lower risk for severe infections compared to other BCMA targeted therapy in a similar patient population. Furthermore, the absence of immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS) adverse events with belamaf in combination, along with the infrequent administration of belamaf, makes it a feasible treatment option in outpatient centres. This offers a significant advantage over other BCMA-targeting therapies that require IVIG administration, specialized cancer centres and inpatient administration.

Taken together, the broad efficacy benefit observed in this appraisal, manageable safety profile, and utility of belamaf in combination as an off-the-shelf, outpatient BCMA therapy, strongly support belamaf in combination as the new SoC at first relapse for patients for whom lenalidomide is unsuitable in 2L. If approved for routine commissioning, belamaf in combination has the potential to redefine the NICE treatment paradigm, offering new hope for patients and their families and low treatment burden on patients and practitioners, making it suitable as the treatment of choice at first relapse.

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 BPd versus DVd, SVd, and hKd in adult patients with RRMM who have had one prior therapy, and whose disease had 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. 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 DREAMM-8 trial.
- Health state utilities for the PFS and PD health states were informed by the DREAMM-8 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 CEM indicates that, for DVd-ineligible population, BPd (Patient Access Scheme [PAS]) dominates hKd and SVd, and BPd could become even more CE over time as the use of daratumumab increases in 1L.
- The base-case CE results for the DVd-eligible population indicated that both hKd and DVd were dominated by BPd, leading to both health benefits and cost savings. By conventional cost-effectiveness criteria, BPd would be a highly CE use of NHS resources.
- Uncertainty around the CE estimates from the base case was explored by probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWSA). The results indicated the robustness of the findings across the various analyses performed, in which BPd remained a CE treatment option.
- Furthermore, scenario analyses were conducted to estimate the impact of structural and model input assumptions on the CE of BPd. Results using the PAS price of BPd demonstrate that the CE conclusions remain consistent with the base case despite variations to the analytical specifications and assumptions.
- As BPd substantially increases time spent in PFS resulting in less subsequent treatment costs (and less PD health state costs), BPd raises mean OS by [redacted] and time spent progression-free by [redacted] with an associated net resource saving for the NHS over the first five years of BPd's approval [redacted]. Collectively, the evidence suggests that BPd 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 supports belamaf in combination as the new SoC at 2L for patients unsuitable to lenalidomide. If approved for routine commissioning, belamaf in combination 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 and April 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+ T RRMM (147).

This SLR was conducted according to the NICE guidelines, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the Cochrane Handbook for Systematic Reviews of Interventions, to ensure methodological quality (148-151).

The economic SLR identified 70 publications that described cost-effectiveness analyses in patients with RRMM (147):

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

In the 20 publications conducted for UK settings:

- 10 publications used a partitioned survival modelling approach (27, 55, 89, 94, 152-157).
- Four publications used Markov model (84, 158-160).
- One publication used both Markov and partitioned survival modelling approaches (161).
- Four publications used other types of models were used (Excel-based individual simulation model, decision-analytic model, discrete event simulation) (162-165).
- One publication did not specify the model structure used (166).

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 BPd for the treatment of adult patients with RRMM who have had at least one previous therapy (including lenalidomide-containing regimen), GSK developed a *de novo* cost-effectiveness model (CEM). The CEM was used to estimate the total costs and quality-adjusted life years (QALYs) associated with BPd compared to relevant comparators as described in section B.1.3.2, that have the potential to be displaced with recommendation of BPd in 2L in England and Wales (i.e., DVd, hKd, and SVd) (148). In this section, hKd refers to high dose carfilzomib (56

mg/m^2) plus dexamethasone which aligns to Kd treatment recommended in the NICE pathway. The NMA conducted provides results for hKd to differentiate between another Kd trial, and therefore, the model nomenclature aligns with the NMA (see section 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 (149). 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-8 (101, 102, 111) trial population: adults (aged ≥18 years) with documented MM, previously treated with one prior LoT (including lenalidomide-containing regimen for at least two consecutive cycles), and with documented disease progression during or after their most recent therapy. The overall ITT population from the DREAMM-8 trial is included within the model as it is reflective of clinical practice, has a large sample size and forms the most robust source of data from the NMA analysis given data availability (sections B.2.2.1 and B.2.9.3).

B.3.2.2 Baseline characteristics

Baseline characteristics for the modelled cohort are based on the statistical analysis of the ITT population of the DREAMM-8 trial and are presented in Table 29.

Table 29. Patient baseline characteristics for the base-case economic analysis

Characteristic	ITT
Baseline mean age (years)	66.1
Baseline weight (kg)	[redacted]
Baseline BSA (m^2)	[redacted]
% of males	60.0%

Abbreviations: BSA, body surface area; ITT, intention-to-treat; kg, Kilogram.
Source: DREAMM-8 (102, 148)

B.3.2.3 Model structure

A *de novo* health economic model was constructed in Microsoft Excel to evaluate the CE of BPd versus DVd, hKd and SVd in patients with 2L lenalidomide-exposed MM. The model adopts the structure of a cohort-based partitioned survival model (PSM). This structure allows health state occupancy to be estimated directly from trial-based estimates of PFS, OS, and TTD data from the DREAMM-8 trial and hazard ratios derived from the NMA. This structure is the standard approach used in oncology HTA submissions, due to its intuitiveness. The model structure has been validated by

clinical experts in a recent Scientific Committee Meeting held by GSK and is also aligned with all of the precedent Technology Appraisals in MM (Table 30).

Table 30. Relevant published models

Factor	NICE TA974 (3)	NICE TA897 (27)	NICE TA870 (55)	NICE TA783 (156)	NICE TA695 (154)	NICE TA658 (155)	NICE TA917 (83)	ICER appraisal 061016V3 (167)	ICER appraisal 0405211 (168)	NICE ID6333 (72)	NICE ID4026 (73)
Intervention	SVd	DVd	IxaRd	Daratumumab	KRd	IsaPd	DRd	KRd, daratumumab, ERd, IxaRd, FVd, and Pd	Ide-cel, cilta-cel, and belamaf	Teclistamab	Elrantamab
Line of therapy	2L, 3L	2L	3L, 4L	4L	2L+	4L	1L	2L+	4L+	4L+	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	Three state PSM	Four 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	Lifetime	Lifetime (25 years)
Cycle length	One week	One week	One week	One week	28 days	One week	Four weeks	One week	One month	One week	One week

Factor	NICE TA974 (3)	NICE TA897 (27)	NICE TA870 (55)	NICE TA783 (156)	NICE TA695 (154)	NICE TA658 (155)	NICE TA917 (83)	ICER appraisal 061016V3 (167)	ICER appraisal 0405211 (168)	NICE ID6333 (72)	NICE ID4026 (73)
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 extrapolated from real-world data	PFS and OS extrapolated directly from observed trial KM data. Estimation of OS using a PFS:OS relationship was explored as a scenario analysis	PFS and OS extrapolated directly from observed trial KM data and validated with real-world data	PFS extrapolated directly from observed trial KM data for lenalidomide and dexamethasone. Hazard ratios from NMA used to derive PFS curves for other interventions. OS estimated from treatment-specific PFS:OS relationships	Intervention PFS and OS and comparator OS extrapolated directly from observed trial KM data. Comparator PFS estimated from PFS:OS relationship derived from NMA	PFS and OS extrapolated directly from observed trial KM data. TTNT was used as a proxy for PFS	PFS and OS extrapolated directly from observed trial KM data. The PFS extrapolated curve crosses the OS curve at approximately 2 year so a constraint has been added to prevent OS dropping below the PFS curve in the Elrantamab arm.

Note: TA658 received a negative recommendation and appeal is underway for re-consideration (ID4067)

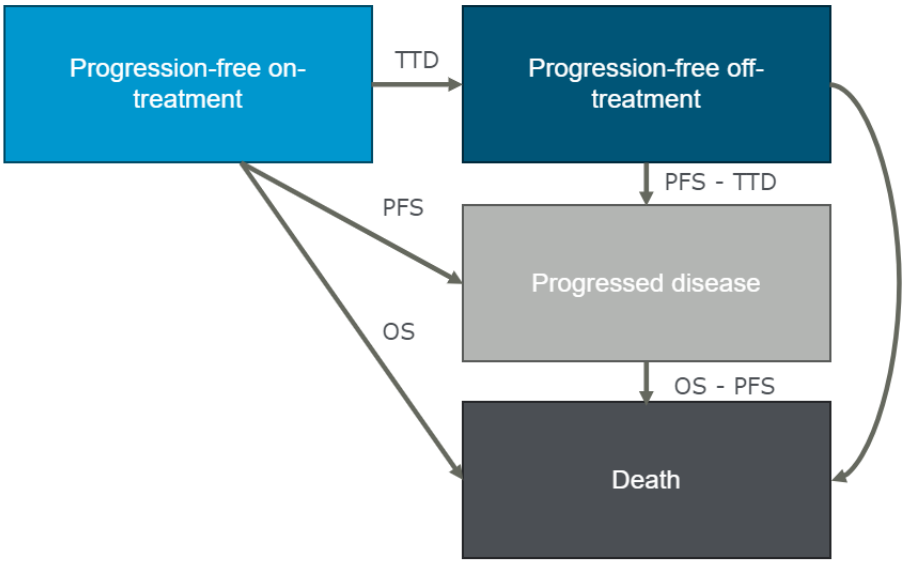
Abbreviations: 1L, first line, 2L second line; 2L+, second line and onwards 3L, third line; 4L, fourth line; 4L+, fourth line onwards; cilta-cel, ciltacabtagene autoleucel; DRd, daratumumab plus lenalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; ERd: elotuzumab plus lenalidomide, and dexamethasone; FVd, panobinostat plus bortezomib, and dexamethasone; ICER, Institute for Clinical and Economic Review; ide-cel, Idecabtagene vicleucel; IsaPd, isatuximab plus pomalidomide, and dexamethasone; IxaRd, ixazomib plus lenalidomide, and dexamethasone; KM, Kaplan Meier; KRd, carfilzomib plus 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 plus 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 28.

Figure 28. Illustration of the 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-8 trial for BPd and PVd.

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-8 withdrew from active treatment before disease progression. PF (on- and off-tx) and PD health states were intended to capture the differences in costs and

quality of life within MM. PF (on- and off-tx) captured the costs and consequences of treatment (acquisition and administration), monitoring, and AEs, whilst PD captured the costs and consequences of subsequent treatments, monitoring and end of life care. Therefore, the model captured the key elements of care for lenalidomide-exposed patients with 2L RRMM from the time they begin treatment to when they completed subsequent treatment and entered terminal care.

For each weekly cycle, costs and QALYs were calculated based on the state membership of patients across the modelled health states. Costs and QALYs were accumulated over the time horizon to calculate total costs and QALYs for BPd and its comparators. The total costs and QALYs were used to calculate incremental results, including the cost per QALY and cost per life year gained, for BPd versus each comparator.

B.3.2.4 Model settings

A summary of the model features and justification is presented in Table 31 alongside a comparison with models included in previous NICE appraisals of treatments for RRMM as these were used to inform the DREAMM-8 model base-case.

Table 31. Comparing recent appraisals with a population of 2L MM patients with DREAMM-8

Parameter	Previous appraisals				DREAMM-8	
Factor	**NICE TA974 (3)**	**TA897 (27)**	**TA695 (154)**	**TA657 (89)**	**DREAMM-8 (102, 103)**	**Justification**
Population and treatment	RRMM patients who have received one or two lines of prior therapy Intervention: Selinexor plus bortezomib, and dexamethasone	Previously treated MM patients Intervention: Daratumumab plus bortezomib, and dexamethasone	RRMM patients who have received one to three lines of prior therapy Intervention: carfilzomib plus lenalidomide, and dexamethasone	Patients with MM who have received at least one prior therapy Intervention: Carfilzomib and dexamethasone	Patients with MM who have received at least one prior therapy including a lenalidomide-containing regimen for at least two consecutive cycles Intervention: Belamaf + pomalidomide + dexamethasone	In line with current decision problem for this submission
Time horizon	35 years (lifetime)	30 years (lifetime)	40 years (lifetime)	40 years (lifetime)	33.9 years (lifetime)	Sufficiently long to be considered a lifetime horizon for 2L+ MM patients with a mean age of 66.1 years and aligned with NICE reference case (149)
Perspective	NHS & PSS	NHS & PSS	NHS & PSS	NHS	NHS & PSS	In line with NICE reference case (149)

Parameter	Previous appraisals				DREAMM-8	
Factor	**NICE TA974 (3)**	**TA897 (27)**	**TA695 (154)**	**TA657 (89)**	**DREAMM-8 (102, 103)**	**Justification**
Discounting	3.5%					In line with NICE reference case
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 B-Pd 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.

Parameter	Previous appraisals				DREAMM-8	
Factor	**NICE TA974 (3)**	**TA897 (27)**	**TA695 (154)**	**TA657 (89)**	**DREAMM-8 (102, 103)**	**Justification**
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-8, as well as based on TA897 and TA695	Aligned with previous approaches in NICE Appraisals
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 (149)

Abbreviations: 1L+, one line and onwards; 2L, second line; BPd, belamaf plus pomalidomide, 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, selinexor plus 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 a regimen consisting of BPd. Belamaf is available in 100 mg vial, which is administered as an IV infusion. In the CEM, a 70 mg formulation, which is not yet an available formulation, is also provided based on cost per mg calculation and is expected to become available at the time of NICE approval. The belamaf dose in the CEM is aligned to the DREAMM-8 trial protocol, with a starting dose of 2.5 mg/kg on Day 1 in Cycle 1 (four-week cycle) and 1.9 mg/kg on Day 1 in Cycle 2 onwards (four-week cycle). The CEM includes functionality to reduce the dose to 1.9 mg/kg or reducing dose frequency as needed. Pomalidomide is given in 4 mg doses administered orally on Days 1-21 of each four-week cycle. Dexamethasone is given as 40 mg oral tablets on Days 1, 8, 15 and 22 of each four-week cycle. This aligns with the DREAMM-8 clinical study report (CSR) and the Summary of Product Characteristics (SmPC) (10, 101, 102).

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

- DVd
- hKd,
- SVd,

Where 'hKd' refers to the carfilzomib and dexamethasone comparator in the NICE treatment pathway (called Kd in section 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 BPd and non-trial comparators. See section B.2.9 and Appendix D for further 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 BPd and PVd are sourced from the DREAMM-8 trial. The economic model incorporates efficacy data for PVd (i.e., PFS, OS, and TTD) to facilitate its use as the reference treatment for estimating survival outcomes of other comparator treatments. Estimates of the relative treatment effect against other comparators have been informed by an NMA (section B.2.9), with hazard ratios applied to PVd extrapolated outcomes as a reference treatment in the base case analysis (see Section B.3.3.2.3, B.3.3.2.6, B.3.3.2.9). PVd was selected over BPd as the reference treatment because

BPd, being a BCMA-targeted therapy, has a different mode of action, whereas PVd shares a more comparable hazard profile with the other comparators. Given the nature of distributions that were deemed clinically plausible, there is little to no effect when either PVd or BPd were selected as reference treatment and a scenario analysis is provided where BPd extrapolated outcomes is the selected reference treatment (see B.3.11.3). In the base-case, unadjusted OS (for treatment switching) was used, which was considered a conservative assumption as in clinical validation meetings, UK clinicians noted that TTD for patients in the PVd arm was notably low with the majority of patients progressed to subsequent treatments. Meanwhile, the OS for patients in the PVd arm was higher than expected indicating that non-NHS aligned salvage therapies may have contributed to this outcome (4). Table 32 summarises the clinical efficacy input data used in the CEM.

Table 32. Clinical inputs for CEM

Endpoint	Source of clinical effectiveness	
	BPd	**Non-trial comparators (DVd, hKd, SVd)**
PFS	Base-case: extrapolation based on DREAMM-8 data	Base-case: HRs vs PVd* as baseline from NMA Scenario: HRs vs BPd as baseline from NMA
OS	Base-case: Unadjusted DREAMM-8 extrapolation Scenario: IPCW adjusted DREAMM-8 extrapolation Scenario: PFS: OS surrogacy	Base-case: HRs vs PVd* as baseline from NMA Scenario: PFS: OS surrogacy using BPd PFS as baseline curve
TTD	Base-case: DREAMM-8 extrapolation	Base-case: PFS HRs vs PVd* as baseline from NMA, used as proxy for TTD HR Scenario: TTD equals PFS for each comparator Scenario: PVd* TTD used as proxy for comparators (capped by the respective comparator's PFS)

*HRs vs PVd from the NMA are used in the economic model when PVd is selected as the baseline treatment for the estimation of PFS, OS, and TTD outcomes
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; CEM, cost-effectiveness model; DREAMM, Driving Excellence in Approaches to Multiple Myeloma; HR, hazard ratio; IPCW, inverse-probability of censoring weighting; KM, Kaplan Meier; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PVd, pomalidomide plus bortezomib, and dexamethasone; TTD, time to treatment discontinuation.
Source: Cost-effectiveness model for BPd in a population of 2L+ multiple myeloma (DREAMM-8) (148)

B.3.3.2 Parametric survival modelling

Parametric survival modelling is implemented to extrapolate survival curves over a lifetime horizon of the cost-effectiveness model. These analyses have been carried out in line with the NICE TSD 14 (149). In brief:

- Six standard parametric distributions have been fitted to KM data using R software (Exponential, Weibull, Gompertz, log-logistic, lognormal 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) and an external Health Economics expert 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 BPd and PVd at 5-, 10-, and 15- year landmarks. As a last step of the exercise, EEs validated the most plausible curves fitted to the data based on clinical plausibility or survival analysis diagnostics (4).
- For the comparators that are not included in the DREAMM-8 trial (i.e., DVd, hKd and SVd), PFS, and OS curves were estimated by applying the NMA HRs for each comparator to the extrapolated PVd data (base case) from corresponding DREAMM-8 trial outcomes. Due to unavailability of published data to inform an NMA for TTD, assumptions were made to fit plausible TTD estimations for DVd, hKd and SVd (Section B.3.9.2).

Table 33 summarises the selection of curves used in the CEM.

Table 33. 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	Weibull	Similar statistical fit between the majority of curves. Good agreement between clinical EE for both comparators based on clinical plausibility of extrapolated outcomes, with a focus on the 5-year landmark estimates (4).	[redacted]
OS	Exponential	Good statistical fit based on AIC and BIC, and unanimous curve choice between EE based on clinical plausibility of 5-,10-, and 20-year landmark estimate (4).	[redacted]
TTD	Weibull	For PVd, it was a unanimous curve choice for Weibull between EE based on the predicted 5-, and 10-year estimates. For BPd, EE unanimously selected the exponential model, but the Weibull model was used in the base case due to the similarity of predicted values with exponential model, and consistency in the curve choice with PVd (4).	[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; BPd, belamaf plus pomalidomide, and dexamethasone; PVd, pomalidomide plus 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 BPd – Progression-free survival

In the DREAMM-8 ITT population, there is a statistically significant and clinically meaningful PFS benefit with BPd compared with PVd, as demonstrated by an HR of 0.52 (95% CI: 0.37, 0.73; p <0.001). The median PFS was not reached in the BPd arm (refer to Section B.2.6.1.1 for more details). Six parametric distributions were fitted to the PFS KM curves collected from DREAMM-8 to extrapolate PFS in the economic model. The AIC/BIC statistical goodness of fit for these six distributions is shown in [redacted], in addition to the landmark survival estimates. Extrapolations of PFS using each model up to 20-years are presented in [redacted] to facilitate the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

29

[redacted] 34 [redacted]

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[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]
Generalised 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]

[redacted]

The best statistically fitting model for BPd PFS according to the AIC and BIC criteria is the Gompertz and exponential distribution, respectively [redacted]. Within the observed trial period, all extrapolated parametric models yield similar visual predictions. It is also worth noting that all curves are considered to provide a comparable fit to the data as their AIC scores are within three points of each other (169). Clinicians advised during the expert elicitation exercise that the driving factor for selecting the most appropriate PFS parametric model was the PFS landmark estimate at 5 years, considering the landmark estimates provided by Weibull or exponential models as the most plausible, while other parametric models were considered to provide overly optimistic extrapolations at 10 and 20 years. All clinical experts unanimously selected the Weibull distribution for modelling BPd PFS (4). Hence, considering the clinical expert opinion, the comparable fit provided by all parametric curves, the evolution of empirical hazards and visual assessment, the Weibull distribution is selected to model BPd PFS.

B.3.3.2.2 PVd – Progression-free survival

Median PFS is 12.7 months for PVd (refer to Section B.2.6.1.1 for more details). Using the same approach as BPd, six parametric distributions were fitted to the PFS KM curves from DREAMM-8 to extrapolate PFS in the model. The AIC/BIC statistical goodness of fit for the six distributions are shown in [redacted], in addition to the landmark survival estimates. Extrapolations of PFS using each model up to 20-years are presented in [redacted] to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

[redacted]

[redacted] 35 [redacted]

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[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]
Generalised 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]
TA427	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Based on DREAMM-8 PFS data for PVd, the log-logistic and exponential distributions are the best statistical fits according to AIC and BIC, respectively, although there is little difference between predicted PFS by all models in the first two years. Health economic experts suggested relying on clinical opinion to select most suitable distributions as it was noted that all curves except for Weibull could also be considered to have comparable fit as they are within three points of each other for their AIC scores (169). Similar to the BPd PFS curve, clinicians advised GSK that the driving factor for curve choice was PFS landmark estimate at 5 years, and considered only exponential or Weibull models to provide clinically feasible extrapolations. The majority of clinical experts selected the Weibull distribution for modelling PVd PFS, which provides very close PFS landmark estimates to the exponential model. Based on clinical expert opinion, long-term landmark estimates, and consistency with the curve choice for BPd PFS, a conservative approach is followed and the Weibull model is selected for extrapolation of PVd PFS (4).

In TA427 the Generalised Gamma was selected as the best fitting curve to extrapolate PVd, based on log-cumulative hazard plots, Q-Q plots, visual inspection and AIC and BIC estimates. Although these distributions were considered, they were not applicable for DREAMM-8 PFS curve selection based on expert clinical opinion.

B.3.3.2.3 Other – Progression-free survival

PFS for non-trial comparators is estimated in the model by applying the corresponding HRs from the DREAMM-8 NMA (Section B.2.9) for each comparator, and applying them to the baseline PFS curve in the model. The model has the functionality to apply these HRs versus either PVd (base case) or BPd (scenario). The HRs versus both BPd and PVd are presented in Table 36.

In the base case analysis, the PFS HRs versus PVd are used. PVd was considered to be a more appropriate baseline curve for non-trial comparators as PVd PFS data in DREAMM-8 are more mature than BPd PFS data with 80 (54%) and 60 (40%) patients reaching the endpoint in PVd and BPd trial arms, respectively. Additionally, whilst BPd has a unique anti-BCMA mode of action which is more distinct to non-trial comparators, PVd shares a more comparable hazard profile with the other comparators, making it a more suitable option for the base case. This choice of PVd was also validated by a health economic expert.

[redacted] 36

	Vs BPd (95% CrI) – Base case	Vs PVd (95% CrI) - Scenario
hKd	[redacted]	[redacted]
SVd	[redacted]	[redacted]
DVd	[redacted]	[redacted]

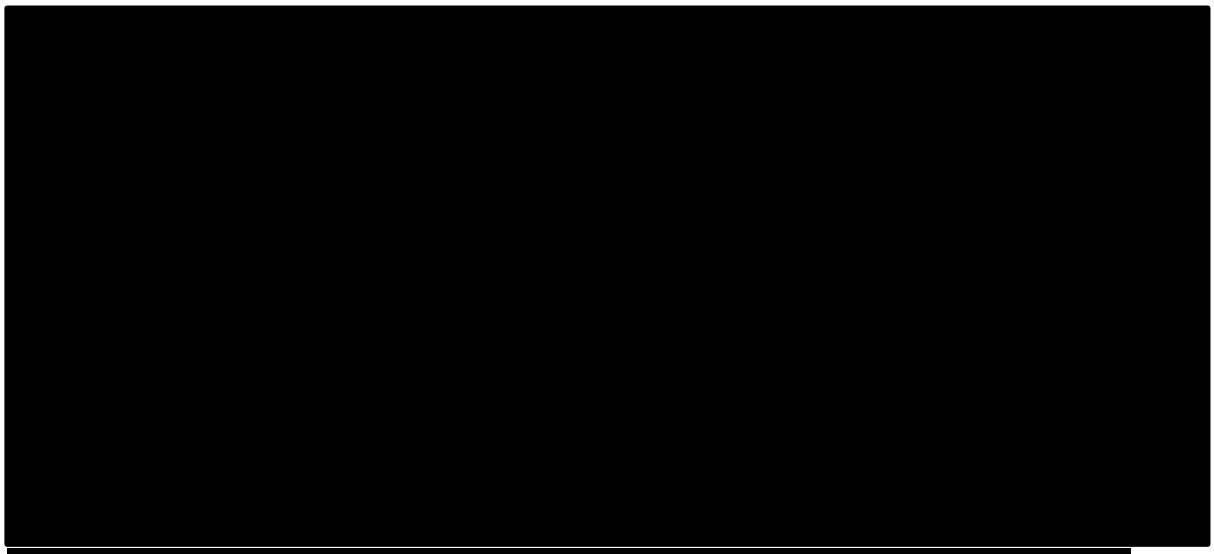
[redacted]

B.3.3.2.4 BPd – Overall survival

The OS was more favourable in the BPd arm vs. the PVd arm. Median OS has not been reached in either treatment arm (refer to Section B.2.6.1.2 for more details).

Six parametric distributions were fitted to the OS KM curves collected from DREAMM-8 to extrapolate OS in the economic model. The AIC/BIC statistical goodness of fit for these six distributions are shown in Table 37, in addition to the landmark survival estimates. Extrapolations of OS using each model up to 20-years are presented in Figure 31 to facilitate the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

[redacted]



[redacted] 37

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[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]
Generalised 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]

[redacted]

Clinicians advised during the expert elicitation exercise that the driving factor for selecting the most appropriate OS parametric model were the landmark estimates at 5, 10 and 20 years. Based on clinical expert opinion, only the exponential and Weibull models provided 5-, 10-, and 20-year extrapolation estimates for BPd OS that were within the clinicians' reported plausible landmark estimate ranges for these time points (4). Additionally, all clinical experts unanimously selected the exponential distribution for modelling BPd OS. Hence, considering the clinical expert opinion, the parametric curve statistical fit, and visual assessment, the exponential distribution has been selected for BPd OS.

Based on the AIC and BIC, exponential is the best statistically fitting curve for BPd OS, however, Weibull, Gompertz, and log-logistic could all be considered comparable as their AIC values are within three points (169). Although these distributions were considered, they were not applicable for DREAMM-8 OS curve selection based on expert clinical opinion.

B.3.3.2.5 PVd – Overall survival

The same approach has been adopted to extrapolate OS data from the PVd arm for DREAMM-8. The AIC/BIC statistical goodness of fit for these six distributions are shown in [redacted], in addition to the landmark survival estimates. Extrapolations of OS using each model up to 20-years is presented in [redacted] to facilitate the investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

[redacted]

[redacted]

[redacted] 38 [redacted]

Distribution	AIC	Rank	BIC	Rank	Median	Years					
	Months					1	2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[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]
Generalised 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]

[redacted]

In TA427, the Generalised Gamma was selected as the best fitting curve to extrapolate PVd, based on log-cumulative hazard plots, Q-Q plots, visual inspection and AIC and BIC estimates (94).

Based on the AIC and BIC, the Gompertz and exponential are the best statistically fitting curves for PVd OS, however all curves could also be considered comparable based on being within three points of the AIC score (169). Nevertheless, Gompertz was not considered as a plausible curve choice because of the flattened tail which results in implausible long-term estimates. Clinicians advised during the expert elicitation exercise that the driving factor for selecting the most appropriate PVd OS parametric model were the landmark estimates at 5, 10 and 20 years. Based on clinical expert opinion, only the exponential model provided 5-, 10-, and 20-year extrapolation estimates for PVd OS that were within their reported plausible landmark estimate ranges for all three time points. Additionally, all clinical experts unanimously selected the exponential distribution for modelling PVd OS. Hence, considering the clinical expert opinion, the parametric curve statistical fit, and visual assessment, the exponential distribution has been also selected for PVd OS (4).

B.3.3.2.6 Other – Overall survival

OS for non-trial comparators is estimated in the model by applying the corresponding HRs from the DREAMM-8 NMA (Section B.2.9) for the key comparators of interest. The model can apply these HRs versus either BPd or PVd, depending on user choice. The HRs versus both BPd and PVd are presented in [redacted].

In the base case analysis, similar to the approach followed for PFS, the OS HRs versus PVd is used in the model (Section B.3.3.2.3). PVd was considered a more appropriate baseline curve for applying OS HRs for non-trial comparators, as PVd OS data in DREAMM-8 are more mature than BPd PFS data, with 56 (38%) and 49 (32%) patients reaching the endpoint in PVd and BPd trial arms, respectively. Additionally, BPd has a unique anti-BCMA mode of action which is more distinct from non-trial comparators, whereas PVd shares a more comparable hazard profile with other comparators. This approach was validated by expert opinion. A scenario analysis was conducted to estimate the impact of applying BPd as the baseline OS curve on the ICER. However, due to the consistent use of the exponential model for BPd OS and PVd OS, this assumption is anticipated to have limited impact on the ICER (Section B.3.3.2.4 and B.3.3.2.5).

[redacted] 39 [redacted]

	Vs BPd (95% CrI)	Vs PVd (95% CrI)
hKd	[redacted]	[redacted]
SVd	[redacted]	[redacted]
DVd	[redacted]	[redacted]

Abbreviations: CrI, credible interval; DVd, Daratumumab plus bortezomib and dexamethasone; hKd, High dose carfilzomib and dexamethasone; HR, Hazard ratio; ITT – Intention-to-treat; NMA, Network meta-analysis; OS, Overall survival; SVd, Selinexor plus bortezomib and dexamethasone.

B.3.3.2.7 BPd – Time to treatment discontinuation

Six parametric distributions have been fitted to the TTD KM curves collected from DREAMM-8 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 [redacted] to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

[redacted] 33 [redacted]

[redacted]

[redacted] 40 [redacted]

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[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]
Generalised 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]

[redacted]

Based on the AIC and BIC, the best statistically fitting curves for BPd TTD are the lognormal and exponential curves, respectively. It is worth noting that the log-logistic, generalised gamma and exponential are also all within 3 AIC points, so they could be considered to provide a similar fit to the data (169).

Based on clinical expert opinion, the Gompertz, log-logistic, and lognormal models provided implausible 10-, and 20-year extrapolation estimates for BPd TTD. Additionally, all clinical experts mentioned that the exponential and Weibull distributions were considered to provide the most clinically plausible extrapolation estimates overall for BPd TTD, while the generalised gamma provided relatively optimistic estimates. The exponential model was the preferred choice for all three clinical experts, although all noted that both exponential and Weibull distributions provide very similar landmark estimates at all time points. Considering the clinical expert opinion, the similarity between exponential and Weibull extrapolation estimates, and consistency for curve selection with PVd TTD (Section B.3.3.2.8), the Weibull model was selected for BPd TTD.

B.3.3.2.8 PVd – Time to treatment discontinuation

Six parametric distributions have been fitted to the TTD KM curves collected from DREAMM-8 to extrapolate TTD in the economic model. The AIC/BIC statistical goodness of fit for these six distributions are shown in Table 41, in addition to the landmark survival estimates. Extrapolations of TTD using each model up to 20-years is presented in [redacted] to facilitate investigation of the visual fit to the observed data and guide the assessment of long-term extrapolation clinical plausibility.

[redacted]

[redacted] 41

Distribution	AIC	Rank	BIC	Rank	Median	Years					
					Months	1	2	5	10	15	20
KM	[redacted]	[redacted]	[redacted]	[redacted]	[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]
Generalised 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]

[redacted]

Based on the AIC and BIC, log-logistic is the best statistically fitting curve for PVd TTD, however, Gompertz could also be considered comparable as it is within three AIC points (169). Based on clinical expert opinion during the expert elicitation exercise, the Gompertz, log-logistic, and lognormal distribution provided implausible extrapolation estimates based on the clinicians' reported landmark estimate ranges. All clinical experts mentioned that the Weibull distribution provides the most plausible extrapolation estimates for PVd TTD, while the exponential and generalised gamma provided relatively pessimistic and optimistic estimates, respectively. All clinicians unanimously concluded that the Weibull distribution is the most appropriate curve choice for modelling PVd TTD. Based on clinical expert opinion, and long-term landmark estimate assessment the Weibull model was selected for PVd TTD.

B.3.3.2.9 Other – Time to treatment discontinuation

As described in Table 32, due to unavailability of publicised data to inform an NMA for TTD, assumptions were made to fit plausible TTD for hKd, SVd and DVd. 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 DREAMM-8 PVd trial arm estimated from the NMA analysis is a plausible estimation of non-trial comparator TTD versus TTD extrapolated from the arms of the trial. In a recent appraisal TA897 a similar approach was taken and agreed with by the EAG (27), while in TA917 the company assumed the second approach listed above (83) 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. Therefore, out of the three scenarios, the most conservative option with regards to comparator TTD was assumed for base-case.

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-8 safety data was used to inform the AEs associated with BPd in the economic model (see Section B.2.10.1). For hKd and SVd, the incidence of AEs were sourced from Usmani 2023 and Bahlis 2018, respectively (170, 171). For DVd, the incidence of AEs were sourced from DREAMM-7 safety data (120).

The AEs included within the base-case CEA for all comparators are presented in Table 42.

Table 42. Incidence of Grade ≥3 adverse events reported in ≥5% of patients in BPd from DREAMM-8 and comparators

Adverse event	BPd	hKd	SVd	DVd
Neutropenia	0.42	0.07	0.19	[redacted]
Anaemia	0.10	0.16	0.04	[redacted]
Thrombocytopenia	0.24	0.16	0.31	0.35
Lymphopenia	[redacted]	0.07	-	[redacted]
Pneumonia	0.17	0.09	-	0.04
Peripheral neuropathy	[redacted]	0.01	-	[redacted]
Hypertension	[redacted]	0.18	-	[redacted]
Fatigue	0.06	0.05	0.23	[redacted]
Keratopathy	[redacted]	-	-	[redacted]
Blurred vision	0.17	-	-	[redacted]
Dry eyes	0.08	-	-	-

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; DVd, daratumumab plus bortezomib, and dexamethasone
Source: Cost-effectiveness model for BPd in a population of 2L+ multiple myeloma (DREAMM-8) (28, 102, 148). DREAMM-7 (172)

The sum product of these incidence rates and disutilities or costs associated with AEs, described in Sections B.3.4.3, were 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 costs were 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 (155).

B.3.4 Measurement and valuation of health effects

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

A SLR was conducted to identify HRQoL studies of patients with MM who have received at least one prior line of therapy. The SLR has been conducted in January

2023 and updated in January 2024, with further update in April 2024. Please see Appendix H for the methods used to identify relevant studies, and detailed description and of identified studies.

Overall, 152 HRQoL publications reporting patient reported outcomes and utility data for RRMM patients with at least one prior treatment are identified. A total of 117 publications reported PRO data, of which three are from a UK perspective, with most of these studies using the EORTC QLQ-C30 questionnaire. A total of 34 publications reported only utility data, of which 13 are from a UK perspective, with most eliciting values from the EQ-5D tool.

Utilities/disutilities are 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 (89, 173). Twelve publications are identified containing both PRO and utility data, of which five are from a UK perspective and used the following questionnaires: EQ-5D, EORTC QLQ-MY20, and EORTC QLQ-C30.

Out of the 152 publications identified in the SLR, two are selected to inform HRQoL in the model. Note that DREAMM-8 health state utility analysis results are not published, and they are not included in the SLR results. The sources selected from the SLR to be included in the model are deemed the most relevant to the decision problem based on population, interventions and recency of publication. TA695 (154) reported pre-progression and post-progression utility values for KRd and Rd. TA897 (27) reported utility values for progression-free survival and post-progression survival for DVd, Vd and Kd. These values are used to inform heath state utility value scenarios in the CEM and are summarised in Table 43. 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 values used is representative of the findings in the data. TA695 (154), TA897 (27) and Brown 2013 (162) all reported adverse events utilities. These adverse event utility decrements are used to inform the CEM base-case.

Table 43. Model health state utility values used in scenario analysis

Source	TA695 (154)	TA897 (27)
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: AE, Adverse event; PD, Progressed disease; PFS, Progression-free survival; TA, Technology appraisal.

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-8. 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 utility data reported in DREAMM-8 were analysed using mixed-effects linear regression, incorporating all available EQ-5D measurements across all visits. 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. 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 resulting disease-specific and treatment-specific utility values associated with the modelled health states are presented in [redacted].

In the base-case, health state utility values were assumed to differ between treatments for the PFS health state. As the DREAMM-8 trial collected utility values for BPd and PVd only, an assumption was made that the utility value in PFS for all relevant comparators was equal to value of PVd. PFS off-treatment utility values are assumed to be the same as on treatment.

[redacted]

Treatment	Utility (95% CI)	Source
PFS (on treatment)	[redacted]	DREAMM-8 (102)
BPd	[redacted]	DREAMM-8 (102)
PVd	[redacted]	DREAMM-8 (102)
hKd	[redacted]	Assumed to be equal to PVd
SVd	[redacted]	Assumed to be equal to PVd
DVd	[redacted]	Assumed to be equal to PVd
PFS (off treatment) **	[redacted]	Assumption **
PD	[redacted]	DREAMM-8 (102)

[redacted]

Abbreviations: BPd, Belamaf plus pomalidomide and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; PD, Progressed disease; PFS, Progression-free-survival; PVd Pomalidomide plus bortezomib and dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone.

Additionally, the base-case model applied age-adjusted utilities, with functionality to exclude these. Age-adjusted utility values were calculated by applying the general population EQ-5D weights published by Hernández Alava et al (2022) (174). Where trial-based utility values exceed the general population age- and sex-adjusted utility values, the age-adjusted utility value were used.

As there are differences amongst the DREAMM-8 utilities, previous TAs and published literature, sensitivity analysis were conducted using values from TA695 (154) and TA897 (27) (see Table 42).

A detailed explanation on sourcing utility values using DREAMM-8 utility data and its interpretation is provided in Appendix N.

B.3.4.3 Adverse events

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

As in TA897 (27) and TA783 (156), AE disutilities were applied in the first model cycle for patients entering the model, under the assumption that AEs are likely to occur very soon after treatment initiation and only require acute care, with the exception of eye-related side effects which are applied in the BPd arm only.

Given the regularity of eye-related side effects in the BPd arm of DREAMM-8, the QoL gathered in the trial are highly likely to account for the HRQoL impact associated with these events. The EQ-5D-3L evidence from DREAMM-8 (section B.2.6.1.7) show a higher QoL profile for BPd than the trial comparator arm PVd. Therefore, for eye-related events the model accounts only for the costs associated with treating eye-related side effects, assuming that their impact on utility is already reflected in the treatment-specific utility values for the PFS health state.

A summary of the AE disutility estimates is presented in Table 45.

Table 45. Adverse events disutilities

Adverse event	Disutility	Source
Neutropenia	0.15	TA695 (154)
Anaemia	0.31	TA695 (154)
Thrombocytopenia	0.31	TA695 (154)
Lymphopenia	0.07	TA897 (27)
Pneumonia	0.19	TA695 (154)
Peripheral neuropathy	0.07	TA897 (27)
Hypertension	0.00	TA695 (154)
Fatigue	0.12	TA695(154)

Abbreviations: CEM, cost-effectiveness model; GSK, GlaxoSmithKline; TA, Technology appraisal
Source: Cost-effectiveness model for BPd in a population of 2L+ multiple myeloma (DREAMM-8) (148)

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 AEs,
- Terminal care costs.

Unit costs were obtained from routinely collected evidence sources, such as NHS reference costs 2021/22 (175) the British National Formulary (BNF) (176-183), and Personal Social Services Research Unit (PSSRU) 2023 (184). 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 in 100 mg vial, which is administered as an IV infusion. In the CEM, a 70 mg formulation is also provided based on cost per mg calculation. The 70mg dose is not yet available in the UK but is expected to become available prior to NICE approval. The list price of belamaf is £[redacted] for the 100 mg vial and the 70 mg vial will be priced at £[redacted], pending confirmation with the Department of Health and Social Care (DHSC). The unit cost of the 100 mg vial is sourced from GSK list price application to the DHSC. As no 70 mg list price is currently available, it is assumed to be 70% of the 100 mg list price based on public statements made by GSK on their intended pricing approach with this dose. A confidential simple PAS discount of [redacted] is provided for belamaf resulting in a PAS price of [redacted] and [redacted] for a 100mg and 70mg belamaf vial, respectively. The drug acquisition cost for BPd is applied every four weeks, in line with the treatment cycle, until treatment discontinuation.

For comparators, the unit size, pack size and cost per pack are sourced from the BNF (177-183). Where multiple unit costs/sizes are available the pack size/dose most aligned to the comparator dosing regimen are selected. 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.

The patent of pomalidomide is due to expire in 2024, and therefore the cost of pomalidomide is likely to reduce in the near future as generic alternatives become available at a lower list price. Based on internal GSK intelligence and the observed price trends for lenalidomide after it became generic, the model inputs and results presented in the following sections assume that the availability of generic pomalidomide will reduce its list price by [redacted].

Unit costs applied for each drug are presented in Table 46.

Table 46. Drug acquisition costs (List)

Drug	Unit size (mg)	Pack size (number of units)	Cost per pack (£)	Unit cost (£)	Source
Belamaf (100mg vial)	100	1	[redacted]	[redacted]	GSK*
Belamaf (70mg vial)	70	1	[redacted]	[redacted]	GSK*
Pomalidomide	4	21	[redacted]	[redacted]	BNF (182)**
Bortezomib	1	1	217.82	217.82	BNF (177)
Dexamethasone	20	10	20	2	BNF (178)
Daratumumab	100	1	360.00	360.00	BNF (179)
Carfilzomib	60	1	1,056.00	1,056.00	BNF (180)
Selinexor	20	8	3,680.00	460.00	BNF (181)

Abbreviations: BNF, British National Formulary; DOF, data on file; GSK, GlaxoSmithKline
Note: *List price has been proposed to the UK Department of Health and Social Care;
**For pomalidomide, a [redacted] price reduction is applied to account for generic alternatives being available in the near future.

B.3.5.1.2 Dosing

The model has functionality to consider various dosing methods for drugs and treatment regimens. For belamaf dosing the model has the following dosing options:

- Dosing based on the label, using RDI to account for dose reductions or delays.
- Dosing based on individual patient data (IPD), without RDI, as IPD dosing is reflective of the doses received by patients including dose reductions and delays.

IPD dosing includes the option to use the actual dose received; or closest SmPC dose.

For other drugs, dosing is based on SmPC label with RDI applied, to account for dose reductions or delays. 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, method of moments (MoM) calculations derive the number of vials need per cycle based on weight or body surface area (BSA). For the base-case, the following settings are applied:

- Belamaf dosing using IPD as per the actual dose received.
- Wastage calculations applied to 100% of administrations.

SmPC aligned dosing for each drug included in the drug acquisition costs are presented in Table 47.

Table 47. Details of treatment administration of BPd and its comparators, based on the Summary of product characteristics (SmPC)

Regimen	Drug	Treatment cycle	Dose
BPd	Belamaf	Treatment cycle 1 (day 1)	2.5mg/kg
		Treatment cycle 2+ (day 1)	1.9mg/kg
	Pomalidomide	All treatment cycles (days 1-21)	4mg
	Dexamethasone	All treatment cycles (days 1, 8, 15, and 22)	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 and 29)	100mg
	Bortezomib	All treatment cycles (days 1, 8, 15 and 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: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; m, metre; mg, milligram; PVd, pomalidomide plus bortezomib and dexamethasone; SmPC, Summary of product characteristics; SVd, selinexor plus bortezomib and dexamethasone

Source: Cost-effectiveness model for BPd in a population of 2L+ multiple myeloma (DREAMM-8) (148)

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 BPd, 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 BPd, given the data availability, individual patient-level data (IPD) was used to track the doses received by patients over time (see Section B.3.5.1.2).

For BPd RDI is sourced from DREAMM-8. For all other comparators, RDI is sourced from publications of the key clinical trials. RDI values are applied by multiplying the RDI by the dose recommended in the administration schedule. RDI values are presented in Table 48.

Table 48. Relative dose intensity

Drug	RDI	Source
Belamaf (100mg vial)	[redacted]	DREAMM-8 CSR (102)
Belamaf (70mg vial)	[redacted]	
Bortezomib	[redacted]	
Dexamethasone*	[redacted]	
Pomalidomide	[redacted]	
Daratumumab	[redacted]	DREAMM-7 CSR (120)
High dose carfilzomib	90.7%	TA695 (154)
Selinexor	78.9%	TA974 (3)
Isatuximab	92.3%	ICARIA-MM (173)

*Dexamethasone RDI is estimated as the average of RDI from BPd and PVd regimens and assumed the same RDI for all comparators.
Abbreviations: CSR, Clinical study report; mg, milligram; RDI, Relative dose intensity

B.3.5.1.3 Belamaf IPD dosing

In the DREAMM-8 trial, clinicians adjusted the dose of belamaf according to the trial protocol, including both dose delays and 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 1.7 mg/kg up to 2.7 mg/kg in 0.1 mg/kg increments in each week of the trial was estimated. Patients receiving higher doses than 2.7 mg/kg and lower doses than 1.7 mg/kg were assumed to have received the closest dose-band (i.e., 1.7 mg/kg and 2.7 mg/kg), but this adjustment was only applied in the few occurrences of these doses (47 total doses throughout the available trial data). The use of these dose-bands enabled the evolution of dose within the trial to be modelled more accurately. Furthermore, this approach also enabled a more accurate estimation of wastage using a methods of moment

(MoM) approach. Dosing was analysed on a weekly basis to enable modelling the schedule changes observed in the trial and was subsequently applied to the extrapolated TTD curve.

Figure 35 illustrates the dose intensity by 6-month time 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 <28 days) divided by 24 weeks (approximately 6 months) times 4 weeks (originally planned dosing schedule). 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. The latter analysis cannot be replicated from the IPD data embedded in the economic model, as the analysis does not track individual patients and serves only as a visual representation of the changing average dose intensity over time, for patients remaining on treatment.

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 embedded in the economic model was therefore directly modelled to account for this time variable trend and more accurately reflect the actual doses of belamaf administered to patients. For comparators treatments, RDI was relatively high (>79%, closely aligning to SmPC dosage) and so time variation of RDI would likely not impact treatment costs.

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Hence, in the base-case, IPD for ITT were used to model the actual belamaf dose received. The IPD provided weekly data 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 percentage of patients receiving each dose as a proportion of the number of patients on treatment is calculated to inform the belamaf acquisition cost per cycle. When the number of patients on belamaf is less than 50, the percentage of patients receiving each dose is calculated using the total number of patients on treatment and the total number of patients receiving each dose in the remaining IPD weeks. This approach was used to extrapolate the dosing after the timepoint where there are less than 50 patients remaining on belamaf. The rationale for this assumption is that the percentage of patients receiving each dose as a proportion of number of patients on treatment may destabilise when the number on treatment is low. The percentage of patients receiving each dose as a proportion of number of patients is stable with 50 patients on treatment, but it becomes increasingly unstable when the number of patients fall below 50. Consequently, using the total number of patients on treatment and the total number of patients receiving each dose in the remaining IPD weeks ensure the percentage of patients receiving each dose is stable.

The belamaf acquisition cost for each dose is calculated using the MoM. 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. The total belamaf acquisition cost per cycle is calculated by summing the belamaf acquisition cost per cycle for all doses (1.7-2.7 mg/kg).

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.3.5.1.4 Wastage

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

For oral treatments, when wastage was not included, the acquisition cost was calculated by multiplying the listed price per capsule (sourced from the BNF) by the exact number of capsules per dose without RDI applied. When wastage was included, the acquisition cost was 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 was not included the acquisition cost was calculated by multiplying the listed price per vial (sourced from the BNF) by the exact number of vials required per dose. When wastage was included, the model used MoM. This used the patients' weight and body surface area from the DREAMM-8 trial (101), and dose to determine the amount of vials required for treatment. For belamaf, the dose was not adjusted by RDI as IPD are used to inform dosing, but for comparators the dose was adjusted by RDI.

The MoM calculation assumed the patients' weight and BSA are distributed according to a lognormal distribution. Therefore, the dose patients receive per cycle was also assumed to follow a log-normal distribution. The cost of vials for each dose was calculated by multiplying the number of whole vials required by the unit cost per vial. For each dose, the cost of vials was weighted by multiplying the cost of vials by the distribution of each dose. The sum of the weighted costs per vial calculated the MoM acquisition cost per administration. An example of the belamaf (2.5 mg/kg dose) MoM calculation using the listed vial price is presented in [redacted].

[redacted]49[redacted]

Dosing (mg)	Distribution (%)	Number of 100 mg vials	Cost (£)
100	25.04	1	[redacted]
200	74.69	2	[redacted]
300	0.28	3	[redacted]
400	0.00	4	[redacted]
500	0.00	5	[redacted]
Unit number of vials per cycle, adjusted with MoM			[redacted]
Costs per cycle adjusted with MoM (£)			[redacted]

Abbreviations: kg, Kilogram; mg, Milligram

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, there was an option to swap between using 100mg vials only or use a combination of 70mg and 100mg vials.

The total treatment cost per cycle was 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 was applied in the first model cycle (i.e., first week) of each treatment cycle, besides BPd where IPD accounts for delays to dosage continuously throughout the model.

B.3.5.1.5 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 the complexity of the infusion.

IV administration complexity is defined as per the Department of Health reference costs and guidance 2011/12 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 (175). Costs of administration are presented in Table 50.

Table 50. Unit cost of administration

Treatment	Admin cost (£)	Source
Subcutaneous administration: Specialist Nursing, Cancer Related, Adult, Face to face	119.00	NHS reference code: N10AF (175)
IV treatment: First administration in a treatment cycle (simple infusion)	286.71	NHS reference code: SB12Z (175)
IV treatment: First administration in a treatment cycle (complex infusion)	353.64	NHS reference code: SB13Z (175)
IV treatment: First administration in a treatment cycle (complex prolonged infusion)	474.94	NHS reference code: SB14Z (175)
IV treatment: Subsequent administrations in a treatment cycle	368.44	NHS reference code: SB15Z (175)
Oral treatment	0.00	Assumed to be 0

Abbreviations: Admin, Administration; IV, Intravenous; NHS, National Health Service.

Administration schedules are sourced from the DREAMM-8 CSR for BPd as well as relevant clinical trials for other comparator regimens. The administration schedules for the intervention regimen and its comparators are presented in Table 51.

Table 51. Administration schedules

Regimen	Drug	Treatment cycle	Treatment cycle duration (days)	Dose	Admin method	Admins per treatment cycle
BPd	Belamaf	Treatment cycle 1 (day 1)	28	2.5mg/kg	IV-Simple	1
		Treatment cycle 2+ (day 1)	28	1.9mg/kg		1
	Pomalidomide	All treatment cycles (days 1-21)	28	4mg	Oral	21
	Dexamethasone	All treatment cycles (days 1, 8, 15 and 22)	28	40mg	Oral	4
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, and 29)	35	100mg	Oral	5
	Bortezomib	All treatment cycles (days 1, 8, 15, and 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
DVd	Daratumumab	Treatment cycles 1-3 (days 1, 8 and 15)	21	16mg/kg	SC	3
		Treatment cycles 4-8 (day 1)	21	16mg/kg	SC	1
		Treatment cycles 9+ (day 1)	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: BPd, Belamaf plus pomalidomide and dexamethasone; DVd, Daratumumab plus bortezomib and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; IV, Intravenous; kg, Kilogram; m, Meter; mg, Milligram; SC, Subcutaneous; SVd, Selinexor plus bortezomib and dexamethasone.

B.3.5.1.6 Drug acquisition and administration summary

A summary of the total acquisition and administration costs used in the model for BPd and comparator treatments is included in Table 52 below, for each combination relevant treatment cycle. As described in Section B.3.5.1.3, IPD is used for belamaf dosing, hence BPd acquisition and administration costs for each treatment cycle are dependent on dose delays and reductions in the IPD.

Table 52. Summary of acquisition and administration costs

Intervention	Treatment cycle	Acquisition cost per treatment cycle (£)	Administration cost per treatment cycle (£)	Total cost per treatment cycle (£)
BPd*	1	[redacted]	[redacted]	[redacted]
	2+ **	[redacted]	[redacted]	[redacted]
hKd	1	10,723.39	2,128.93	12,852.32
	2+	12,909.07	2,128.93	15,038.00
SVd	1	13,834.58	476.02	14,310.59
	2+	13,834.58	476.02	14,310.59
DVd	1	15,788.90	595.02	16,383.91
	2-3	15,788.90	595.02	16,383.91
	4-8	6,816.68	476.02	7,292.70
	9+	4,486.11	119.00	4,605.11

Notes: *Costs presented account for Belamaf PAS price, and pomalidomide anticipated list with a [redacted] price reduction to account for generic alternatives being available in the near future.
**For treatment cycles 2+, costs presented for BPd are the average costs across treatment cycles 2+.
Abbreviations: BPd, Belamaf plus pomalidomide and dexamethasone; DVd, Daratumumab plus bortezomib and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; IPD, Individual patient-level data; SVd, Selinexor plus bortezomib and dexamethasone.

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 paucity of 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 (27, 83). 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 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 is assumed to be a reasonable proxy for the median duration of subsequent treatments, sourced from Kumar et al. (2012) (185) as per TA897 (27). The treatment costs for each subsequent treatment are summarised in Appendix K.

The proportion of patients on BPd who progress and start a subsequent treatment was collected in the DREAMM-8 study. However, results of the study showed that despite an improved PFS and OS observed in DREAMM-8 only [redacted]% of patients in the BPd arm received a first line of subsequent treatment, while the equivalent proportion of patients in the PVd 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) (54) in the base-case, while a scenario was conducted using estimates from Yong (2016) (53). 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 53.

Table 53. Proportion of patients who require subsequent treatment

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

Source: Raab (2019) (54)
Abbreviations: BPd, Belamaf plus pomalidomide and dexamethasone; DVd, Daratumumab plus bortezomib and dexamethasone; hKd – High dose carfilzomib plus dexamethasone; IV, Intravenous; SC, Subcutaneous; SVd, Selinexor plus bortezomib and dexamethasone.

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 (1). Post 2L and 3L subsequent therapies were confirmed with EEs, making sure all subsequent treatments were aligned with NICE approved therapies. Distribution values were adjusted to fit the target population of patients for whom lenalidomide treatment is unsuitable. There was a difficulty highlighted by clinicians in aligning distribution of proportion of patients across different subsequent treatments with NICE approved therapy given limited

treatment options available, and slightly deviating clinical context. Detailed information on subsequent treatments is provided in Appendix M.

B.3.5.2.1 First subsequent treatment

Given the similarity in the responses provided by the three external experts during the clinical validation, GSK have included the average proportion of the subsequent treatments elicited values from the three EEs in the CEM base-case, as these values closely reflect clinician choice among NICE approved therapies, centring the evidence used in the cost-effectiveness analysis on current clinical guidelines (149).

The distributions for first subsequent treatments are presented in Table 54. Note this table presents all available 3L treatments at the time of expert elicitation, but IxaRd and Rd are not viable options for patients for whom lenalidomide is unsuitable.

Table 54. Distribution of first subsequent treatments across treatment arms

Subsequent treatment	Treatment arm			
	BPd	**hKd**	**SVd**	**DVd**
IxaRd	0.0%	0.0%	0.0%	0.0%
PanoVd	33.3%	36.7%	100.0%	36.7%
Rd	0.0%	0.0%	0.0%	0.0%
SVd	66.7%	63.3%	0.0%	63.3%

Source: Clinical validation (4)
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; IxaRd, Ixazomab plus lenalidomide and dexamethasone; hKd, high dose carfilzomib plus dexamethasone; PanoVd, Panobinostat plus bortezomib and dexamethasone; Rd, Lenalidomide plus dexamethasone; SVd, Selinexor plus bortezomib, and dexamethasone

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.

The distributions for second subsequent treatments are presented in Table **55**. Note this table presents all available 4L treatments at the time of expert elicitation, but IxaRd and Rd are not viable options for patients for whom lenalidomide is unsuitable.

Table 55. Distribution of second subsequent treatments across treatment arms

Subsequent arms	Treatment arms			
	BPd	hKd	SVd	DVd
Dara	16.7%	16.7%	16.7%	16.7%
IxaRd	0.0%	0.0%	0.0%	0.0%
Pd	81.1%	81.2%	83.3%	81.2%
PanoVd	2.2%	2.1%	0.0%	2.1%
Rd	0.0%	0.0%	0.0%	0.0%

Source: Clinical validation (4)
Abbreviations: BPd, Belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, High dose carfilzomib and dexamethasone; IxaRd, Ixazomab plus lenalidomide and dexamethasone; PanoVd, Panobinostat plus bortezomib and dexamethasone; Pd, Pomalidomide plus dexamethasone; Rd, Lenalidomide plus dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone.

A summary of one-off subsequent treatment costs applied in the model are presented in Table 56.

Table 56. Summary of subsequent treatment costs

Treatment arm	First subsequent treatment cost (£)	Second subsequent treatment cost (£)
BPd	45,309	[redacted]
hKd	46,969	[redacted]
SVd	78,520	[redacted]
DVd	46,969	[redacted]

Note: Costs presented account for Belamaf PAS price, and pomalidomide anticipated list with a [redacted] price reduction to account for generic alternatives being available in the near future.
Abbreviations: BPd, belamaf plus pomalidomide, and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone
Source: Cost-effectiveness model for BPd in a population of 2L+ multiple myeloma (DREAMM-8) (148)

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 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 BPd treatment arm and were additionally assumed to be required for the first four treatment cycles as per the draft SmPC (10). Considering that all three EE provided similar estimates of HCRU frequency, the average frequency for the use of resource was used in the base case.

Given the commonality of dose delays for the belamaf component of BPd, 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. Therefore, four-weekly resource use estimates for BPd was a conservative assumption for the model base-case. A scenario analysis was therefore conducted in which frequency of symptom management and monitoring resources were sourced from TA897 (27) and were assumed to be equal across all comparators.

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 Unit costs for each resource are derived from NHS reference costs 2021/22 (175). The frequency of healthcare resource utilisation was based on the simple average resource use estimates provided by the three clinical experts, as the estimates provided were well-aligned (Appendix O).

Table 57 below summarises the health state-specific disease management costs per cycle applied in each model cycle for each treatment arm.

Table 57. Costs associated with routine monitoring and management of MM

Healthcare resource	Unit cost (£)	Health state	Resource use per model cycle (per week)				Source
			BPd	hKd	SVd	DVd	
Haematologist visit	209.41	PFS (on treatment)	0.25	0.25	0.25	0.25	NHS code WF01A (175)
		PFS (off treatment)	0.17	0.17	0.17	0.17	
		PD	0.21	0.21	0.21	0.21	
Full blood count	2.96	PFS (on treatment)	0.25	0.50	0.50	0.50	NHS code DAPS05 (175)
		PFS (off treatment)	0.17	0.17	0.17	0.42	
		PD	0.22	0.22	0.22	0.22	
Biochemistry	1.55	PFS (on treatment)	0.25	0.25	0.25	0.25	NHS code DAPS04 (175)
		PFS (off treatment)	0.17	0.17	0.17	0.17	
		PD	0.22	0.22	0.22	0.22	
Protein electrophoresis	1.55	PFS (on treatment)	0.21	0.21	0.21	0.21	NHS code DAPS04 (175)
		PFS (off treatment)	0.17	0.17	0.17	0.17	
		PD	0.21	0.21	0.21	0.21	
Immunoglobin	1.55	PFS (on treatment)	0.21	0.21	0.21	0.21	NHS code DAPS04 (175)
		PFS (off treatment)	0.17	0.17	0.17	0.17	
		PD	0.21	0.21	0.21	0.21	
Serum free light chain	1.55	PFS (on treatment)	0.21	0.21	0.21	0.21	NHS code DAPS04 (175)
		PFS (off treatment)	0.17	0.17	0.17	0.17	
		PD	0.21	0.21	0.21	0.21	
Opthalmologist (belamaf only - 4 Tx cycles)	143.93	PFS (on treatment)	0.33	0.00	0.00	0.00	NHS code WF01A (175)
		PFS (off treatment)	0.00	0.00	0.00	0.00	
		PD	0.00	0.00	0.00	0.00	
Total health state cost (£)		PFS (on treatment)	54.45	55.19	55.19	55.19	-
		PFS (off treatment)	36.43	36.43	36.43	37.17	
		PD	45.60	45.60	45.60	45.60	
		Ophthalmologist cost (applied to first 4 Tx cycles)	47.98	-	-	-	-

Estimates from the clinical validation meeting were used for healthcare resource use (4)

Abbreviations: BPd, Belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; MM, Multiple myeloma; NHS, National Health Service; PD, Progressed disease; PFS, Progression-free survival; SVd, Selinexor plus bortezomib and dexamethasone; Tx, treatment

B.3.5.4 Adverse event costs

The model considers how treatment-related AEs impact the costs and quality of life 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 (27). AE incidence data for BPd are sourced from DREAMM-8. AE incidence data for comparator treatments are sourced from their respective randomised controlled trials (RCTs), as identified in the clinical SLR, and are presented in [redacted], section B.3.3.3.

As AEs have a minor impact on the cost-effectiveness results, a simple naïve comparison of AEs has been 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 are sourced from the NHS reference costs 2021/2022 (175) and are presented in Table 58.

Table 58. 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
Fatigue	824.90

Source: NHS reference costs 2021/2022
Abbreviations: AE, Adverse event

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 BPd arm as a one-off cost. The eye-related side effects considered are keratopathy, blurred vision and dry eyes. Incidence of these AEs is informed by DREAMM-8 (102).

Based on belamaf [ID2701] (186), “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)”. Hence, frequency for resource use associated with eye-related events (i.e., ophthalmologist visits and artificial tear usage) were assumed to be 1 for mild cases, 1 for moderate cases, and 5 for severe cases. The average cost of moderate and severe cost was used to approximate Grade 3+ events (£505.87). This cost was applied as a one-off cost for Grade 3+ events occurring for keratopathy, blurred vision and dry eyes ([redacted]).

Unit 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 59 and Table 60, respectively.

Table 59. Eye-related side-effect incidence

Eye-related side-effect	Grade ≥3 incidence	Source
Keratopathy	[redacted]	DREAMM-8 (102)
Blurred vision	17%	DREAMM-8 (102)
Dry eyes	8%	DREAMM-8 (102)

Abbreviations: AE, Adverse event.

Table 60. Eye-related side-effect unit costs

Eye-related side-effect	Grade ≥3 unit cost (£)	Source
Keratopathy	505.87	NHS code WF01B (175)
Blurred vision	505.87	Cost assumed the same as keratopathy
Dry eyes	505.87	Cost assumed the same as keratopathy

Abbreviations: AE, Adverse event.

In addition, the model included resource use of ophthalmologist directly, once per cycle for the first 4 treatment cycles (BPd arm only – patients on treatment) to account for the recommendation in the SmPC (10). The model therefore accounts for both initial monitoring ophthalmologists visit costs and the cost of keratopathy associated with the management of eye-related side-effects. This approach likely introduces some degree of double counting between these two estimates, as some of these eye-related side-effects are expected to be resolved in initial ophthalmologist monitoring visits. The combined costs are therefore likely to be lower in clinical practice.

A summary of AEs costs is presented in the Table 61 below.

Table 61. Summary of total AE costs

Total AE costs	BPd	hKd	SVd	DVd
One-off costs (£)	1,883.17	1,245.47	1,254.76	1,488.54

Abbreviations: AE, Adverse event; BPd, belamaf plus pomalidomide, and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, high dose carfilzomib and dexamethasone; SVd, Selinexor plus 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 (184).

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) (51) 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) (174). 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 62). No QALY shortfall was reported in TA897, TA974, so a comparison with previous submissions was not completed (Table 63) (3, 27).

Table 62. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to Section in submission
Sex distribution	60% male	B.3.2.2
Starting age	66.1	B.3.2.2

Abbreviations: QALY, quality adjusted life year.

Table 63. 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
hKd	10.63	[redacted]	[redacted]	[redacted]
SVd	10.63	[redacted]	[redacted]	[redacted]
DVd	10.63	[redacted]	[redacted]	[redacted]

Abbreviations: DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; QALY, quality adjusted life year; SVd, selinexor plus 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 individualised. 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 BPd and PVd based on a median follow-up of 21.8 months, there is also uncertainty in the projection of PFS and OS in the longer-term, as well as in the comparative efficacy compared to hKd, SVd, and DVd. A set of methods have been considered within this submission to minimise 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. Clinical expert opinion was sought from three UK based clinical experts to inform assumptions around these model parameters.

Uncertainty around the aforementioned model parameters is explored in Section B.3.11.3 to determine the impact of different scenarios related to these parameters on the cost-effectiveness of BPd for treating with MM, previously treated with one prior LoT (including lenalidomide-containing regimen for at least two consecutive cycles). The limitations associated with these components of the economic evaluation of BPd 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 inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 64.

Table 64. Summary of variables applied in the base-case economic analysis

Parameter	Mean Value	SE	PSA distribution	Reference to location in submission
Model settings				
Cohort size	1	-	-	-
Time horizon (years)	34	-	-	B.3.2.2; B.3.2.4
Age (years)	66	-	-	
Discount rate costs (%)	3.5	-	-	
Discount rate outcomes (%)	3.5	-	-	
Survival inputs				
PFS baseline comparator curve	PVd			B.3.3.2
OS baseline comparator curve	PVd			
OS BPd source of data	Unadjusted			
OS PVd source of data	Unadjusted			
OS extrapolation method	Direct extrapolation			
TTD baseline comparator curve	PVd			
TTD method	Direct extrapolation/hazard ratio			
PFS BPd extrapolation method	Direct extrapolation			
PFS PVd extrapolation method	Direct extrapolation			
OS BPd extrapolation method	Direct extrapolation			
OS PVd extrapolation method	Direct extrapolation			
TTD BPd extrapolation method	Direct extrapolation			
TTD PVd extrapolation method	Direct extrapolation			
BPd - PFS	Weibull			
BPd - OS	Exponential			
BPd - TTD	Weibull			

Parameter	Mean Value	SE	PSA distribution	Reference to location in submission
PVd - PFS	Weibull			
PVd - OS	Exponential			
PVd - TTD	Weibull			
PFS HR - hKd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
PFS HR - SVd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
PFS HR - DVd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
OS HR - hKd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
OS HR - SVd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
OS HR - DVd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
TTD HR - hKd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
TTD HR - SVd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
TTD HR - DVd vs PVd	[redacted]	[redacted]	LOG-NORMAL	
Drug acquisition costs				
BPd Pomalidomide RDI	[redacted]	[redacted]	BETA	B.3.5.1.2; B.3.5.1.6
BPd Dexamethasone RDI	[redacted]	[redacted]	BETA	
hKd cost per treatment cycle 1 (£)	10,723.39	-	-	
hKd cost per treatment cycle 2+ (£)	12,909.07	-	-	
hKd Carfilzomib RDI	91%	0.18	BETA	
hKd Dexamethasone RDI	[redacted]	[redacted]	BETA	
SVd cost per treatment cycle (£)	13,834.58	-	-	
SVd Selinexor RDI	79%	0.16	BETA	
SVd Bortezomib RDI	86%	0.17	BETA	
SVd Dexamethasone RDI	[redacted]	[redacted]	BETA	
DVd cost per treatment cycle 1-3 (£)	15,788.90	-	-	
DVd cost per treatment cycle 4-8 (£)	6,816.68	-	-	
DVd cost per treatment cycle 9+ (£)	4,486.11	-	-	

Parameter	Mean Value	SE	PSA distribution	Reference to location in submission
DVd Daratumumab RDI	[redacted]	[redacted]	BETA	
DVd Bortezomib RDI	[redacted]	[redacted]	BETA	
DVd Dexamethasone RDI	[redacted]	[redacted]	BETA	
Drug administration costs				
Administration cost per treatment cycle with hKd treatment cycle 1 (£)	2,128.93	425.79	GAMMA	B.3.5.1.5
Administration cost per treatment cycle with hKd treatment cycle 2+ (£)	2,128.93	425.79	GAMMA	
Administration cost per treatment cycle with SVd treatment cycle 1 (£)	476.02	95.20	GAMMA	
Administration cost per treatment cycle with SVd treatment cycle 2+ (£)	476.02	95.20	GAMMA	
Administration cost per treatment cycle with DVd treatment cycle 1 (£)	595.02	119.00	GAMMA	
Administration cost per treatment cycle with DVd treatment cycle 2-3 (£)	595.02	119.00	GAMMA	
Administration cost per treatment cycle with DVd treatment cycle 4-8 (£)	476.02	95.20	GAMMA	
Administration cost per treatment cycle with DVd treatment cycle 9+ (£)	119.00	23.80	GAMMA	
Subsequent treatments				
BPd one-off subsequent treatment cost (£)	45,309	9062	GAMMA	B.3.5.2

Parameter	Mean Value	SE	PSA distribution	Reference to location in submission
hKd one-off subsequent treatment cost (£)	46,969	9394	GAMMA	
SVd one-off first subsequent treatment cost (£)	78,520	15704	GAMMA	
DVd one-off first subsequent treatment cost (£)	46,969	9394	GAMMA	
BPd one-off second subsequent treatment cost (£)	[redacted]	[redacted]	GAMMA	
hKd one-off second subsequent treatment cost (£)	[redacted]	[redacted]	GAMMA	
SVd one-off second subsequent treatment cost (£)	[redacted]	[redacted]	GAMMA	
DVd one-off second subsequent treatment cost (£)	[redacted]	[redacted]	GAMMA	
BPd first subsequent treatment, % patients	81%	0.16	BETA	
hKd first subsequent treatment, % patients	81%	0.16	BETA	
SVd first subsequent treatment, % patients	81%	0.16	BETA	
DVd first subsequent treatment, % patients	81%	0.16	BETA	
Second subsequent treatment, % patients	34%	0.07	BETA	
Disease management costs				
BPd PFS on tx disease management total cost (£)	54	11	GAMMA	B.3.5.3
BPd PFS off tx disease management total cost (£)	36	7	GAMMA	

Parameter	Mean Value	SE	PSA distribution	Reference to location in submission
BPd PD disease management total cost (£)	46	9	GAMMA	
BPd PFS on tx disease management - opthalmologist cost (£)	48	10	GAMMA	
hKd PFS on tx disease management total cost (£)	55	11	GAMMA	
hKd PFS off tx disease management total cost (£)	36	7	GAMMA	
hKd PD disease management total cost (£)	46	9	GAMMA	
SVd PFS on tx disease management total cost (£)	55	11	GAMMA	
SVd PFS off tx disease management total cost (£)	36	7	GAMMA	
SVd PD disease management total cost (£)	46	9	GAMMA	
DVd PFS on tx disease management total cost (£)	55	11	GAMMA	
DVd PFS off tx disease management total cost (£)	37	7	GAMMA	
DVd PD disease management total cost (£)	46	9	GAMMA	
AEs costs				
BPd adverse event total cost (£)	1,883.17	376.63	GAMMA	B.3.5.4
hKd adverse event total cost (£)	1,245.47	249.09	GAMMA	
SVd adverse event total cost (£)	1,254.76	250.95	GAMMA	
DVd adverse event total cost (£)	1,488.54	297.71	GAMMA	

Parameter	Mean Value	SE	PSA distribution	Reference to location in submission
Eye-related adverse event total cost (BPd only) (£)	[redacted]	[redacted]	GAMMA	
End of life costs				
End of life cost (£)	12,397.00	2,479.40	GAMMA	B.3.5.5
Quality of life				
Utility: PD	[redacted]	[redacted]	BETA	B.3.4.2
BPd treatment utility	[redacted]	[redacted]	BETA	
hKd treatment utility	[redacted]	[redacted]	BETA	
SVd treatment utility	[redacted]	[redacted]	BETA	
DVd treatment utility	[redacted]	[redacted]	BETA	
BPd adverse event total disutility	0.21	0.04	BETA	B.3.4.3
hKd adverse event total disutility	0.14	0.03	BETA	
SVd adverse event total disutility	0.16	0.03	BETA	
DVd adverse event total disutility	0.18	0.04	BETA	

Abbreviations: AEs, adverse events; BPd, Belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PVd, Pomalidomide plus bortezomib and dexamethasone; RDI, relative dose intensity; SVd, Selinexor plus bortezomib and dexamethasone; TTD, time to treatment discontinuation; Tx, treatment.

B.3.9.2 Assumptions

A summary of modelling assumptions is provided, divided by aspect of the CEM in Table 65.

Table 65. List of assumptions for the base-case cost-effectiveness analysis

Category	Assumption	Justification
Population and comparators	The DREAMM-8 trial is representative of patients with RRMM in the 2L setting in the UK	The clinical trial population for DREAMM-8 assessed belamaf in patients with RRMM, with several clinical trials sites located in the UK.

Category	Assumption	Justification
Comparators	Clinical expert opinion	Only lenalidomide-sparing comparators at 2L are considered given the proposed population of patients with MM who have been previously treated with one prior LoT (including lenalidomide-containing regimen for at least two consecutive cycles).
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 (187).
	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 (156), and this has an impact to treatment and monitoring costs.
	Lifetime horizon of 36 years	The mean age of the population is 66.1 years (based on the mean age in DREAMM-8) therefore a 33.9-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.
	The model looks at the perspective of the NHS & PSS	This is in line with the NICE reference case (187).

Category	Assumption	Justification
Clinical effectiveness	In the absence of TTD data for non-trial comparators, PFS HRs from the NMA applied to PVd TTD are used as a proxy for treatments given until progression.	PFS HRs applied to PVd TTD was determined to be the most conservative assumption to estimate non-trial comparator TTD.
	Grade 3+ AE incidences occurring with <5% in the BPd arm of DREAMM-8 or reported in the pivotal trials of other comparators are not included	Grade 3+ AEs occurring in small amounts of patients (i.e., <5%) are not likely to impact the relative cost-effectiveness of comparator treatments.
Cost and resource use inputs	Belamaf dosing is informed by the actual DREAMM-8 dose received.	Dose delays / interruptions were frequent, to manage 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 BPd treatment that is expected to be reflective in clinical practice.
	RDI is assumed to be constant throughout treatment for all other comparators than BPd.	Dose delays and reductions for all other comparators to BPd in the model were limited (all treatments included in combinations with large cost impact were estimated to have >70 RDI). Limited cost-effectiveness impact is expected from constant RDI methods for daratumumab (DVd) versus IPD usage based on GSK's DREAMM-7 study (188). Paucity of IPD dosage data for other non-trial comparators (i.e., hKd and SVd) means constant RDI assumptions were necessary.
	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) occurring in ≥5% of patients are incorporated as one-off events	AEs are likely to occur very soon after treatment initiation and only require acute care.

Category	Assumption	Justification
	and the impact is attributed to the first cycle of treatment for patients entering the model.	
	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-8 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) (54) in the base-case, while a scenario was conducted using estimates from Yong (2016) (53).
	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 did not present major differences, GSK have included the average subsequent treatments estimates provided by the three clinical experts in the CEM base case, as these values closely reflect clinician choice among NICE approved therapies, centring the evidence used in the base case on current clinical practice.
	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 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 treatments, 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 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 accrue end-of-life care costs before they die and therefore, they are applied within the cycle that patients die in the model death.

Category	Assumption	Justification
Health-related quality of life	EQ-5D utility scores from DREAMM-8, 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-8 clinical trial. The model also includes scenarios with alternative sources for utilities.
	Eye-related side effects QALYs	Eye-related side effects were common in the DREAMM-8 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-state specific utilities are applied in each cycle to the differing health states (PF and PD). PF utility was also assumed to differ between treatments BPd and other comparators (for SVd and hKD utilities were assumed to be equal to PVd from DREAMM-8).	EQ-5D-3L change from baseline data was collected in the DREAMM-8 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, as well as 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: 2L, second-line; AEs, adverse events; BPd; belamaf plus pomalidomide and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; HRs, hazard ratios; HRQoL, Health-related quality of life; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LoT; Line of therapy; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PSM, partitioned survival model; PVd, pomalidomide plus bortezomib and dexamethasone; QALYs, quality0adjusted life years; RDI, relative dose intensity; SVd, Selinexor plus bortezomib and dexamethasone; TTD, time to treatment discontinuation; Tx, treatment; UK, United Kingdom;

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. Given that SVd is only approved by NICE in the 2L population for patient's refractory to both daratumumab and lenalidomide, SVd is not considered a relevant comparator for this subpopulation.
- 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 BPd cannot be compared against DVd (but can be compared against any other approved lenalidomide-sparing regimen, including SVd).

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

DVd eligible subpopulation

Total costs, life years gained (LYG), QALYs, and the incremental cost-effectiveness ratio (ICER) for BPd versus DVd and hKd are presented in Table 66. In the deterministic base case analysis, BPd resulted in the highest average QALYs ([redacted]) (no severity modifier was applied) and LYs (4.67) compared to all other treatments and was a cost saving option compared to other treatments for DVd eligible patients, with average costs of [redacted] over a patient's lifetime. A fully incremental analysis is not presented, as both hKd and DVd were dominated by BPd which was estimated to lead to both health benefits and cost savings. In the assessment of the incremental net health benefit (INHB), the INHB of BPd for a willingness to pay threshold (WTP) threshold of £20,000 per QALY gained versus hKd and DVd is [redacted] and [redacted], respectively, while for a WTP threshold of £30,000 per QALY gained the equivalent INHB is [redacted] and [redacted].

DVd ineligible subpopulation

Total costs, LYG, QALYs, and the ICER for BPd versus hKd and SVd are presented in Table 67. In the base-case, similar to the results of the DVd eligible subpopulation, BPd resulted in the highest average QALYs ([redacted]) (no severity modifier was applied) and LYs (4.67) compared to all other treatments and was a cost saving option compared to other treatments for DVd ineligible patients, with average costs of [redacted] over a patient's lifetime. A fully incremental analysis is not presented, as both hKd and SVd were dominated by BPd which was estimated to lead to both health benefits and cost savings. The INHB of BPd for a WTP threshold of £20,000 per QALY gained versus hKd and SVd is [redacted] and [redacted], respectively, while for a WTP threshold of £30,000 per QALY gained the equivalent INHB is [redacted] and [redacted], respectively.

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

Table 66. DVd eligible subpopulation – Pairwise cost-effectiveness results (PAS vs list, deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)	INHB at £20,000	INHB at £30,000
BPd	[redacted]	4.67	[redacted]	-	-	-	-	-	-
hKd	[redacted]	3.30	[redacted]	[redacted]	1.37	[redacted]	Dominating	[redacted]	[redacted]
DVd	[redacted]	3.84	[redacted]	[redacted]	0.83	[redacted]	Dominating	[redacted]	[redacted]

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

Table 67. DVd ineligible subpopulation – Pairwise cost-effectiveness results (PAS vs list, deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)	INHB at £20,000	INHB at £30,000
BPd	[redacted]	4.67	[redacted]	-	-	-	-	-	-
hKd	[redacted]	3.30	[redacted]	[redacted]	1.37	[redacted]	Dominating	[redacted]	[redacted]
SVd	[redacted]	3.43	[redacted]	[redacted]	1.23	[redacted]	Dominating	[redacted]	[redacted]

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years; SVd, selinexor plus bortezomib and dexamethasone.

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) (189). 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.

Section B.3.9 presents the parametric distributions that were assigned to model parameters, 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 68. The incremental cost-effectiveness plane scatter plot (Figure 36), cost-effectiveness acceptability curve (CEAC) (Figure 37), and cost-effectiveness acceptability frontier (CEAF) (Figure 38) 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 both hKd and DVd being dominated by BPd (no severity modifier applied). A fully incremental analysis is not presented, as both hKd and DVd were dominated by BPd which was estimated to lead to both health benefits and cost savings. The INHB of BPd for a WTP threshold of £20,000 per QALY gained versus

hKd and DVd is [redacted] and [redacted], respectively, while for a WTP threshold of £30,000 per QALY gained the equivalent INHB is [redacted] and [redacted].

The incremental cost-effectiveness plane (Figure 36) demonstrates that in the majority of simulations BPd is more effective and less costly than hKd and DVd. When compared to hKd, [redacted]% and [redacted]% of simulations fall in the SE (i.e., less costly and more effective) and SW quadrant (i.e., less costly and less effective), respectively. When compared to DVd, [redacted]% and [redacted]% of simulations fall in the SE, and SW quadrant, respectively. The CEAC and CEAF show that at a WTP threshold of £30,000 per QALY gained, BPd has a 100% probability of being a cost-effective treatment option (Figure 37, Figure 38).

Table 68. DVd eligible subpopulation – Pairwise cost-effectiveness results (PAS vs list, probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)	INHB at £20,000	INHB at £30,000
BPd	[redacted]	4.72	[redacted]	-	-	-	-	-	-
hKd	[redacted]	3.42	[redacted]	[redacted]	1.30	[redacted]	Dominating	[redacted]	[redacted]
DVd	[redacted]	3.96	[redacted]	[redacted]	0.76	[redacted]	Dominating	[redacted]	[redacted]

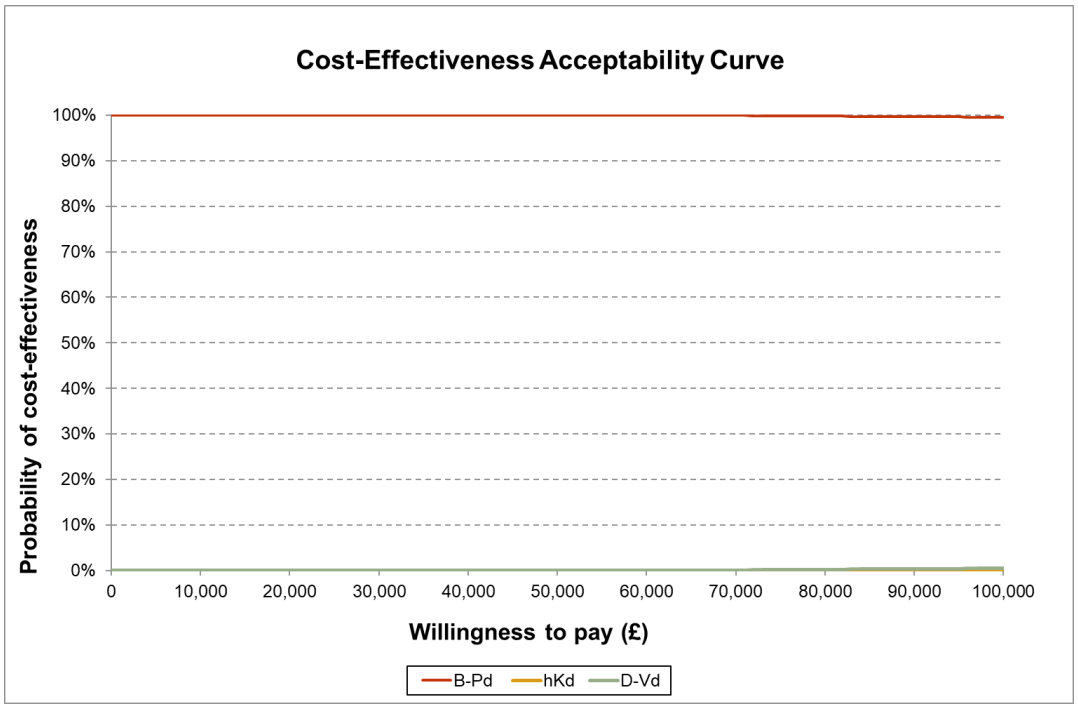
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

36

[redacted]

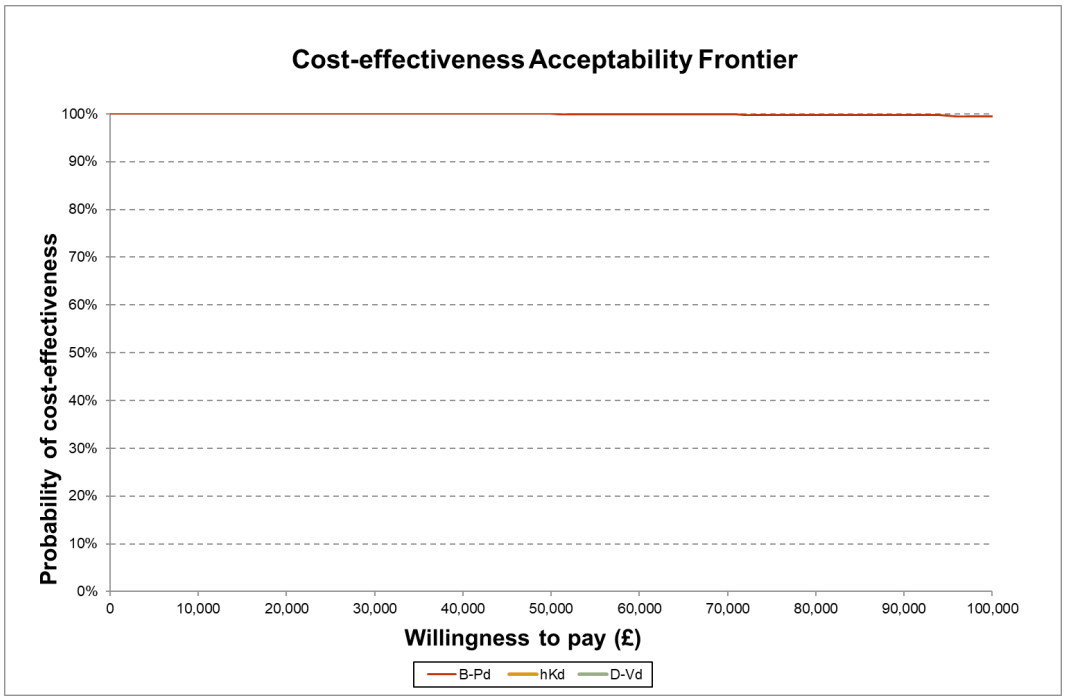
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; WTP, willingness-to-pay.

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



Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone.

Figure 38. DVd eligible subpopulation - Cost-effectiveness acceptability frontier



Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone.

B.3.11.1.2 DVd ineligible subpopulation

Results of the probabilistic analysis for the DVd ineligible subpopulation are presented in tabulated form in Table 69. The incremental cost-effectiveness plane scatter plot (Figure 39), CEAC (Figure 40), and CEAF (Figure 41) were also reported to provide a graphical illustration of the level of variability and uncertainty in the results.

Results of the PSA for the DVd ineligible population were highly consistent with results from the deterministic base-case analysis, with both hKd and SVd being dominated by BPd (no severity modifier applied). A fully incremental analysis is not presented, as both hKd and SVd were dominated by BPd which was estimated to lead to both health benefits and cost savings. The INHB of BPd for a WTP threshold of £20,000 per QALY gained versus hKd and SVd is [redacted] and [redacted], respectively, while for a WTP threshold of £30,000 per QALY gained the equivalent INHB is [redacted] and [redacted].

The incremental cost-effectiveness plane (Figure 39) demonstrates that in the majority of simulations BPd is more effective and less costly than hKd and SVd. When compared to hKd, [redacted]% and [redacted]% of simulations fall in the SE (i.e., less costly and more effective) and SW quadrant (i.e., less costly and less effective), respectively. When compared to SVd, [redacted]% and [redacted]% of simulations fall in the SE, and SW quadrant, respectively. The CEAC and CEAF show that at a WTP threshold of £30,000 per QALY gained, BPd has a 100% probability of being a cost-effective treatment option (Figure 40, Figure 41).

Table 69. DVd ineligible subpopulation – Pairwise cost-effectiveness results (PAS vs list, probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)	INHB at £20,000	INHB at £30,000
BPd	[redacted]	4.72	[redacted]	-	-	-	-	-	-
hKd	[redacted]	3.42	[redacted]	[redacted]	1.30	[redacted]	Dominating	[redacted]	[redacted]
SVd	[redacted]	3.59	[redacted]	[redacted]	1.13	[redacted]	Dominating	[redacted]	[redacted]

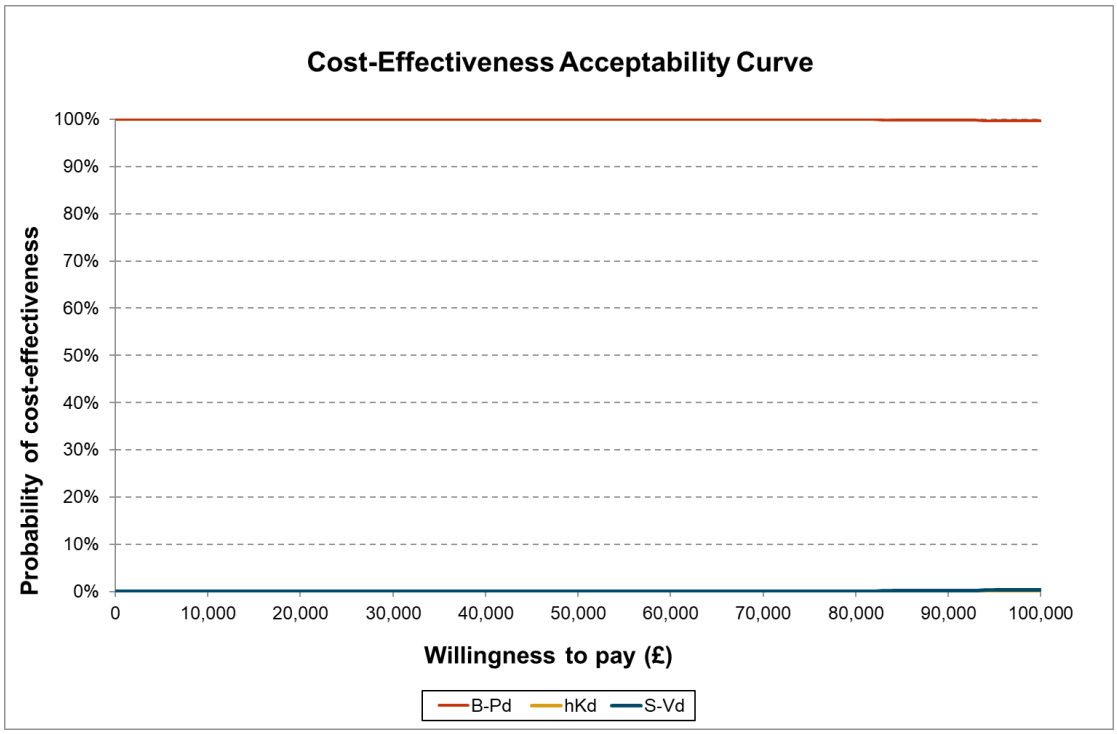
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; LYG, life years gained; QALYs, quality-adjusted life years.

39

[redacted]

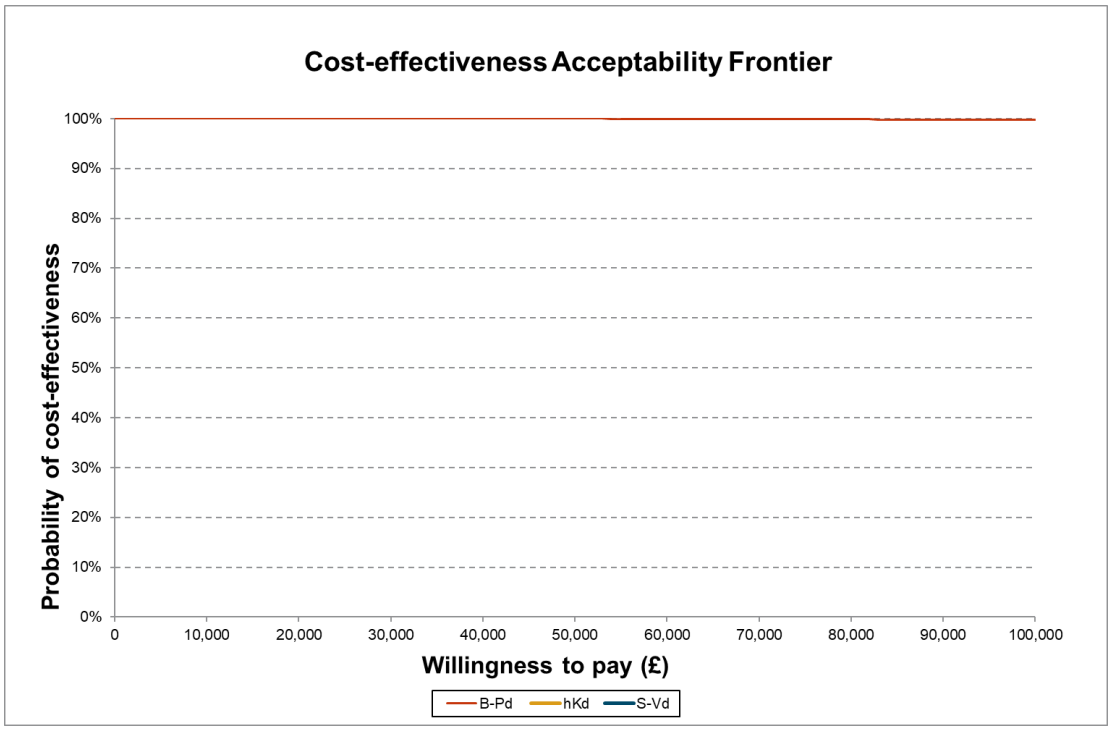
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; SVd, selinexor plus bortezomib and dexamethasone; WTP, willingness-to-pay.

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



Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; SVd, selinexor plus bortezomib and dexamethasone.

Figure 41. DVd ineligible subpopulation - Cost-effectiveness acceptability frontier



Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; SVd, selinexor plus 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 BPd against hKd, SVd, and DVd were developed to graphically present the parameters for variables that have the greatest effect on the incremental net monetary benefit (INMB), at a WTP threshold of £30,000 per QALY gained. The INMB was used as an alternative to the ICER in order to avoid negative or SW ICERs within the OWSA, as all comparators are dominated by BPd in the base case. The top 15 most influential parameters on the ICER from the OWSA for BPd compared with hKd, SVd, and DVd are presented in the form of tornado diagrams in Figure 42, Figure 43, and Figure 44. Results of the OWSA are also presented in tabulated format in Appendix O, Section 6.

Considering the purpose OWSA is to identify the most influential parameters in pairwise comparisons, it was not conducted separately for the DVd eligible and DVd ineligible subpopulations. Results in all three comparisons are most sensitive to the comparator treatment's TTD and OS HR applied to the PVd corresponding curves estimate TTD and OS for each comparator, the RDI for each comparator, and the proportion of patients who receive subsequent treatment as well as the total cost of subsequent treatments. All variations in model parameters resulted in INMBs which indicated that BPd was cost-effective vs. all comparators. Specifically, INMB estimates for all OWSA conducted did not fall below £70,000.

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[redacted]

B.3.11.3 Scenario analysis

A number of scenario analyses was conducted to estimate the impact of structural and model input assumptions on the cost-effectiveness of BPd. The list of scenarios explored in the model, and the corresponding rationale are presented in Table 70. The inputs used for each scenario are presented in Appendix O, Section 7.

Table 70. Scenario analyses explored in the model

Model setting	Base case	Scenario analysis	Rationale
Time horizon	33.9 years	30 years	33.9 years represents lifetime horizon (see Table 31). 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	Baseline comparator curve: PVd (PFS, OS, TTD)	Baseline comparator curve: BPd (PFS, OS, TTD)	In the base case, PFS, OS, and TTD for BPd and PVd treatment arms of the DREAMM-8 trial were modelled independently, because it was not possible to conclusively determine whether the PH assumption holds (Appendix O.2). As described in Section B.3.3.2, the data from the BPd arm and PVd arm of the DREAMM-8 study were used to model the PFS, OS, and TTD curves for BPd and PVd, respectively. The equivalent outcomes for comparator treatments (i.e., hKd, SVd, DVd) were estimated by applying NMA HRs to the PVd baseline curve. To estimate the impact of using PVd PFS, OS, and TTD as baseline curves on the ICERs, a scenario analysis was conducted assuming BPd PFS, OS, and TTD curves as baseline curves.
	BPd PFS curve: Weibull	BPd PFS curve: Generalised Gamma	In the base case, a Weibull distribution is assumed to extrapolate BPd and PVd PFS. In these two scenarios, a generalised gamma distribution is selected to offer a more optimistic view of BPd and PVd PFS over time, as the generalised gamma distribution provided 5- and 10-year landmark estimates close to the EE elicited values.
	PVd PFS curve: Weibull	PVd PFS curve: Generalised Gamma	
	BPd OS curve: Exponential	BPd OS curve: Log-logistic	In the base case, an exponential distribution is assumed to extrapolate BPd OS. In this scenario, a log-logistic distribution is selected to offer a more optimistic view of BPd OS over time, as the log-logistic distribution provided a close fit to the exponential distribution (i.e., AIC difference ≤3), and it provided 5- and 10-year landmark estimates close to the EE elicited values.

Model setting	Base case	Scenario analysis	Rationale
	OS curves using direct extrapolation from parametric model and HRs for comparators (PVd as baseline curve)	OS extrapolated using PFS:OS surrogacy (BPd as baseline curve)	In the base case, OS for BPd was modelled using direct extrapolation in OS from DREAMM-8 trial. For hKd, SVd, and DVd, OS was modelled by applying the NMA OS HRs to the OS PVd curve from DREAMM-8. However, alternative approaches have been explored in scenario analysis. A scenario analysis was conducted in which OS was extrapolated assuming a surrogacy between PFS and OS outcomes (Appendix O.4) using BPd as the baseline curve. HRs (reflecting the surrogacy between PFS and OS) for each comparator are applied to the PFS curve of each comparator to estimate OS for each comparator. In this scenario, BPd PFS curve was used as the baseline treatment curve.
	BPd and PVd OS curves: Exponential – unadjusted for treatment switching	BPd and PVd OS curves: Exponential – adjusted for treatment switching	In the base case, OS curve for BPd and PVd was modelled based on DREAMM-8 with no further adjustments. However, in DREAMM-8, a proportion of patients switched to a subsequent therapy following progression which are not available in the UK treatment pathway or are not yet NICE approved. To improve generalisability of the DREAMM-8 trial to NHS clinical practice, this effect was accounted for, by reweighting trial results to reflect only NICE-approved subsequent treatment pathways. An IPCW analysis has been performed by GSK to understand the true OS benefits of BPd and PVd in DREAMM-8 (Appendix O.3). In this scenario, independent exponential distributions fitted to the IPCW adjusted OS KM data of the BPd and PVd arms from DREAMM-8 were assumed to extrapolate BPd and PVd OS, respectively.
Treatment duration	BPd TTD curve: Weibull	BPd TTD curve: Exponential	In the base case, a Weibull distribution is assumed to extrapolate BPd and PVd TTD. In these two scenarios, an exponential distribution is selected to offer a more pessimistic view of BPd and PVd TTD over time as the exponential model provided very similar landmark estimates to the Weibull model, and it was the recommended choice of curve by EEs for BPd.
	PVd TTD curve: Weibull	PVd TTD curve: Exponential	

Model setting	Base case	Scenario analysis	Rationale
	PFS HRs for hKd/ SVd/DVd applied to PVd TTD using direct extrapolation from parametric model	TTD equal to PFS for hKd, SVd, and DVd	Due to paucity of publicised data to inform an NMA for TTD, PFS HRs for hKd, SVd, and DVd were applied to the PVd TTD curve, based on clinical and health economic expert opinion. This is the most conservative assumption and is consistent with TA897 (27). Two scenario analyses were conducted: - The first assuming that TTD is equal to PFS for hKd, SVd, and DVd which is consistent with TA917 (83) - The second scenario assumed that PVd TTD from DREAMM-8 can be used as a proxy for hKd, SVd, and DVd TTD curves.
		PVd TTD as a proxy for hKd, SVd, and DVd 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-8	IPD off-label dosing: Per SmPC dose	In the base case, belamaf dosing in BPd is based on IPD from the DREAMM-8 trial. The use of IPD-based dosing as per actual dose received in DREAMM-8 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-8, while still accounting for the time-variable trend in RDI observed in DREAMM-8. 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.

Model setting	Base case	Scenario analysis	Rationale
Health care resource use	Clinical experts' opinion (simple average of 3 EE)	Sourced from TA897	Clinical expert opinion was used in the base case analysis to inform the frequency of use of various monitoring and disease management costs (Table 57) in different model health states. In a scenario analysis the impact of informing health care resource use based on TA897 (27) was explored. An assumption was made in this scenario that frequency of use was equal among all treatment arms. Inputs for this scenario are presented in Appendix O.7.1.
Subsequent treatment	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) (54), 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) (54) 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) (53) (Appendix O.7.2).
Utilities		Equal health state utility for all	In the base case utility values for health states were informed from an analysis of EQ-5D-3L collected in DREAMM-8, using a mixed-effects

Model setting	Base case	Scenario analysis	Rationale
	Treatment specific utilities sourced from DREAMM-8	comparators sourced from DREAMM-8	linear regression. The fitted models (adjusted for baseline utility score), demonstrated higher improvement in utility scores in the BPd arm compared to PVd arm patients. Hence treatment-specific health state utilities were used in the base case. BPd treatment-specific utilities were sourced directly from DREAMM-8 while utilities for hKd, SVd, and DVd were assumed to be equal to PVd treatment-specific utilities from DREAMM-8. 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 utilities: 1. In the first scenario utility data from DREAMM-8 were used assuming no differential effect of treatment on health state utilities 2. In the second scenario health state utilities were informed from TA897 3. In the third scenario health state utilities were informed from TA695 Inputs for these scenarios are presented in Appendix O.7.3.
		Health state utility sourced from TA897	
		Health state utility sourced from TA695	
	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-8 EQ-5D-3L data, a scenario is conducted assuming no additional impact of AE on health state utilities.

Abbreviations: AE, adverse event; AIC, Akaike Information Criterion; BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; EE, external experts; hKd, high-dose carfilzomib and dexamethasone; HR, hazard ratio; HTA, Health Technology Assessment; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; OS, overall survival; PH, proportional hazards; PFS, progression-free survival; PVd, pomalidomide plus bortezomib and dexamethasone; 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: BPd vs hKd

The results of the scenario analyses with BPd discounted price for BPd vs. hKd are presented in Table 71.

Table 71. Scenario analyses: ICERs for BPd vs. hKd (BPd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Base Case	[redacted]	[redacted]	**Dominating**	**0 (NMB = [redacted])**
Time horizon: 30 years	[redacted]	[redacted]	Dominating	[redacted]
Time horizon: 20 years	[redacted]	[redacted]	Dominating	[redacted]
Discount rates for costs and outcomes: 0%	[redacted]	[redacted]	Dominating	[redacted]
Discount rates for costs and outcomes: 6%	[redacted]	[redacted]	Dominating	[redacted]
Baseline comparator curve: BPd (PFS, OS, TTD)	[redacted]	[redacted]	Dominating	[redacted]
BPd PFS curve: Generalised gamma	[redacted]	[redacted]	Dominating	[redacted]
PVd PFS curve: Generalised gamma	[redacted]	[redacted]	Dominating	[redacted]
BPd OS curve: Log-logistic	[redacted]	[redacted]	Dominating	[redacted]
OS extrapolated using PFS:OS surrogacy (BPd baseline curve)	[redacted]	[redacted]	Dominating	[redacted]
BPd and PVd OS curves: Exponential – adjusted for treatment switching	[redacted]	[redacted]	Dominating	[redacted]
BPd TTD curve: Exponential	[redacted]	[redacted]	Dominating	[redacted]
PVd TTD curve: Exponential	[redacted]	[redacted]	Dominating	[redacted]
TTD equal to PFS for hKd, SVd, and DVd	[redacted]	[redacted]	Dominating	[redacted]
PVd TTD as a proxy for hKd, SVd, and DVd TTD	[redacted]	[redacted]	Dominating	[redacted]

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
No wastage costs included	[redacted]	[redacted]	Dominating	[redacted]
IPD off-label dosing: Per SmPC dose	[redacted]	[redacted]	Dominating	[redacted]
HCRU sourced from TA897	[redacted]	[redacted]	Dominating	[redacted]
Application of subsequent Tx costs: First cycle	[redacted]	[redacted]	Dominating	[redacted]
Source for % of patients continuing to subsequent Tx lines: Yong et al. 2016 (53)	[redacted]	[redacted]	Dominating	[redacted]
Equal health state utility for all comparators sourced from DREAMM-8	[redacted]	[redacted]	Dominating	[redacted]
Health state utility sourced from TA897	[redacted]	[redacted]	Dominating	[redacted]
Health state utility sourced from TA695	[redacted]	[redacted]	Dominating	[redacted]
AE disutilities not included	[redacted]	[redacted]	Dominating	[redacted]

Note: *NMB values were calculated based on a WTP threshold of £30,000/QALY gained.
Abbreviations: AE, adverse event; BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; HCRU, healthcare resource utilisation; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; IPD, individual patient data; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PVd, pomalidomide plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics.

B.3.11.3.2 Scenario results: BPd vs SVd

The results of the scenario analyses with BPd discounted price for BPd vs. SVd are presented in Table 72.

Table 72. Scenario analyses: ICERs for BPd vs. SVd (BPd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Base Case	[redacted]	[redacted]	**Dominating**	**0 (NMB = [redacted])**

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Time horizon: 30 years	[redacted]	[redacted]	Dominating	[redacted]
Time horizon: 20 years	[redacted]	[redacted]	Dominating	[redacted]
Discount rates for costs and outcomes: 0%	[redacted]	[redacted]	Dominating	[redacted]
Discount rates for costs and outcomes: 6%	[redacted]	[redacted]	Dominating	[redacted]
Baseline comparator curve: BPd (PFS, OS, TTD)	[redacted]	[redacted]	Dominating	[redacted]
BPd PFS curve: Generalised gamma	[redacted]	[redacted]	Dominating	[redacted]
PVd PFS curve: Generalised gamma	[redacted]	[redacted]	Dominating	[redacted]
BPd OS curve: Log-logistic	[redacted]	[redacted]	Dominating	[redacted]
OS extrapolated using PFS:OS surrogacy (BPd baseline curve)	[redacted]	[redacted]	Dominating	[redacted]
BPd and PVd OS curves: Exponential – adjusted for treatment switching	[redacted]	[redacted]	Dominating	[redacted]
BPd TTD curve: Exponential	[redacted]	[redacted]	Dominating	[redacted]
PVd TTD curve: Exponential	[redacted]	[redacted]	Dominating	[redacted]
TTD equal to PFS for hKd, SVd, and DVd	[redacted]	[redacted]	Dominating	[redacted]
PVd TTD as a proxy for hKd, SVd, and DVd TTD	[redacted]	[redacted]	Dominating	[redacted]
No wastage costs included	[redacted]	[redacted]	Dominating	[redacted]
IPD off-label dosing: Per SmPC dose	[redacted]	[redacted]	Dominating	[redacted]
HCRU sourced from TA897	[redacted]	[redacted]	Dominating	[redacted]
Application of subsequent Tx costs: First cycle	[redacted]	[redacted]	Dominating	[redacted]
Source for % of patients continuing to subsequent Tx lines: Yong et al. 2016 (53)	[redacted]	[redacted]	Dominating	[redacted]

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Equal health state utility for all comparators sourced from DREAMM-8	[redacted]	[redacted]	Dominating	[redacted]
Health state utility sourced from TA897	[redacted]	[redacted]	Dominating	[redacted]
Health state utility sourced from TA695	[redacted]	[redacted]	Dominating	[redacted]
AE disutilities not included	[redacted]	[redacted]	Dominating	[redacted]

Note: *NMB values were calculated based on a WTP threshold of £30,000/QALY gained.
Abbreviations: AE, adverse event; BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; HCRU, healthcare resource utilisation; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; IPD, individual patient data; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PVd, pomalidomide plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics.

B.3.11.3.3 Scenario results: BPd vs DVd

The results of the scenario analyses with BPd discounted price for BPd vs. DVd are presented in Table 73.

Table 73. Scenario analyses: ICERs for BPd vs. DVd (BPd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Base Case	[redacted]	[redacted]	Dominating	**0 (NMB = [redacted])**
Time horizon: 30 years	[redacted]	[redacted]	Dominating	[redacted]
Time horizon: 20 years	[redacted]	[redacted]	Dominating	[redacted]
Discount rates for costs and outcomes: 0%	[redacted]	[redacted]	Dominating	[redacted]
Discount rates for costs and outcomes: 6%	[redacted]	[redacted]	Dominating	[redacted]
Baseline comparator curve: BPd (PFS, OS, TTD)	[redacted]	[redacted]	Dominating	[redacted]
BPd PFS curve: Generalised gamma	[redacted]	[redacted]	Dominating	[redacted]

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
PVd PFS curve: Generalised gamma	[redacted]	[redacted]	Dominating	[redacted]
BPd OS curve: Log-logistic	[redacted]	[redacted]	Dominating	[redacted]
OS extrapolated using PFS:OS surrogacy (BPd baseline curve)	[redacted]	[redacted]	Dominating	[redacted]
BPd and PVd OS curves: Exponential – adjusted for treatment switching	[redacted]	[redacted]	Dominating	[redacted]
BPd TTD curve: Exponential	[redacted]	[redacted]	Dominating	[redacted]
PVd TTD curve: Exponential	[redacted]	[redacted]	Dominating	[redacted]
TTD equal to PFS for hKd, SVd, and DVd	[redacted]	[redacted]	Dominating	[redacted]
PVd TTD as a proxy for hKd, SVd, and DVd TTD	[redacted]	[redacted]	Dominating	[redacted]
No wastage costs included	[redacted]	[redacted]	Dominating	[redacted]
IPD off-label dosing: Per SmPC dose	[redacted]	[redacted]	Dominating	[redacted]
HCRU sourced from TA897	[redacted]	[redacted]	Dominating	[redacted]
Application of subsequent Tx costs: First cycle	[redacted]	[redacted]	Dominating	[redacted]
Source for % of patients continuing to subsequent Tx lines: Yong et al. 2016 (53)	[redacted]	[redacted]	Dominating	[redacted]
Equal health state utility for all comparators sourced from DREAMM-8	[redacted]	[redacted]	Dominating	[redacted]
Health state utility sourced from TA897	[redacted]	[redacted]	Dominating	[redacted]
Health state utility sourced from TA695	[redacted]	[redacted]	Dominating	[redacted]
AE disutilities not included	[redacted]	[redacted]	Dominating	[redacted]

Note: *NMB values were calculated based on a WTP threshold of £30,000/QALY gained.
Abbreviations: AE, adverse event; BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; HCRU, healthcare resource utilisation; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; IPD, individual patient data; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PVd, pomalidomide plus bortezomib and dexamethasone; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics.

B.3.11.3.4 Scenario analyses conclusions

Results of the scenario analyses using the PAS price of BPd demonstrate that the CE conclusions remain consistent with the base case despite variations to the analytical specifications and assumptions. BPd remained dominant under all scenarios versus hKd, SVd, and DVd. The results versus all comparators were most sensitive to changes in treatment acquisition costs from scenarios using PVd TTD as a proxy for comparator TTD, or assuming that TTD is equivalent to PFS for comparators. Modelling OS using the PFS:OS surrogacy relationship, had a large increase in INMB versus hKd and SVd, however alternative survival assumptions had a relatively little effect on the CE for all comparators. The subsequent treatment assumptions also had a non-trivial impact on the results, however, the distribution of the ICERs from these scenarios shows the base case is cost-effective under more conservative assumptions. In conclusion, none of the scenarios had an impact on the CE conclusions of the analysis.

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 (83). Therefore, most patients entering 2L today will be eligible for daratumumab, and therefore 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 BPd 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 BPd will gradually drop over time.

The benefit of the pomalidomide-dexamethasone combinations (Pd backbone), providing clinical and patient choice and flexibility is not captured in the QALY calculation due to inherent limitation in capturing patient preferences in partitioned survival modelling approaches. During 1:1 interviews, EE noted Pd backbone offers several advantages. A Pd backbone is typically administered orally, reducing frequency of hospital visits and offering flexibility to patients. It is well tolerated with a manageable side effect profile, suitable for elderly patients, as it offers an alternative to bortezomib-dexamethasone combinations (Vd backbone) and may improve efficacy by having it available at an earlier line of treatment (4).

Finally, an indirect benefit of offering BPd 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 notes that in principle the ‘option

value' of the choice between BVd and BPd could be simulated by estimating the number of patients who would counterfactually do better on BPd than BVd and then reducing this value by taking an estimate of how accurately clinicians can assign patients to the correct treatment. This necessarily results in an improved cost-effectiveness versus the results presented in this dossier (provided clinicians can assign patients to treatment better than chance)

GSK notes that accepting this benefit in the case of BPd would not set precedent, as it is highly unusual for NICE to be assessing two indications for the same treatment (with different backbones) at the same time.

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. 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.

B.3.14 Validation of cost-effectiveness analysis

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 (190, 191). 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 8.

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 July 2024 (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 due to the complex treatment pathways that require clinical judgment for selecting and sequencing specific treatments. Unlike at the 1L, where a well-defined SoC has emerged, patient entering the 2L are faced with limited options and limited scope for long PFS. This challenge is exacerbated in patients for whom lenalidomide is an unsuitable treatment (which GSK expects to be most of patients at 2L). 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 is to access medications with new and effective mechanisms of action (MoAs) to enhance the ability to find an optimal treatment pathway through the disease stages. In this sense, interpretation of the economic evidence should also include consideration of rewarding innovative new MoAs like belamaf.

The DREAMM-8 trial evaluated the efficacy and safety or BPd compared to a EU 2L SoC and EHA-ESMO recommended regimen PVd for the treatment of adult RRMM patients. Findings from the trial were consistent across all endpoints and subgroups, including patients with lenalidomide-refractory or high-risk cytogenic MM. Given that PVd is not recommended by the NHS, a robust NMA was conducted to indirectly compare BPd with NHS-recommended treatments DVd, hKd, and SVd. The NMA was conducted according to DSU gold standard methodologies previously accepted in recent MM NICE HTAs, driven by a recently performed SLR. External clinical advice was sought to drive the comparators to be included and validate key assumptions (Appendix M). All relevant comparators, costs and outcomes required to assess the cost-effectiveness of BPd 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 minimise the risk to BPd cost-effectiveness. Uncertainty in extrapolation of the immature DREAMM-8 OS data was managed through clinician validation, statistical analysis, 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 BPd

cost-effectiveness. An IPCW analysis to adjust the DREAMM-8 OS data for NHS-aligned subsequent treatments further strengthened BPd OS outcomes compared to PVd (Appendix O).

Belamaf has 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 dosage sourced directly from DREAMM-8 IPD. The extrapolation of this analysis is conservative, assuming dosage trends do not continue on a downwards gradient where data is limited.

The base-case results for the CEA compares BPd to hKd and DVd for the DVd eligible population and hKd and SVd for the DVd ineligible population. As described in Section B.1.3.2, it is likely that over time 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, those eligible for and ineligible for DVd, which differ only by their relevant comparators. Both analyses indicate that BPd (PAS) is a cost-effective treatment option for these two subpopulations, dominating comparators in both groups i.e., increased health benefits and cost savings.

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

In general, the DREAMM-8 trial efficacy results demonstrate that belamaf in combination represents a ‘step change’ for MM community. Section B.2 describes how BPd reduces the risk of progression or death by nearly 50% and achieves a complete response rate (CRR) that is more than double that of PVd. Section B.3 demonstrates that the anticipated increase in life years and QALYs can be delivered in a cost-efficient manner, representing the optimal use of NHS resources. The economic analysis presented provides robust evidence of the cost-effectiveness of approving BPd to address the high unmet need in 2L treatment for patients for whom lenalidomide is unsuitable. This analysis shows that BPd is likely to be more cost-effective than all comparators it might replace. Furthermore, introducing a medication with a new MoA like belamaf could benefit the entire MM pathway by increasing the availability of treatments in subsequent lines, although this benefit is challenging to quantify 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 belamaf in combination as the new SoC at first relapse for patients who were exposed of refractory to lenalidomide. Should BPd be approved for routine commissioning, it has the potential to redefine the NICE treatment paradigm, offering new hope for patients and their families in the UK.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

Summary of Information for Patients (SIP)

August 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
ID6211 Belantamab mafodotin with pomalidomide and dexamethasone Summary of Information for Patients v1.0 7August2024.docx	**V1.0**	**No**	**07 August, 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 are adult patients diagnosed with multiple myeloma (MM) who have either had the disease come back after a period of improvement (relapsed) or did not respond to the first therapy tried (resistant). When a patient can no longer have a certain treatment it is said that the myeloma is 'refractory' or 'resistant' to that treatment. The same treatment will not be offered to a patient because it is very unlikely to work in the second line (2L). In this submission, the first therapy (prior therapy) must include lenalidomide. 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 pomalidomide and dexamethasone. This is a common approach which is taken in the treatment of myeloma as it is known that combining treatments can lead to better outcomes. The combination treatment will be referred to as BPd 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:

BPd does not yet have a license for use in the population in this submission. The regulatory submission for DREAMM-8 was made in July 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 several 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:

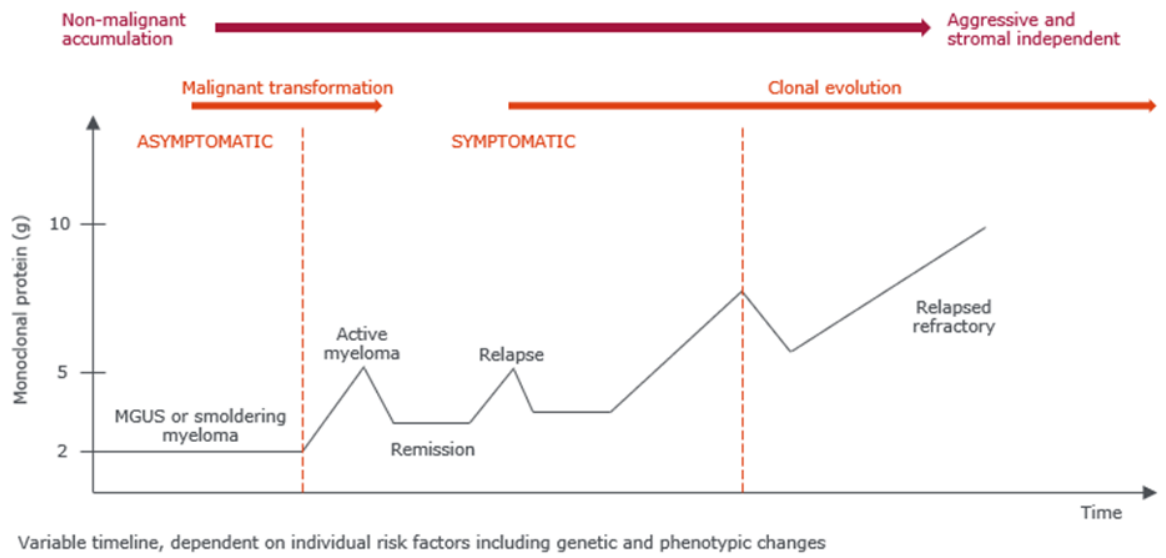
Multiple myeloma (MM) is a rare and debilitating condition caused by an abnormality in the cells of the bone marrow, called plasma cells (abnormal plasma cells are myeloma cells) [1]. Normally, these cells help fight infections, but in the case of MM, they grow uncontrollably and cause harm to the patient [1]. We do not know why plasma cells sometimes turn into myeloma cells [2].

MM makes up about 2% of all new cancer cases, with an estimated 4,660 new cases of MM in the UK each year, and causes approximately 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:** Patient with MM are at risk of having a low number of red blood cells (anaemia). This can cause extreme tiredness, weakness, and shortness of breath. This reason for this is that too many myeloma cells crowd the bone marrow, making it hard for body to produce enough red blood cell that carry oxygen around the body.
- **Persistent infection:** Myeloma patients are more likely to get infections, and these infections can last longer than usual. This happens because there are not enough healthy white blood cells to fight infection. The myeloma cell crowding the bone marrow makes it difficult for the body to produce important infection fighting cells.
- **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. If the myeloma affects the spine, it can compress the spinal bones and nerves, which send information from the hands and feet to the brain. This can cause nerve damage, leading to tingling in the hands and feet and sometimes more serious issues. Unfortunately, these symptoms can be extremely painful.
- **Kidney damage:** The weakening of the bones can change the balance of chemistry in your blood. Bones contain calcium, and your body needs a certain amount of calcium to remain healthy. However, when small pieces of bone break off into the blood stream due to myeloma bone disease, too much calcium can enter the bloodstream. This excess calcium can be very harmful because it overworks the kidneys, which are responsible for processing calcium. This can be dangerous, especially since some of the medications used to treat myeloma are also processed in the kidneys, putting extra strain on them.

Unfortunately, there is no current cure for MM. There are multiple effective treatment available, but over time, the cancerous cells will change (mutate) and become resistant to these treatments [4]. The patient journey of MM 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 Kurtin et al. [5].
Abbreviations: MGUS, monoclonal gammopathy of undetermined insignificance.

Treatment for MM is therefore very complicated, and the options available to patients depends on the treatments they have already tried and found that they are no longer effective (that they have relapsed on). In this submission, BPd is expected to be used by patients at second line (2L) of treatment for relapsed or resistant multiple myeloma (RRMM). This is especially relevant in patients for whom lenalidomide is not a suitable option.

These patients have already received one line of treatment that included lenalidomide and are unsuitable to be treated with any therapy that contains lenalidomide after this because:

- the myeloma has does not respond to (resistant to) lenalidomide, or
- their doctor believes lenalidomide is not a good choice (for example, due to severe skin reactions or unpredictable kidney function).

There are limited options for this group of patients and data suggests that their outcomes are poor (see section 2c for more information). For these patients with poor outcomes, BPd offers a new treatment which has the chance of working and 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 challenging because of how rare it is. Most General Practitioners (GP) do not see it often- on average a GP will see one new case of MM every 8-10 years [6]. Furthermore, the symptoms are often vague and can be mistaken for other conditions, making it harder to identify.

In general, when MM is suspected, a blood or urine test can be used to identify it. This is because the myeloma cells produce a large amount of non-functioning protein (known as 'paraprotein' or 'M protein') [1]. Finding this paraprotein in the blood or urine is a sign that there are myeloma cells in the body.

This is not always perfectly accurate for diagnosing MM because there are non-cancerous (benign) conditions like Monoclonal Gammopathy of Undetermined Significance (MGUS), that can also produce paraprotein[7]. While MGUS can sometimes turn into MM, this is quite rare [7]. Therefore, doctors often order more tests to determine whether the paraprotein is caused by MM (which needs treatment) or a benign condition like MGUS (which doesn't need treatment).

These additional tests might include an x-ray to check for bone damage, which is common in MM but very rare in MGUS, or taking a sample of bone marrow to look for myeloma cells under a microscope. However, these are not the only tests you may be offered. Besides diagnosing myeloma, patients may also be offered tests to identify the most appropriate treatment.

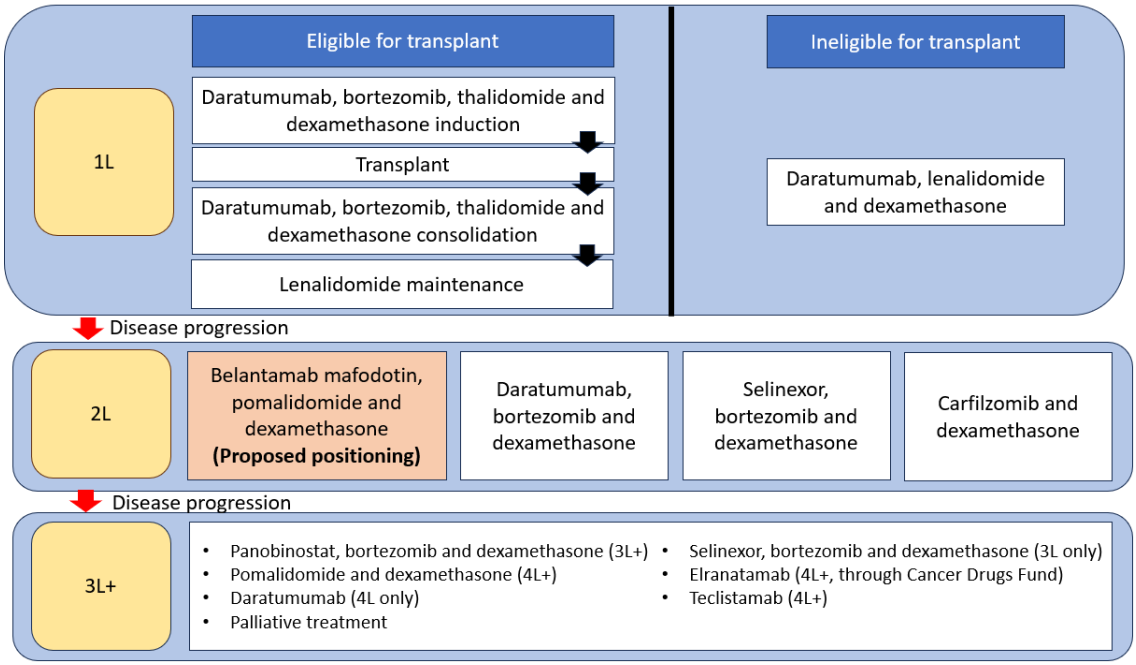
2c) Current treatment options:

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 BPd in the 2L (second line, where patients have received one prior therapy containing lenalidomide). 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 few 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:

First line (1L) treatment

- 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 first line (1L) 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 destroy 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.

Second line (2L) treatment

- If the disease comes back despite the 1L treatment, patients will usually then receive more treatment called the second line of treatment (2L). A combination of three drugs is usually recommended over two drugs, although some patients who are too frail may receive only two drugs.

- NICE currently recommends six treatment regimens for 2L RRMM patients, of which only three are a combination of three drugs. If a patient did not have lenalidomide in their first line treatment, they may benefit from carfilzomib plus lenalidomide and dexamethasone (KRd) or Rd for their 2L treatment. However, since lenalidomide is very often used in 1L treatment and patients will have to stop responding to those treatment to need a 2L treatment, these two regimens are not helpful.
- In the UK, 2L treatment choices that do not use lenalidomide are 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 as clinicians almost always prefer to give a combination therapy if one is available). This leaves Kd, DVd and SVd as options but they do not work well in patients that do not respond to lenalidomide in 1L.

Third line onwards (3L+) treatment

- If the disease come back again 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 a 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 serious disease that significantly impact the lives of those who have it. Compared to people without myeloma, patients often find that the disease greatly affects their physical abilities and social activities [13]. Since myeloma is progressive, patients also report that symptoms get worse over time[14], highlighting importance of treatments that not only address the disease but also help maintain a good quality of life.

Besides physical symptoms, MM also has a mental health impact. For example, learning that MM has come back (relapsed) can be very difficult to process and can lead to a decline in mental health well-being [15]. The symptoms of MM can also make it hard for a person to work[15], resulting in financial worry about having to stop working or reduce their income [16].

Caregivers, who are often close family members, are also affected by MM. They may feel emotional burden due to concerns of the patient's suffering and the possibility of death [17]. The responsibilities 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.

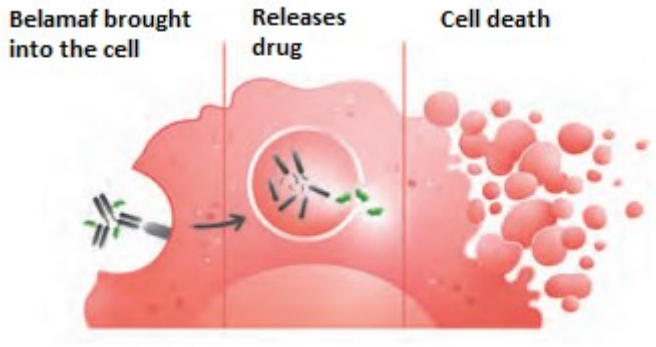
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

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.

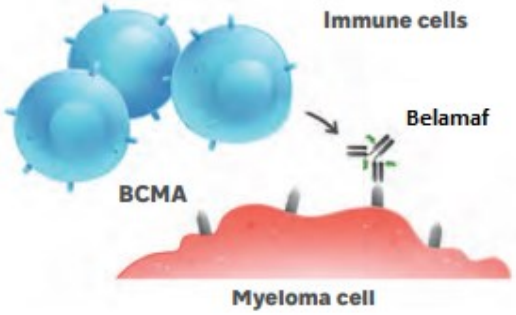
Belamaf therefore works in two ways:

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 an innovative treatment because it is the first antibody-drug conjugate that targets BCMA for patients with RRMM. Other treatments work in different ways, so when the disease change and no longer responds to a treatment (becomes resistant), it may still respond to belamaf. Its novel mechanism of action addresses the unmet need arising in RRMM patients at 2L, who have already received lenalidomide and may have limited options.

Belamaf would provide a valuable treatment option for RRMM patients, including those patients that are not suitable for lenalidomide at their 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 pomalidomide, and dexamethasone. In RRMM, the combination of Belamaf with pomalidomide and dexamethasone can improve 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].

Pomalidomide, also known as Imnovid®, is an immunomodulatory drug (IMiD) used in the treatment of myeloma [20]. Pomalidomide works by affecting the body's immune system. It helps to kill myeloma cells in several different ways:

- Directly killing or stopping the growth of myeloma cells
- Blocking the formation of new blood vessels that myeloma cells need to grow
- Boosting the immune response against the myeloma cells
- Altering the production of chemical messages involved in the growth and survival of the myeloma cells

Pomalidomide is a capsule which is taken orally (by mouth) [20].

Dexamethasone is a steroid drug used in the treatment of myeloma [21]. It belongs to a group of steroids called glucocorticoids and works by mimicking naturally occurring hormones in the body. Dexamethasone is effective at killing myeloma cells and can make other anti-myeloma drugs work better. Additionally, it can also prevent inflammation which can help to reduce pain associated with myeloma bone disease.

Dexamethasone can be given as a tablet or intravenously (into a vein). Usually, it is given as a tablet for the treatment of myeloma [21].

Please see section 3g for information relating to possible side effects with belamaf in combination with pomalidomide 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 an intravenous (into patient's vein) drip infusion taking about thirty minutes. When belamaf is used together with pomalidomide and dexamethasone, the recommended dose for belamaf is 2.5mg/kg in the first 4 weeks then 1.9mg/kg every 4 weeks after that.

Typically, belamaf will be given until the treatment stops working (cancer become resistant to treatment). However, some patients may experience side effects that require them to stop the treatment earlier and try a different one. Often, these side-effects can be managed by reducing the dose or extending the time between doses.

As part of the BPd treatment combination, pomalidomide is given by mouth (orally) 4mg per day on Days 1 to 21 of each 28-day (4 week) cycle. Dexamethasone is given orally 40mg per day on days 1, 8, 15, and 22 of each 28-day (4 week) cycle. Patients who are older (over 75 years), have other health issues, or cannot tolerate the 40mg dose of dexamethasone dose can receive a lower dose of 20mg.

Existing treatment combinations at 2L that patients (for whom lenalidomide is unsuitable) may be offered 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 (K) is given as an injection into the vein (intravenous)[10].
- SVd: in this treatment combination, Selinexor (S) 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-8

DREAMM-8 (NCT04484623) is an ongoing Phase 3 clinical trial providing a reliable data source on the efficacy and safety of belamaf in combination with pomalidomide and dexamethasone (BPd).

This trial compared the treatment combination of BPd with that of pomalidomide plus bortezomib and dexamethasone (PVd), a standard of care in Europe.

A total of 302 patients participated in the trial, with 155 receiving BPd and 147 receiving PVd. It was conducted in 95 MM specialty centres in 18 countries, including 5 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 including a lenalidomide-containing regimen	• Prior BCMA targeted therapy • Received prior treatment with or intolerant to pomalidomide • Intolerance to bortezomib or refractory to 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 13 October 2020. Primary analysis was completed on 29 January 2024. Additional data from the DREAMM-8 trial will be released in the future.

Details are available at Study Details | Belantamab Mafodotin Plus Pomalidomide and Dexamethasone (Pd) Versus Bortezomib Plus Pd in Relapsed/Refractory Multiple Myeloma | 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 pomalidomide and dexamethasone (BPd) has been shown to be an effective treatment with positive primary analysis results from the DREAMM-8 clinical trial.

BPd was compared against PVd, a standard of care for patients in Europe at 2L. The trial was designed to test whether BPd was better than PVd, and hence support a case that belamaf in

combination should become the new best available treatment on the NHS. To prove this, several different outcomes were explored. Some key outcomes are summarised below [22] [23]:

- **Progression free survival (PFS):** This measures how long a patient lives with the disease without it getting worse during or after treatment. In the trial, patients treated with BPd had a statistically significant and clinically meaningful PFS benefit compared to those treated with PVd, showing nearly 50% reduction in risk of disease progression or death.
- **Overall survival (OS):** This measures the duration a patient lives from the start of treatment until their death, no matter the cause. The initial analysis showed a trend favouring the patients receiving BPd. OS is an important outcome measure to assess the effectiveness of treatments and their impact on patients' survival rates. Additional OS follow-up is ongoing.
- **Duration of response (DoR):** Patients demonstrated longer DoR with BPd compared to those treated with PVd. Additional DoR follow up is ongoing.
- **Overall response rate (ORR):** A greater proportion of patients responded to the BPd treatment than the PVd treatment (77% vs 72%)

A special type of statistical analysis (a 'network meta-analysis' [NMA]) was undertaken to demonstrate how BPd would probably have worked if it had been compared with other 2L treatments (especially those available to NHS patients for whom lenalidomide is unsuitable). Results from this analysis indicated improvement in key outcomes (PFS and OS) compared to treatments including DVd, Kd and SVd.

These results suggest that belamaf in combination 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 profile, 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-8 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-8 trial, no difference in quality of life between the BPd and PVd arms were observed over time. This is despite the higher frequency of eye-related side effects seen in the BPd 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 BPd in DREAMM-8 was consistent with what has been previously described for belamaf, even though patients stayed on treatment for longer compared to the DREAMM-2 and DREAMM-3 trials. All patients in the DREAMM-8 trial experienced at least one side effects, which is any health problem that occurs after a treatment.

Side effects, also knowns as adverse evets (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 those that pose a threat to a patient's life or ability to function.

When comparing the BPd and PVd treatment arms, there was higher rates of grade 3 or 4 AEs (91% vs 73%) and serious AEs (63% vs 45%) in the BPd group. However, patients were on BPd twice as long as PVd, so a method was used to adjust AE rates based on total exposure to treatment. The adjustment helps make a fair comparison of AE rates when the length treatment differs between groups. After adjustment:

- rates of grade 3 or 4 AEs were 66 per 100 person-years for BPd and 78 for PVd
- rates of serious AEs were 46 per 100 person-years and 48 for PVd

In total, 22 patients (15%) in the BPd arm vs 18 (12%) in the PVd arm discontinued treatment due to side effects. Deaths from serious AEs were reported in 17 patients (11%) in the BPd arm and 16 (11%) in the PVd arm. Infection rates was comparable between treatment arms (82% in BPd arm vs 68% in PVd arm).

Eye-related side effects, like blurry vision and dry eyes, are a known issue with belamaf, were manageable and resolved with dose modifications, including delays and reductions. These side effects were reported in 91% of patients in the BPd arm and 37% in the PVd arm, suggesting there are some eye-related issues already in the general MM population.

Using preservative-free artificial tears (eye drops) four times a day until the end of therapy can help manage these side effects for patients on belamaf. Although eye-related side effects led to a higher rate of dose delays (86%) and reductions (66%) in the BPd group, the overall discontinuation rate was low at 9%. Importantly, despite the higher frequency of eye-related side effects in the BPd arm, overall health-related quality of life did not differ between two treatment groups.

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 pomalidomide and dexamethasone can be summarised as:

- **Clinical benefit:** Within the DREAMM-8 trial the treatment has represented significant clinical benefit in comparison to PVd, a standard of care according to European guidelines. The belamaf in combination may offer a new standard of care for RRMM patients for whom lenalidomide is unsuitable in the 2L.
- **Novel mechanism of action:** BPd 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 the 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. Belamaf is an off-the-shelf, outpatient therapy which means it has a broad deliverability.
- **Infection profile:** The rate of infections, including opportunistic infections (infections that occur more frequently and are more severe in people with weakened immune systems), a known risk with other BCMA options, was similar between treatment arms in the DREAMM-8 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 BPd aims to improve quality of life and prolong survival; the treatment may not be effective for every patient.

Like all medications, BPd 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. This model helps determine whether the benefits of the drug for patients are worth the costs to the NHS. The benefits are expressed in 'quality adjusted life years' (QALYs). One QALY is equivalent to one year of life lived in perfect health. For example, living two years of life at 50% of perfect health is equivalent to one QALY. A key concept in this type of analysis is the 'incremental cost-effectiveness ratio threshold'. This is a number published by NICE. If a treatment can provide a QALY for less than this number, then it is considered to be cost-effective and should be made available through the NHS.

When evaluating the cost effectiveness of belamaf, it's important to look beyond the duration of the DREAMM-8 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.

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 (BPd) 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 a EU standard of care PVd. A NMA conducted has also shown improvements in key outcomes compared to the UK standard of care DVd. Although belamaf is associated with higher costs, these have been shown 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 21.8

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.

Because belamaf often requires dose delays and dose reductions, researchers used detail patient data to create a model. This model helps to provide realistic estimates of how much belamaf is used when combined with pomalidomide and dexamethasone in real life situations. This information is used 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 pomalidomide 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 (for whom lenalidomide is unsuitable). It should be noted, however, that the decision of cost-effectiveness of belamaf is made by the appraisal committee and takes into account a wide range of factors, including ICERs that may be different to company's economic analysis due to differing assumptions and confidential discounting of comparator treatments.

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 pomalidomide 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 new combination has some innovative features that are important for 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 needs of RRMM patients who have already had one line of treatment, especially those who cannot use lenalidomide when their disease returns. 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 PVd, a current European standard of care at 2L, in the DREAMM-8 trial. The treatment combination has demonstrated it extends the length of time patients spend disease free. Therefore, belamaf in combination 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: 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-8 study is registered on clinicaltrials.gov: Study Details | Belantamab Mafodotin Plus Pomalidomide and Dexamethasone (Pd) Versus Bortezomib Plus Pd in Relapsed/Refractory Multiple Myeloma | 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
- BPd: belantamab mafodotin plus pomalidomide and dexamethasone
- PVd: pomalidomide 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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10. NICE. Carfilzomib for previously treated multiple myeloma: NICE; 2020 [Available from: https://www.nice.org.uk/guidance/ta657/chapter/1-Recommendations.

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22. Trudel S et al. Results from the randomized phase 3 DREAMM-8 study of belantamab mafodotin plus pomalidomide and dexamethasone (BPd) vs pomalidomide plus bortezomib and dexamethasone (PVd) in relapsed/refractory multiple myeloma. American Society Of Clinical Oncology 2024.
23. GSK announces positive results from DREAMM-8 phase III trial for Blenrep versus standard of care combination in relapsed/refractory multiple myeloma [press release]. GSK, 07 March 2024.
24. EuroQol. EQ-5D-3L [Available from: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-3l/.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

Clarification questions

September 2024

File name	Version	Contains confidential information	Date
ID6211 Belantamab mafodotin RRMM Clarification letter v1.0 [REDACT]	**1**	**Yes**	**16/09/2024**

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Clinical effectiveness data and company systematic literature review (SLR)

A1. Company submission (CS), sections B.1.3.2 and B.2.3.2.2. The company has positioned belantamab mafodotin with pomalidomide and dexamethasone (BPd) as a second-line treatment for patients who are refractory to lenalidomide. In the DREAMM-8 trial, only 52.5% of patients had received only one prior line of treatment. Please provide the baseline characteristics for a) patients who had received only one prior line of treatment and b) patients who had received lenalidomide as part of their first line treatment. Please use the same layout as CS, Table 7.

In this submission, GlaxoSmithKline (GSK) considers the clinical and cost-effectiveness of belamaf plus pomalidomide and dexamethasone (BPd) for the treatment of adults with relapsed/refractory multiple myeloma (RRMM) who have had one prior line of therapy (LoT) and for whom lenalidomide is unsuitable.

GSK notes that in the DREAMM-8 trial, all patients enrolled had previously received lenalidomide as part of their treatment regimen. Therefore, any patients who has received only one prior line of treatment (population a) must have received

lenalidomide as part of that first line treatment (population b), given the trials inclusion criteria. Thus population (a) and (b) are the same.

The baseline characteristics (taken at screening) for patient who had received only one prior line of treatment (2L) are provided in the tables below.

Table 1. Summary of disease characteristics at screening for 2L population

Characteristics	**BPd (N=82)**	**PVd (N=77)**
Age, median (range), years[a]	[redacted]	[redacted]
Age category, n (%)		
19 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	[redacted]	[redacted]
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
Mixed race	[redacted]	[redacted]
ISS stage at screening, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Cytogenetic risk, n (%)[b]		
Standard[c]	[redacted]	[redacted]
High[d]	[redacted]	[redacted]
t(4;14)	[redacted]	[redacted]
t(14;16)	[redacted]	[redacted]
del(17p13)	[redacted]	[redacted]
Missing or not evaluable	[redacted]	[redacted]
Extramedullary disease, n (%)		
Yes	[redacted]	[redacted]

Characteristics	BPd (N=82)	PVd (N=77)
No	[redacted]	[redacted]
Myeloma immunoglobulin, n (%)		
IgG	[redacted]	[redacted]
Prior lines of therapy, n (%)		
1	[redacted]	[redacted]
2 or 3	[redacted]	[redacted]
4+	[redacted]	[redacted]
Time to relapse on latest prior line of therapy, n (%)[e]		
≤12 months	[redacted]	[redacted]
>12 months	[redacted]	[redacted]
Prior anti-CD38, n (%)	[redacted]	[redacted]
Prior ASCT, n (%)	[redacted]	[redacted]
Positive refractory status by agent, n (%)		
Lenalidomide	[redacted]	[redacted]
Anti-CD38 treatment	[redacted]	[redacted]

[a] Age was imputed when full date of birth was not provided.
[b] Participants may have been included in more than 1 category. Only positive results were summarized.
[c] If the participant had negative results for all high-risk abnormalities: t(4;14), t(14;16), or 17p13del.
[d] If the participant had at least 1 high-risk abnormality: t(4;14), t(14;16), or 17p13del.
[e] Time to relapse was defined as the time from the start date of the first prior line of the therapy to the date of randomization for participants with 1 prior line or to the start date of the second prior line of the therapy for participants with >1 prior line.
Abbreviations: ASCT, autologous stem cell transplant; BPd, belamaf plus pomalidomide, and dexamethasone; ITT, intention-to-treat; IgG, immunoglobulin; PD, progressive disease; PVd, pomalidomide plus bortezomib, and dexamethasone; ISS, International Staging System.
Source: DREAMM-8 Supplementary Statistical Analysis

A2. CS, Appendix D. Please confirm the number of trials included in the clinical effectiveness SLR. The PRISMA diagrams in Appendix D (Figures 1, 2 and 3) suggest that 70 trials overall were included in the company's review (47+12+11). In Appendix D, Table 11 shows 38 included phase 3 trials and Table 12 shows 26 included phase 2 trials, making a total of 64 included trials. Please explain the difference between the 70 trials in the PRISMA diagrams and the 64 trials listed in Tables 11 and 12.

GSK apologises for the lack of clarity in the PRISMA diagrams across the original SLR and SLRs updates. The differences in the total number of included trials present in the PRISMA is due to the clinical effectiveness SLR being updated twice. Some clinical trials were identified multiple times across the original SLR, Update 1 and

Update 2. In Table 11 and Table 12, any trials identified which are duplicates across the various SLR updates were removed to give one consolidated list of identified clinical trials. For example, while CASTOR was identified in both the original SLR and Update 1; it features only once in Table 11 and appears in both the original and Update 1 PRISMA.

Network meta-analyses (NMAs)

A3. CS, section B.2.9.2.1. The company NMAs included data from 12 of the 70 studies identified by the company SLR. Please provide a table showing, for each of the 58 excluded studies, the reason(s) for exclusion.

Thank you for the opportunity to clarify the rationale for exclusion for the NMA data. The original SLR search resulted in 47 final extractions, which were used in the NMA feasibility assessment. While no formal feasibility assessment was conducted on the additional studies identified following the SLR updates, a naïve assessment ruled out inclusion of any of the new studies identified studies in the NMA. These 47 papers were reduced to 17 based on those studies that were able to form a connected network of evidence. This was detailed in the NMA feasibility assessment that has been shared separately as part of this clarification response.

The 17 studies were further reduced to a final 12 studies, based on exclusion of studies that evaluated interventions that were either not approved by FDA / EMA or not considered a globally relevant comparator to BPd currently or in the future. Table 2 has been provided below to outline the rationale for excluding these five studies.

Table 2: Studies excluded due to lack of EMA/FDA approval or relevant comparator

Trial name	Reason for exclusion
BELLINI	Not approved by FDA / EMA or considered a relevant comparator
NCT00602511	Not approved by FDA / EMA or considered a relevant comparator
NCT01602224	Not approved by FDA / EMA or considered a relevant comparator
DREAMM-7	Not approved by FDA / EMA or considered a relevant comparator
LEPUS	Not approved by FDA / EMA or considered a relevant comparator

Abbreviations: EMA, European Medicines agency; FDA, Food and drug administration.

A4. CS, section B.2.9. Please provide data inputs (and sources) for the progression-free survival (PFS; lenalidomide-exposed fixed effects) and overall survival (OS; lenalidomide-exposed plus ITT, fixed effects) NMAs. Please confirm that the data used in these NMAs are the latest available data.

Table 3 and Table 4 below display all relevant data pertaining to lenalidomide-exposed PFS and lenalidomide-exposed + ITT OS study networks. All data provided are based on the most recent data available obtained from the January 2024 SLR update.

Table 3: Study data used in the lenalidomide-exposed PFS network

Study	Source	Comparators	Sample size	HR	95% CI (lower and upper)
DREAMM-8	GSK data on file	BPd	155	0.52	0.37, 0.73
		PVd	147		
ARROW	Moreau et al. (2018)	Kd	207	0.72	0.56, 0.94
		hKd	194		
BOSTON	Mateos et al. (2020)	SVd	77	0.63	0.41, 0.97
		Vd	77		
CANDOR	Usmani et al. (2022)	hKDd	123	0.49	0.33, 0.74
		hKd	74		
CASTOR	Weisel et al. (2019)	DVd	89	0.40	0.28, 0.58
		Vd	120		
ENDEAVOR	Dimopoulos et al. (2016)	hKd	177	0.69	0.52, 0.92
		Vd	177		
IKEMA	Moreau et al. (2021)	IhKd	72	0.58	0.35, 0.96
		hKd	59		
OPTIMISMM	Beksac et al. (2023)	PVd	281	0.56	0.46, 0.68
		Vd	278		

Abbreviations: BPd, Belamaf plus pomalidomide, and dexamethasone; CI, confidence interval; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib plus daratumumab and dexamethasone; HR, hazard ratio; IhKd, Isatuximab plus high dose carfilzomib and daratumumab; PFS, progression-free survival; PVd, pomalidomide plus bortezomib and dexamethasone; SVd, selinexor plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone

Table 4: Study data used in the lenalidomide-exposed + ITT OS NMA network

Study	Source	Comparators	Sample size	HR	95% CI (lower and upper)
DREAMM-8	GSK data on file	BPd	155	0.77	0.53, 1.14
		PVd	147		

Study	Source	Comparators	Sample size	HR	95% CI (lower and upper)
ARROW	Moreau et al. (2018)	Kd	240	0.80	0.56, 1.14
		hKd	238		
BOSTON	Grosicki et al. (2020)	SVd	195	0.84	0.57, 1.23
		Vd	207		
CANDOR	Usmani et al. (2023)	hkDd	123	0.74	0.49, 1.11
		hKd	74		
CASTOR	Sonnevel d et al. (2023)	DVd	251	0.74	0.59, 0.92
		Vd	247		
ENDEAVOR	Orlowski et al. (2019)	hKd	177	0.88	0.67, 1.16
		Vd	178		
IKEMA	Martin et al. (2023)	IhKd	179	0.78	0.54, 1.12
		hKd	123		
NCT00813150	Kropff et al. (2017)	CyVd	47	0.85	0.41, 1.73
		Vd	43		
NCT1478048	Jakubowi ak et al. (2016)	EVd	77	0.61	0.32, 1.15
		Vd	75		
OPTIMISMM	Beksac et al. (2023)	PVd	281	0.76	0.62, 0.93
		Vd	278		
PANORAMA-1	San-Miguel et al. (2016)	PanoVd	387	0.94	0.78, 1.14
		Vd	381		
GEM_KyCyDex	Puertas et al. (2023)	CyKd	97	1.40	0.90, 2.20
		Kd	100		

Abbreviations: BPd, Belamaf plus pomalidomide and dexamethasone; CI, confidence interval; CyKd, cyclophosphamide plus high dose carfilzomib, daratumumab, and dexamethasone; CyVd, cyclophosphamide plus bortezomib and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; EVd, elotuzumab plus bortezomib and dexamethasone; hKd, high dose carfilzomib and dexamethasone; hKDd, high dose carfilzomib plus daratumumab and dexamethasone; HR, hazard ratio; IhKd, Isatuximab plus high dose carfilzomib and daratumumab; ITT, intent to treat; Kd, carfilzomib and dexamethasone; NMA, network meta-analysis; OS, overall survival; PanoVd, Panobinostat plus bortezomib and dexamethasone; PVd, pomalidomide plus bortezomib and dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone; Vd, bortezomib and dexamethasone

A5. CS, Appendix D. Informative priors are listed in Appendix D, Table 50 and were extracted from Turner et al. (2015). Please justify why the lognormal (-2.99, 1.72^2) was considered more appropriate than the overall average lognormal (-2.56, 1.74^2).

The prior obtained from Turner et al. was specified individually and used in the comparison for pharmacological vs. pharmacological studies since all studies being considered were pharmacological vs. pharmacological.

Subsequently, the lognormal prior (-2.99) was used for continuous outcomes based on a generic prior for a general healthcare setting. As there are no binary NMA outcomes presented in the DREAMM-8 submission dossier, the overall average lognormal prior (-2.56) was not used and only the lognormal prior was included.

A6. CS, section B.2.9.2.3. The company states that "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 (line of therapy) across the included studies" (CS, p70). Please provide evidence to demonstrate that no major differences were identified.

PFS was used as the primary method of evaluating whether a factor was a treatment effect modifier (TEM) as PFS is the primary endpoint of DREAMM-8 and is most consistently reported across subgroups in appraisal. The results indicated that prior LOT may be TEMs in the ITT population as displayed in Table 49 of Appendix D. It was therefore anticipated that PFS treatment effect may reduce (i.e., HRs would increase) with more prior LOT, but this would only lead to an expected increase in HR when the proportion of patients with higher prior LOT is greater in the comparator trials relative to DREAMM-8. The potential TEMs were assessed through evaluation of their distribution across studies included in the network. A comparison of baseline characteristics across the included studies, displayed in Table 46 of Appendix D indicated that no major differences were found across the studies regarding prior LOT.

A7. CS, section B.2.9.2.1. The company states that the final network of evidence comprises 8 studies (CS, p67). However, the OS lenalidomide-exposed plus ITT NMA included data from 12 studies. Please explain why, in the OS lenalidomide-

exposed plus ITT NMA, it was necessary to add data from 4 additional studies rather than using the data from the 8 studies included in the final network of evidence.

The OS lenalidomide-exposed plus ITT NMA was conducted for the purposes of facilitating comparison to all comparators considered in the appraisal. As demonstrated in Figure 19 of Document B, only four comparators reported OS data in a lenalidomide-exposed population (only hKd within the scope of this submission), thereby necessitating the lenalidomide-exposed plus ITT NMA to produce OS estimates for the remaining comparators (SVd, DVd).

The network was conducted from a global perspective and therefore included some comparators not within scope of this appraisal as the patient populations were not 100% lenalidomide-exposed. When comparing network results for comparators included in both the lenalidomide-exposed and lenalidomide-exposed + ITT OS networks, HRs and CrIs were consistent, indicating that the additional comparators did not bias treatment effects. Further, the additional four comparators (PanoVd, EVd, CyVd and CyKd) were end-nodes and therefore their inclusion did not impact the relative efficacy estimates of BPd versus other comparators.

Section B: Clarification on cost effectiveness data

B1. CS, section B.3.5.1.1, Table 46. Please re-run all cost effectiveness analyses using the current list price for pomalidomide.

Given that generic pomalidomide is anticipated by the end of 2024 (based on GSK internal insights), GSK believe it would be inaccurate to re-run all cost effectiveness analyses using the current list price of pomalidomide. Doing so would significantly overestimate the true treatment costs borne by the NHS for BPd at the time of recommendation.

As stated in the CS, section B.3.5.1.1, based on internal GSK intelligence and the observed price trends for lenalidomide after it became generic in March 2022 (1, 2), the model inputs and results presented in the CS assume that the availability of generic pomalidomide will reduce its list price by [redacted]. The rationale for this discount is grounded in similarities between pomalidomide and lenalidomide, both of which belong to the immunomodulatory agent class, and the fact that since the generic availability of lenalidomide; 10 new market entrants have been listed on the

BNF to produce generic lenalidomide (3). These market entries have substantially reduced the cost of lenalidomide, and similar changes are expected for generic pomalidomide.

However, for illustrative purposes the deterministic PAS vs list pairwise cost-effectiveness results are outlined below with a scale of pomalidomide discounts to the list price (from [redacted] provided in the company base-case, to a conservative discount assumption of [redacted]) including the DVd eligible and DVd ineligible subpopulations (Table 5 and Table 6).

Table 5. DVd eligible subpopulation - Pairwise cost-effectiveness results (PAS vs list, deterministic)

Pomalidomide price discount (%)	BPd		DVd			hKd		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	Costs (£)	QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 6. DVd ineligible subpopulation - Pairwise cost-effectiveness results (PAS vs list, deterministic)

Pomalidomide price discount (%)	BPd		SVd			hKd		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	Costs (£)	QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SVd, selinexor plus bortezomib and dexamethasone.

B2. CS, section B.3.3.1. When modelling the relative treatment effect of DVd (daratumumab, bortezomib and dexamethasone), hKd (high dose carfilzomib and dexamethasone) and SVd (selinexor, bortezomib and dexamethasone), the company rationale for using PVd (pomalidomide, bortezomib and dexamethasone) rather than BPd as the reference treatment was:

> *"PVd was selected over BPd as the reference treatment because BPd, being a BCMA-targeted therapy, has a different mode of action, whereas PVd shares a more comparable hazard profile with the other comparators." (CS, pp111-112)*

Please explain why the company considers it important to highlight that BCMA-targeted therapy has a different mode of action when PVd, DVd, hKd and SVd include drugs with various modes of action.

Please also explain what is meant by '…whereas PVd shares a more comparable hazard profile with the other comparators'.

When modelling the relative treatment effect of DVd, hKd and SVd, PVd rather than BPd was used as the reference treatment. GSK would like to clarify that the rationale for doing so concerns the observation that DVd, hKd, SVd, and PVd all contain a proteasome inhibitor backbone (either bortezomib or carfilzomib in combination with dexamethasone), whereas BPd contains an immunomodulatory backbone (pomalidomide in combination with dexamethasone). Proteasome inhibitors and immunomodulatory agents are two well-defined and distinct treatment pillars for the management of RRMM.

This difference manifests in a differing observed trend in terms of hazard profiles identified in the DREAMM-8 trial versus comparator trials. The hazard rate profile refers to the PFS and OS hazard rate trends over time, as seen in the hazard rate plots. PVd was therefore selected as a reference treatment to model PFS, OS, and TTD for comparator treatments for the NMA HRs based on more similar trends identified in a visual assessment of the hazard plots. Specifically, in the ITT PFS hazard plots for hKd (ENDEAVOR study), SVd (BOSTON study), and DVd (CASTOR study) (Figure 2), it is observed that hazard rates demonstrate an initial increase (or reduction followed by an increase, such as in CASTOR) and a subsequent reduction

over the first 15-20 months. When comparing the aforementioned PFS hazard plots with BPd and PVd empiric hazard plots in the first 20 months (Figure 1), we note that the hazard rate in the PVd arm in DREAMM-8 follows a more similar trend (i.e., an initial increase in hazard rate, followed by subsequent decrease), compared to BPd arm in which the hazard rate consistently declines over time. In addition, it is important to note that hazard rates at the tail end of the DREAMM-8 PFS data are uncertain due to low patient numbers at risk (at 20 months, only 25 patients are still at risk).

While there are some similar observed hazard profiles between CASTOR and DREAMM-8 (Figure 3, Figure 4) OS was characterized by uncertainty due to the immature OS data from DREAMM-8, posing challenges in inferring the comparability of hazard rate trends. Therefore, it was assumed that the hazard rate trends for OS would follow similar patterns to those observed for PFS and PVd was applied as the reference arm.

1

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Nevertheless, in the Document B of NICE submission (Section B.3.11.3.1) GSK have presented a scenario analysis in which BPd was considered as the reference curve for PFS, OS, and TTD. However, the 'Baseline comparator curve: BPd (PFS, OS, TTD)' did not have any impact on the base case, as BPd remained a dominating treatment strategy when compared to hKd (Table 71), SVd (Table 72), and DVd (Table 73).

B3. CS, section B.3.4.2. The company submission states that "In the base-case, health state utility values were assumed to differ between treatments for the PFS health state. As the DREAMM-8 trial collected utility values for BPd and PVd only, an assumption was made that the utility value in PFS for all relevant comparators was equal to value of PVd" (CS, p133). Please clarify the basis for the company assumption that, in the PFS health state, the same utility value was applied for patients treated with DVd, hKd and SVd (equal to that for DREAMM-8 trial patients treated with PVd).

As stated in the response for B2 above, the basis for this assumption relates to the observation that DVd, hKd, SVd, and PVd all contain a proteasome inhibitor backbone,

as opposed to BPd which contains an immunomodulatory backbone. Please see response for B2 for further details.

As stated in the response for B2 above, the basis for this assumption relates to the similarities in the mechanism of action shared by DVd, hKd, and SVd with PVd targeting proteasome inhibition, immunomodulation, and anti-inflammatory effects, as opposed to the novel and highly specific mechanism of action brought by the BCMA-targeted therapy which potentially minimises off-target effects resulting in a different impact on quality of life for patients on BCMA targeted therapy. Please see response for B2 above for further details.

Additionally, a scenario analysis was conducted using alternative treatment-specific utility values in PFS for all relevant comparators, compared to the base-case in the CS. For the DVd arm, the treatment-specific utility value for DVd derived from the DREAMM-7 trial was used in this scenario to model the DVd PFS utility. In the absence of relevant data to inform the hKd and SVd PFS treatment-specific utilities, a conservative assumption was made in this scenario that the utility value in PFS for these comparators was equal to the value of BPd (Table 7). The results for this scenario analysis are provided in Table 8. In summary, the results showed that BPd remained dominant vs. hKd, SVd and DVd, consistent with the base-case.

[redacted]

Treatment	Utility (95% CI)	Source
PFS (on treatment and off treatment) *		
BPd	[redacted]	DREAMM-8 (4)
hKd	[redacted]	Assumed to be equal to BPd
SVd	[redacted]	Assumed to be equal to BPd
DVd	[redacted]	DREAMM-7 (5)
PD	[redacted]	DREAMM-8 (4)

[redacted]

Abbreviations: BPd, Belamaf plus pomalidomide and dexamethasone; hKd, High dose carfilzomib plus dexamethasone; PD, Progressed disease; PFS, Progression-free-survival; SVd, Selinexor plus bortezomib and dexamethasone.

Table 8. Scenario analysis supporting B3

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	NMB* (NMB change from base case) (£)
BPd vs. hKd				
Base Case	[redacted]	[redacted]	Dominating	[redacted]

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	NMB* (NMB change from base case) (£)
hKd PFS utility assumed to be equal to BPd	[redacted]	[redacted]	Dominating	[redacted]
BPd vs. SVd				
Base Case	[redacted]	[redacted]	Dominating	[redacted]
SVd PFS utility assumed to be equal to BPd	[redacted]	[redacted]	Dominating	[redacted]
BPd vs. DVd				
Base Case	[redacted]	[redacted]	Dominating	[redacted]
DVd PFS utility derived from DREAMM-7	[redacted]	[redacted]	Dominating	[redacted]

Note: *NMB values were calculated based on a WTP threshold of £30,000/QALY gained.
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year; SVd, selinexor plus bortezomib and dexamethasone.

Section C: Textual clarification and additional points

C1. CS, section B.1.2. In Table 2, it is stated that: ”The Great Britain conditional 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” (CS, p11). Please provide more information about the Annual Renewal Procedure and expected authorisation date.

Following the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) confirmation of its recommendation to not renew the conditional marketing authorisation (cMA) for belantamab mafodotin (Dec 2023), and recent discussions with the Medicines and Healthcare products Regulatory Agency (MHRA) on the annual renewal of the Great Britain (GB) cMA, GSK have accepted the MHRA’s opinion to revoke the cMA for belantamab mafodotin. The revocation was not due to a safety concern. The Commission on Human Medicines (CHM) had no major objections regarding clinical safety.

The GB cMA for belantamab mafodotin in the following indication was revoked on 30th August 2024:

“…as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one

proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy."

C2. CS, section B.2.1. The search dates for the company's SLRs (clinical effectiveness and cost-effectiveness) ranged between January 2008 and February 2024 (CS, p25). Please explain the rationale for selecting 2008 as starting point of the searches.

In the original SLR, a 15 year period was determined to be sufficient to capture all relevant trials due to the rapidly evolving multiple myeloma treatment patterns. Evidence identified prior to January 2008 were expected to be of little relevance to today's clinical practice.

C3. Please check the table caption for CS, Table 22.

GSK can confirm the data in Table 22 is for the lenalidomide-exposed population for both PFS and OS. Although this is the ITT population for the DREAMM-8 trial, the secondary analysis within the NMA results have been referred to as the 'lenalidomide-exposed + ITT' analysis. To avoid confusion the caption is intended to be read as 'Goodness of fit summary statistics for all endpoints (primary analysis – lenalidomide-exposed population)'.

C4. In 4 places in the CS (p76, 78, p80 and p82), the company states *'… results for all relevant comparators were statistically significant to a 95% CrI'*. Please explain what is meant by this phrase.

GSK acknowledges that statistical significance in the classical sense is not applicable to Bayesian analysis using CrIs. The intention of this sentence was to indicate the comparators showed substantial posterior predictive information criteria (e.g., DIC) differences with CrI that do not cross one, indicating strong evidence in favour of the model including an effect.

C5. Please provide an abbreviations list for the CS (Document B).

The following table provides the list of abbreviations for the CS:

Table of abbreviations	
1L	First-line
2L	Second-line
3L	Third-line
ADC	Antibody-drug conjugate

AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike Information Criterion
ASCT	Autologous stem cell transplant
BCMA	B-cell maturation antigen-targeted
BCVA	Best corrected visual acuity
BIC	Bayesian Information Criterion
BNF	British National Formulary
BoR	Best overall response
BOR	Bortezomib
BPd	Belamaf plus pomalidomide and dexamethasone
BSA	Body surface area
BVd	Belamaf plus bortezomib and dexamethasone
CBR	Clinical benefit rate
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CMRG	Canadian Myeloma Research Group
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRAB	Hypercalcaemia, renal insufficiency, anaemia, and bone lesions
CrI	Credible interval
CRR	Complete response rate
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DHSC	Department of Health and Social Care
DIC	Deviance Information Criterion
DOF	Data on file
DoR	Duration of response
DRd	Daratumumab plus lenalidomide and dexamethasone
DREAMM	DRiving Excellence in Approaches to Multiple Myeloma
DSU	Decision Support Unit
DVd	Daratumumab plus bortezomib and dexamethasone
DVTd	Daratumumab plus bortezomib, thalidomide, and dexamethasone
EAG	External assessment group
EAIR	Exposure-adjusted incidence rates
ECOG	Eastern Cooperative Oncology Group
EE	External clinical experts
EHA	European Haematology Association
EMA	European Medicines Agency
EMC	Electronic medicines compendium
EMD	Extramedullary disease
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Questionnaire Module 20
EOT	End of treatment
EQ-5D	European Quality of life-5 Dimensions
Erd	Elotuzumab plus lenalidomide, and dexamethasone
ESMO	European Society for Medical Oncology
FDA	Food and drugs administration
FLC	Free light chains
FVd	Panobinostat plus bortezomib, and dexamethasone

GSK	GlaxoSmithKline
HCP	Healthcare practitioners
HCRU	Healthcare resource utilisation
HDT	High dose therapy
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Interim analyses
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio
Ide-cel	Idecabtagene vicleucel
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgG	Immunoglobulin G
IMWG	International Myeloma Working Group
INHB	Incremental net health benefit
INMB	Incremental net monetary benefit
IPCW	Inverse-probability of censoring weighting
IPD	Individual patient data
IR	Incidence rates
IRC	Independent review committee
IRT	Interactive Response Technology
IsaPd	Isatuximab plus pomalidomide, and dexamethasone
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IVIG	Intravenous immunoglobulin
IVRS	Interactive Voice Response System
IxaRd	Ixazomib plus lenalidomide, and dexamethasone
Kd	Carfilzomib and dexamethasone
KM	Kaplan meier
KRd	Carfilzomib plus lenalidomide
KVA	Keratopathy Visual Acuity
LFU	Last follow-up
LoT	Line of therapy
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of undetermined insignificance
MHRA	Medicines, and Healthcare Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MM	Multiple myeloma
MoA	Mechanism of action
MoM	Method of moments
MR	Minimal response
MRD	Minimum residual disease
NA	North America
NCI	National Cancer Institute
NCRAS	National Cancer Registration and Analysis Service
NGS	Next generation sequencing
NHS	National Health Service
NICE	National institute for health and care excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NPP	Named-patient programme
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis

PAS	Patient Access Scheme
PASLU	Patient Access Schemes Liaison Unit
PD	Progressive disease
PF	Progression-Free
PFS	Progression-free survival
POM	Pomalidomide
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analysis
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PVd	Pomalidomide plus bortezomib and dexamethasone
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trials
RDI	Relative dose intensity
RMST	Restricted Mean Survival Time
RR	Relapsed/Refractory
RRMM	Relapsed/refractory multiple myeloma
SACT	Systemic anti-cancer therapies
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Standard deviations
SE	Standard errors
SLR	Systematic literature review
SMC	Scottish Medicine Consortium
SmPC	Summary of Product Characteristic
SoA	Schedule of activities
SoC	Standard of care
SOC	System Organ Class
SPEP	Serum protein electrophoresis
SUCRA	Surface under the cumulative ranking curve
SVd	Selinexor plus bortezomib and dexamethasone
TA	Technology appraisal
TEM	Treatment effect modifiers
TFI	Treatment free interval
TRSAE	Treatment-related serious adverse event
TSD	Technical Support Document
TSNT	Time to start of next therapy
TTBR	Time to best response
TTD	Time to treatment discontinuation
TTDD	Time to treatment discontinuation or death
TTNT	Time to next treatment
TTNTD	Time to next treatment or death
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
UPEP	Urine protein electrophoresis
US	United States
VGPR	Very good partial response
VPPR	Very poor partial response
VTd	Bortezomib plus thalidomide and dexamethasone
WTP	Willingness to pay

C6. The Appendix D reference pack does not fully match the Appendix D reference list. Please provide the full reference pack for Appendix D.

The full reference pack for Appendix D is provided in the attached folder (folder name: Appendix D_reference pack).

References

1. International Myeloma Foundation. First Generic Revlimid (lenalidomide) Launched 2022 [Available from: https://www.myeloma.org/blog/first-generic-revlimid-lenalidomide-launched].
2. GaBi. Revlimid (lenalidomide) generics launch across Europe 2022 [Available from: https://gabionline.net/generics/news/revlimid-lenalidomide-generics-launch-across-europe].
3. National Institute for Health and Care Excellence (NICE). Medicinal forms-Lenalidomide [Specialist drug] 2024 [Available from: https://bnf.nice.org.uk/drugs/lenalidomide-specialist-drug/medicinal-forms/].
4. GSK. DREAMM 8: A Phase III Study of Belantamab Mafodotin plus Pomalidomide and Dexamethasone vs. Pomalidomide, Bortezomib and Dexamethasone in Participants with RRMM-Primary analysis clinical study report [Data on file]. 2024.
5. GSK. DREAMM 7: A Multicenter, Open-Label, Randomized Phase III Study to Evaluate the Efficacy and Safety of the Combination of Belantamab Mafodotin, Bortezomib, and Dexamethasone (B Vd) Compared with the Combination of Daratumumab, Bortezomib and Dexamethasone (D-Vd) in Participants with Relapsed/Refractory Multiple Myeloma (DREAMM 7)-Primary analysis clinical study report (Data on file) 2023.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

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.

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 May, June and July 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. Currently, there is no cure for myeloma. However treatments can halt its progression 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. Complications which result from myeloma can drastically impact patients' quality of life. These can effect patients in different ways and can range from 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] ***"It was a heart wrenching decision but with a severely weakened body, poor immune system and transient symptoms of 'chemo brain', I simply wasn't up to the task of running a hectic international business."*** Myeloma is incurable and is a relapsing and remitting cancer. This means that over time people with myeloma become resistant to treatment. There is a huge psychological impact for patients and their families, who are always aware that they require a range of novel treatments for different stages of their myeloma journey to keep them in remission for as long as possible. Switching treatments brings the possibility and hope of potential greater remission times and fewer side effects to treatment. However, it can also bring with it the stress and worry of having to adjust and adapt to a treatment which may not be as effective or may incur new unpleasant side effects. The adjustment to new treatment side effects and a change in hospital visits can have a social, practical and financial impact for patients and their families. Patients and family members can also be worried regarding their immunocompromised state when visiting and/or caring for patients who are undergoing treatment. ***"Myeloma has impacted a lot. I have a big family and even with close family, a lot of the time they won't even come into the house because they are scared they are going to make me ill."*** Due to the heterogenous nature of myeloma, some patients may tolerate a treatment well and others may not. This uncertainty of tolerability can be a significant concern for patients. Patients are also aware that when each new treatment is needed, their treatment options are reduced and life expectancy decreases. **"*I was told this was going to be the last treatment …I remember thinking oh this is it, I'm coming to the end of the line…"*** As myeloma evolves and becomes resistant to treatment, it is essential that there are a variety of treatments with different mechanisms of action available to patients at all stages of the myeloma pathway. This is important as usually if a drug is not effective or causes serious

	side effects to the patient, it will not be made available to the patient again, even if it is offered in a different combination. Therefore patients need to have access to a range of different treatments which work in different ways when they need it. 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, both physically and emotionally for patients and their families. ***"When you have a cancer diagnosis, however long or short that journey is, you drag everyone else along with 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, 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. ***"I once again found myself beyond the scope of NICE approved treatment options and for the third time, I was told there was little that could be done and it might finally be time to 'hang up my boots'*** Patients know that everyone's experience of a treatment is different and sometimes unpredictable. Due to myeloma being an incredibly heterogenous condition patients know that the level of effectiveness and side effects can differ, 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. 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. ***"as an Oligosecretory patient, I was advised I might not be allowed to join drug trials, as serological results were the most commonly accepted marker for drug efficacy. With this double whammy, my confidence in being able to access newer treatments, started to become an unwelcome stress in of itself – adding to my existing worries about the disease."*** 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. ***"A side effect of my treatment was peripheral neuropathy. The intention was to have 8-9 cycles for 5 weeks. I only got as far as 4 before I started to develop the tightening of a calf muscle. I couldn't walk easily down the stairs."***

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-8 clinical trial evaluated the use of belantamab mafodotin in combination with Pomalidomide and dexamethasone (BPd), and compared it to pomalidomode plus bortezomib (Velcade) and dexamethasone (PVd). The results from the trial show that progression free survival (PFS) was not reached in patients treated with BPd compared to 12.7 months with PVd. The 12 month PFS rate was 71% with BPd vs 51% with PVd. This demonstrates a statistically significant and clinically meaningful PFS benefit with BPd vs PVd. The hazard ratio of 0.52 represents a 48% reduction in patients relapsing whilst receiving BPd . The overall response rate (ORR) was 77% for BPd vs 72% for PVd. Median duration of response was not reportable for BPd vs 17.2 months with PVd. The trial demonstrates that BPd also led to deeper and more durable responses. 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'm still on Belantamab now. The paraproteins are undetectable, they are tiny. My liver function is working really well. The numbers are amazing. I am in biochemical remission. So for me the treatment is working really well…the rest of the treatments I've had have been quite toxic and weren't doing a good job of keeping the paraproteins and light chains low. Now they have been missing in action for over two years so that's pretty good"*** ***"The current treatment is doing its job, I was in remission within 2 months"*** ***"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.

	"Various drug combinations were discussed but for one reason or another, they were either not available to me… In the end, my consultant managed to secure access to Belantamab Mafodotin from GSK, on compassionate grounds – something that I'm exceptionally grateful for!" Whilst belantamab mafodotin used in combination with bortezomib and dexamethasone (Bvd) is not under consideration for this appraisal, results from the DREAMM-7 trial which compared Bvd with daratumumab, bortezomib and dexamethasone (DVd) showed positive quality of life data with no reported reduction in quality of life for Bvd against Dvd. Pain, fatigue and overall quality of life, were comparable in patients treated with BVd vs DVd. For patients treated with BVd who reported a clinically meaningful deterioration in vision-related functioning, overall quality of life was consistent with the DVd arm. This demonstrates belantamab mafodotin used in this treatment combination has no greater quality of life impact than the current standard of care treatment. 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.

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. In the DREAMM-8 trial, 99% of patients in the trial experienced at least one side effect from treatment with belantamab mafodotin, pomalidomide and dexamethasone (BPd). Side effects are graded from 1-4 in terms of severity (1 being mild, 4 being life-threatening). Grades 3 and 4 treatment-related side effects were reported in 43% of patients treated with BPd and 2% of patients treated with Pomalidomide, bortezomib and dexamethasone (PVd). Ocular side effects (affecting the eye and vision) were more frequent on BPd vs PVd (89% vs 30%) and were 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 Blenrep has been challenging due to the eyesight issues, there are no other major problems, at least none which I can attribute for certain to the treatment."*** ***"The side effects that I've had with belantamab are minimal in comparison to those of other treatments. The eyesight problem is the only thing, but it's not a big issue and it does correct itself."*** ***"I can't identify any other side effect apart from the eye issues. But as long as I do the drops there are no other side effects. With the treatments I've had before, I could give you a long list of side effects. But with Belantamab I really struggle to try and think of something. Theres the eyes but its very manageable."*** 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.[4] 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. ***"…the eye issue for me is very manageable .At the start I had belantamab every 3 weeks, and my eyes were very sore, almost like they had grit in them. The consultant pushed the treatment back to every 4 weeks instead. I didn't think that would make too much difference. But it really helped. My eyes have been more or less fine since just a little dry."***

	"I think the eyes could be a stumbling block, some patients would have to undertake an assessment of the risks. In my case I would take the side effects if it means my myeloma goes into remission." ***"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. ***"In comparison with previous treatments I have had the side effects have definitely been more severe. However, I would do it again because, over all compared to what I've had before this is the best response I've had in all the years of treatment. It really is."*** ***"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."***

[4] Lonial S, Lee HC, Badros A, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer*. 2021;127:4206.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients feel that there should be robust channels of cooperation between haematology and ophthalmology teams for the management of eye-related toxicity associated with belantamab mafodotin. Ideally, this cooperation should be based on a shared understanding concerning dose modification as there seems to be some discomfort with the current 'trial and error' approach. One patient we interviewed explained: ***"Although the eye-related side effects seem to be reversible, no one seems to know how long it might take for things to stabilise following treatment. There doesn't seem to be clear guidance within the special access scheme on how long to pause the treatment due to these side effects. This is a little unsettling."***

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a clear 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 pomalidomide 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.

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Single Technology Appraisal

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

Clinical expert statement

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The deadline for your response is **5pm** on **24 December 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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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	Dr Karthik Ramasamy
2. Name of organisation	UKMS/ BSH/ RCP/ RCPath
3. Job title or position	Executive member and 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?	There are no established treatment guidelines. Treatment usually follows NICE approved indications available at each treatment line. 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 Panobinostat 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?	Pomalidomide 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.

• 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)	Treatment is given in day treatment units in secondary care setting 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?	Data presented in NEJM paper shows OS analysis is immature but a positive trend favouring Bela Pom dex Data presented at ASH meeting 2024 shows no decrement in QoL in comparison with control population. https://ash.confex.com/ash/2024/webprogram/Paper200299.html
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)	The treatment is given in day unit as current standard of care. Patients would receive eye specialist appointments prior to first 3 doses of Belantamab Mafodotin

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	No
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 vents 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?	PVD as control arm is not available in UK practice as this was not submitted to NICE MRD negativity rates, PFS and OS

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	MRD negativity rates predicts for PFS 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?	Nil 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:

BPD shows superior MRD negativity and PFS compared to controls in relapsed refractory MM

BPD shows improved PFS even in daratumumab refractory patients

This is an outpatient therapy applicable for all ages of myeloma patients

This is the first BCMA targeted therapy used earlier in disease course

Belantamab mafodotin as monotherapy was used in a compassionate use scheme with a good take up across UK centres

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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	Rakesh Popat
2. Name of organisation	University College London Hospitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory multiple myeloma? ☐ 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?	To prolong survival and maintain quality of life

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A response rate (50% reduction in paraprotein) of 30% of greater is considered significant in the context of relapsed myeloma
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory multiple myeloma?	There continues to be a large unmet need for patients with RRMM as their response durations can be short and the number of patients that are able to receive subsequent treatments reduces at each line due to disease or treatment related mortality. As a result we need a well tolerated highly efficacious treatment, particularly at 2nd line where patients typically still maintain a good performance status and can enjoy a good quality of life.
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?	Treatment for RRMM follows NICE guidance and therefore is quite homogeneous across the UK following a very well defined pathway. There will be individual variations within the pathway due to prior responsiveness to treatment, treatment related toxicities, performance status, co-morbidities and patient choice. This technology would make a substantial impact on the pathway as the treatment is highly effective and well tolerated. It will therefore displace other treatments in preference.
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?	This technology will be a day case treatment, similar to other treatments for RRMM. The frequency of Belantamab infusion is less than other IV or SC treatments which will reduce day case resources. However patients will require an ocular assessment at baseline, prior to the first 3 infusions and as required thereafter. This will require set-up of a pathway and resource use within ophthalmology/ optometry services.

• 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)	This treatment should be used in secondary care, it is not suitable in primary care
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?	The clinical trial randomised patients against a treatment not funded for use in the UK and demonstrated an improvement in progression free survival. However it would be expected that the PFS benefit can be translated to UK standard treatments. Currently the trial follow-up is too short to demonstrate a survival benefit. HRQOL is expected to stay similar compared to current treatments.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, this treatment appears to be suitable for all patients.
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)	In many ways the treatment will be easier as the infusion is short and given infrequently (minimum interval is 4 weekly). Clinical trial data shows that it tends to be given every 12 week after 12 months. However the ocular management will require pathways to be in place and interpretation of results in order to safely dose patients. Once clinicians are familiar with this process it is not burdensome and overall the treatment is easy to administer.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will be commenced when a patient has relapsed following prior treatment. It will be interrupted for grade 3 or above toxicities but may be restarted upon recovery to grade 2. Treatment will be stopped in the event of disease progression, unacceptable toxicities or patient/ clinician choice.

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	The infrequent administration of Belantamab Mafodotin (every 4 weeks, potentially being extended to less frequent dosing as per tolerability) provides substantial convenience to the patient.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is a first-in-class antibody drug conjugate to be licensed for myeloma. This is important as myeloma patients are sequentially exposed to multiple classes of therapy and resistance evolves to them. This treatment has shown to be effective in patients exposed to proteasome inhibitors, immunomodulatory drugs and CD8 monoclonal antibodies which are now commonly used at 1st or 2nd line. As a result this treatment does represent a "step change" in the management.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side effect is blurring of vision. Clinical trial data shows that this does not adversely impact upon global quality of life scores. Responding patients show improvements in QOL.
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?	The DREAMM-8 clinical trial used a comparator that is not funded within the NHS. However Pomalidomide is used at 4th line and beyond either with dexamethasone alone or with Isatuxamab. Bortezomib and Dex is used at 2nd line. It is likely that Bela-Pom Dex would be an improvement to current treatments at 2nd line and beyond, particularly in the current era of myeloma 1st lime therapies where many 2nd line treatment are no longer appropriate (due to prior exposure or refractoriness). The most important outcome is PFS and overall survival which were primary and secondary endpoints on the trial. In the DREAMM-7 trial, the improvement of

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	PFS correlated with an improved OS. The trend in DREAMM-8 is towards an improved OS but longer follow-up is required. No new adverse events have been reported.
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?	Real world data from the UK with Belantamab Mafodotin as monotherapy for heavily pre-treatment myeloma is favourable compared to the DREAMM-2 clinical trial. There is no real world data with this combination.
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	There are no equality issues here

• 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:

Belantamab Mafodotin with Pom Dex is an efficacious treatment for early relapsed myeloma

The treatment can be well tolerated with appropriate dose modifications and interruptions with no detriment to HRQOL

Treatment can be given infrequently (ie every 4 weeks extending to every 12 weeks) according to tolerability

Robust ocular reviews are required and ocular reports require careful interpretation

This treatment may be applicable to a wide range of patients

Thank you for your time.

Your privacy

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Single Technology Appraisal

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with relapsed or refractory multiple myeloma or caring for a patient with relapsed or refractory multiple myeloma.

The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on 6 January 2025. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with relapsed or refractory multiple myeloma

Table 1 About you, relapsed or refractory multiple myeloma current treatments and equality

1. Your name	David Robinson
2. Are you (please tick all that apply)	☒ A patient with relapsed or refractory multiple myeloma ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or refractory multiple myeloma ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myeloma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory multiple myeloma ? **If you are a carer (for someone with relapsed or refractory multiple myeloma) please share your experience of caring for them**	I was first diagnosed with Myeloma in May 2021. Each of the three treatments that I have had, including the current clinical trial have been successful in dealing with the paraprotein to the extent that on each occasion after starting a new treatment, the paraprotein has been undetectable within a few months. I have therefore felt generally in good health and been able to carry out normal chores and exercise without any significant adverse affect. I did develop peripheral neuropathy in both my feet whilst on the combination of Velcade and thalidomide from May 2021 to October 2021. It was stopped earlier than planned due to me developing peripheral neuropathy in my feet. I was in remission though until May 2022 when the paraprotein was rising and I was given a different treatment with Ixazomib, Lenalidomide and Dexamethasone. I was in remission after a few months of starting this treatment until December 2023 when again the paraprotein was rising again.

	On the current treatment (ProMMise) with belantamab and Dexamethasone it has affected the cornea of both my eyes. This was after about four months.
7a. What do you think of the current treatments and care available for relapsed or refractory multiple myeloma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The care I have received by the NHS both at the Royal Gwent Hospital, Newport and UHW Heath Hospital, Cardiff, has been exemplary in all respects and I could not have wished for better treatment.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory multiple myeloma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I don't feel that I am qualified to comment on this.
9a. If there are advantages of Belantamab mafodotin with pomalidomide and dexamethasone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Belantamab mafodotin with pomalidomide and dexamethasone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I don't feel that I am qualified to comment on this.

10. If there are disadvantages of Belantamab mafodotin with pomalidomide and dexamethasone over current treatments on the NHS please describe these. For example, are there any risks with Belantamab mafodotin with pomalidomide and dexamethasone ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Not applicable.
11. Are there any groups of patients who might benefit more from Belantamab mafodotin with pomalidomide and dexamethasone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I don't feel that I am qualified to comment on this.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory multiple myeloma and Belantamab mafodotin with pomalidomide and dexamethasone ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	I don't feel that I am qualified to comment on this.

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.	
13. Are there any other issues that you would like the committee to consider?	Two side affects of dexamthasone and Co-Trimoxozole in the current treatment. Dexamethasone is prescribed as 20 x 2mg once a week. It's phycological by if there were less tablets, say 5 x 8mg or even 10 x 4mg they would be easier to swallow. I experience a side affect of sweating in bed on the night having taken these tablets. Co-Trimoxozole I take 1 x 160mg tablet both in the morning and evening twice a week. The first day is a Monday and the second is a Thursday (one day after taking Dexamethasone on a Wednesday). I don't generally experience any side affects after taking the tablets on a Monday, but on a Thursday night, I regularly experience sleep deprivation to the extent that some Thursday nights I get no sleep at all.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- For me, this clinical trial is working.
- There are some side effects but none that are affecting me greatly.
- The treatment I am getting from doctors and nurses could not be better and is giving me a quality of life that I wouldn't have had without this treatment.

Thank you for your time.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 168481

Completed 11th October 2024

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

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Contributions of authors

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic evidence
Angela Boland	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical, statistical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the company search strategy
Joanne McEntee	Critical appraisal of the company submission
Gillian Brearton	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike Information Criterion
ASCT	Autologous stem cell transplant
BIC	Bayesian Information Criterion
BNF	British National Formulary
BPd	Belantamab mafodotin plus pomalidomide and dexamethasone
BVd	Belantamab mafodotin plus bortezomib and dexamethasone
CI	Confidence interval
CR	Complete response
CrI	Credible interval
CRR	Complete response rate
CSR	Clinical study report
DoR	Duration of response
DREAMM-8	DRiving Excellence in Approaches to Multiple Myeloma. The key trial discussed in the company submission
DVd	Daratumumab plus bortezomib and dexamethasone
DVTd	Daratumumab plus bortezomib, thalidomide, and dexamethasone
EAG	External assessment group
EAIR	Exposure-adjusted incidence rates
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Questionnaire Module 20
EQ-5D	European Quality of life-5 Dimensions
FE	Fixed effects
hKd	High dose Selinexor and dexamethasone
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analyses
ICER	Incremental cost-effectiveness ratio
ISS	International Staging System
ITT	Intention-to-treat
Kd	Carfilzomib and dexamethasone
MHRA	Medicines, and Healthcare Regulatory Agency
MM	Multiple myeloma
MR	Minimal response
MRD	Minimum residual disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis

NMB	Net monetary benefit
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PVd	Pomalidomide plus bortezomib and dexamethasone
QALY	Quality-adjusted life years
RCT	Randomised controlled trials
RDI	Relative dose intensity
RR	Relapsed/Refractory
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SVd	Selinexor plus bortezomib and dexamethasone
TEM	Treatment effect modifier
TEAE	Treatment emergent adverse event
TTD	Time to treatment discontinuation

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.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of EAG key issues

	Summary of issue	Report sections
Issue 1	Generalisability of DREAMM-8 trial results to NHS patients	3.2
Issue 2	Limitations of company PFS and OS NMAs	3.6
Issue 3	Lack of evidence to support modelling different overall survival for the intervention and comparator treatments	6.2
Issue 4	Remove wastage of medications taken as tablets	6.4
Issue 5	RDI used for costing all treatments	6.5
Issue 6	Use alternative utility values	6.6

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life in a quality adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. The EAG has revised the company model by:

- setting OS equal for all treatments
- removing wastage for medications taken as tablets
- using RDI to estimate all treatment costs
- using ENDEAVOUR trial PFS and PD utility values

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Generalisability of DREAMM-8 trial results to NHS patients

Report section	Section 3.2
Description of issue and why the EAG has identified it as important	The focus of the company submission is on patients who have only received one prior line of therapy that includes a lenalidomide-containing regimen and for whom lenalidomide is unsuitable All DREAMM-8 trial patients had previously been treated with lenalidomide; however, only 52.5% of these patients had been treated with lenalidomide in the first-line setting. No clinical effectiveness evidence has been provided by the company for all patients for who lenalidomide is unsuitable Only 25% of DREAMM-8 trial patients had received prior treatment with daratumumab. Clinical advice to the EAG is that this limits the generalisability of the trial results to NHS patients as, moving forward, most NHS patients will receive daratumumab in the first-line setting. The impact of limited prior daratumumab exposure on DREAMM-8 trial results is not known DREAMM-8 trial data are immature (median OS has not been reached in the BPd arm or the PVd arm and PFS has only been reached in the PVd arm)
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; EAG=External Assessment Group; OS=overall survival; PVd=pomalidomide plus bortezomib and dexamethasone

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Limitations of company PFS and OS NMAs

Report section	Section 3.6
Description of issue and why the EAG has identified it as important	The EAG highlights that it was not possible to explore the effect of TEMs on company NMA results and has the following concerns about the data used to conduct the company NMAs: • DREAMM-8 trial data were immature (median OS had not been reached in the BPd or the PVd arm and median PFS had only been reached in the PVd arm) • none of the trials included only patients treated in the second-line setting • in the OS NMAs, not all patients had been previously treated with lenalidomide • where trial data were available, very few patients had been previously treated with daratumumab • only the OPTIMISMM trial (PVd vs Vd) HR used in the company OS (lenalidomide-exposed+ITT) NMA was estimated using a Cox proportional hazard model with subsequent therapy as a time-dependent covariate and adjusting for stratification factors The EAG therefore considers that company PFS NMA results may be unreliable, and the company OS NMA results should not be used to inform decision-making
What alternative approach has the EAG suggested?	Generate cost effectiveness results that do not rely on company OS NMA results
What is the expected effect on the cost effectiveness estimates?	See Issue 3
What additional evidence or analyses might help to resolve this key issue?	None

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; EAG=External Assessment Group; HR=hazard ratio; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PVd=pomalidomide plus bortezomib and dexamethasone; VD=bortezomib plus dexamethasone; TEMs=treatment effect modifiers

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 3 Lack of evidence to support modelling different overall survival for the intervention and comparator treatments

Report section	Section 6.2
Description of issue and why the EAG has identified it as important	In the company model, it is assumed that OS for patients treated with BPd is longer than OS for patients treated with any of the comparator treatments. However, the company OS NMA credible intervals all crossed 1. Further, the EAG considers that company OS NMA results are unreliable and should not be used to inform decision-making (see Issue 2)
What alternative approach has the EAG suggested?	Assume that OS for patients treated with BPd, DVd, hKd and SVd is the same
What is the expected effect on the cost effectiveness estimates?	This EAG revision increases the sizes of the company base case ICERs per QALY gained
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on the validity of the EAG approach

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; EAG=External Assessment Group; hKd=high dose carfilzomib and dexamethasone; ICER=incremental cost effectiveness ratio; NMA=network meta-analysis; OS=overall survival; PVd=pomalidomide plus bortezomib and dexamethasone; QALY=quality adjusted life year; SVd=selinexor plus bortezomib and dexamethasone

Issue 4 Remove wastage of medications taken as tablets

Report section	Section 6.4
Description of issue and why the EAG has identified it as important	When estimating the cost of medications taken as tablets, the company has included the cost of wastage. As all modelled medications taken as tablets come in sizes that allow doses to be lowered without wastage, the EAG considers that wastage should not be included in the cost effectiveness the analysis
What alternative approach has the EAG suggested?	Remove wastage costs associated with medications taken as tablets
What is the expected effect on the cost effectiveness estimates?	This EAG revision increases the sizes of the company base case ICERs per QALY gained
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on the validity of the EAG approach

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Issue 5 RDI used for costing all treatments

Report section	Section 6.5
Description of issue and why the EAG has identified it as important	The company has used DREAMM-8 trial individual patient data to estimate the cost of belantamab mafodotin and used RDI to estimate the cost of all other drugs. This is problematic as the two approaches can generate different costs
What alternative approach has the EAG suggested?	All drug costs estimated using the RDI-based approach
What is the expected effect on the cost effectiveness estimates?	This EAG revision increases the sizes of the company base case ICERs per QALY gained
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; RDI=relative does intensity

Issue 6 Use alternative utility values

Report section	Section 6.6
Description of issue and why the EAG has identified it as important	DREAMM-8 trial data suggest that patients who are progression-free and treated with BPd experience a better health-related quality of life than patients treated with PVd. Given the ocular toxicity experienced by patients treated with BPd, clinical advice to the EAG is that this difference in health-related quality of life may be unrealistic
What alternative approach has the EAG suggested?	Use PFS and PD health state utility values (sourced from the ENDEAVOUR trial) that do not differ by treatment (BPd, DVd, hKd, SVd)
What is the expected effect on the cost effectiveness estimates?	This EAG revision increases the sizes of the company base case ICERs per QALY gained
What additional evidence or analyses might help to resolve this key issue?	None

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; EAG=External Assessment Group; hKd=high dose carfilzomib and dexamethasone; ICER=incremental cost effectiveness ratio; PD=progressed disease; PFS=progression-free survival; PVd=pomalidomide plus bortezomib and dexamethasone; SVd=selinexor plus bortezomib and dexamethasone

1.6 Summary of EAG's preferred assumptions and resulting ICERs per QALY gained

Table B Probabilistic results for BPd versus DVd, PAS price for belantamab mafodotin

EAG revisions	Incremental		ICER
	Cost	QALYs	£/QALY
A. Company base case	[redacted]	[redacted]	**BPd dominates**
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]
R1) DVd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=Patient Access Scheme; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table C Probabilistic results for BPd versus hKd, PAS price for belantamab mafodotin

EAG revisions	Incremental		ICER
	Cost	QALYs	£/QALY
A. Company base case	[redacted]	[redacted]	**BPd dominates**
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]
R1) hKd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=Patient Access Scheme; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table D Probabilistic results for BPd versus SVd, PAS price for belantamab mafodotin

EAG revisions	Incremental		ICER
	Cost	QALYs	£/QALY
A. Company base case	[redacted]	[redacted]	**BPd dominates**
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]
R1) SVd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=Patient Access Scheme; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Modelling errors identified and corrected by the EAG are described in Section 6. For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.1 to Section 6.8.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this National Institute for Health and Care Excellence (NICE) appraisal is on belantamab mafodotin with pomalidomide and dexamethasone (BPd) as a treatment option for patients with relapsed or refractory multiple myeloma (RRMM) who have received ≥1 prior line of treatment including a lenalidomide-containing regimen.

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. In addition to the CS, the company provided further information in response to the clarification letter.

2.2 Background

2.2.1 Multiple myeloma

Myeloma is a rare, incurable type of haematological cancer that develops from bone marrow plasma cells. Patients are diagnosed with multiple myeloma when more than one bone marrow site is affected.[1]

In the UK, myeloma accounts for approximately 2% of cancer cases[2] and 12.4% of haematological malignancies.[3] Between 2017 and 2019, the average number of new cases of myeloma in the UK was 6240; >43% of cases are diagnosed in patients aged ≥75 years and a myeloma diagnosis is rare for patients aged <40.[2] Myeloma is more commonly diagnosed in men than in women and, compared to the White ethnic group, myeloma is more commonly diagnosed in the Black ethnic group, and less commonly diagnosed in the Asian ethnic group.[2] In England, the 5-year and 10-year survival rates for patients with myeloma are 55% and 30%, respectively.[4]

2.2.2 Intervention

The intervention is belantamab mafodotin plus pomalidomide and dexamethasone.

Belantamab mafodotin (brand name: Blenrep™) is a humanised immunoglobulin Gκ monoclonal antibody conjugated with a cytotoxic agent (maleimidocaproyl monomethyl auristatin F). It binds to cell surface B-cell maturation antigen 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.[5]

Pomalidomide is an immunosuppressant that has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma tumour cell growth.[6]

Dexamethasone is a highly potent and long-acting glucocorticoid.[7]

Belantamab mafodotin is administered as an intravenous (IV) infusion. Pomalidomide and dexamethasone are administered orally. The BPd treatment regimen in the DREAMM-8[8] trial (the key trial providing clinical effectiveness evidence for BPd) is shown in Table 1. Treatment continues until disease progression or unacceptable toxicity.

Table 1 DREAMM-8 trial BPd treatment regimen

Treatment	Dose	Administration	Timing
Belantamab mafodotin	2.5mg/kg (cycle 1) 1.9mg/kg thereafter	Intravenous	4-week cycle
Pomalidomide	4mg	Oral	Days 1 to 21
Dexamethasone	40mg	Oral	Days 1, 8, 15 and 22

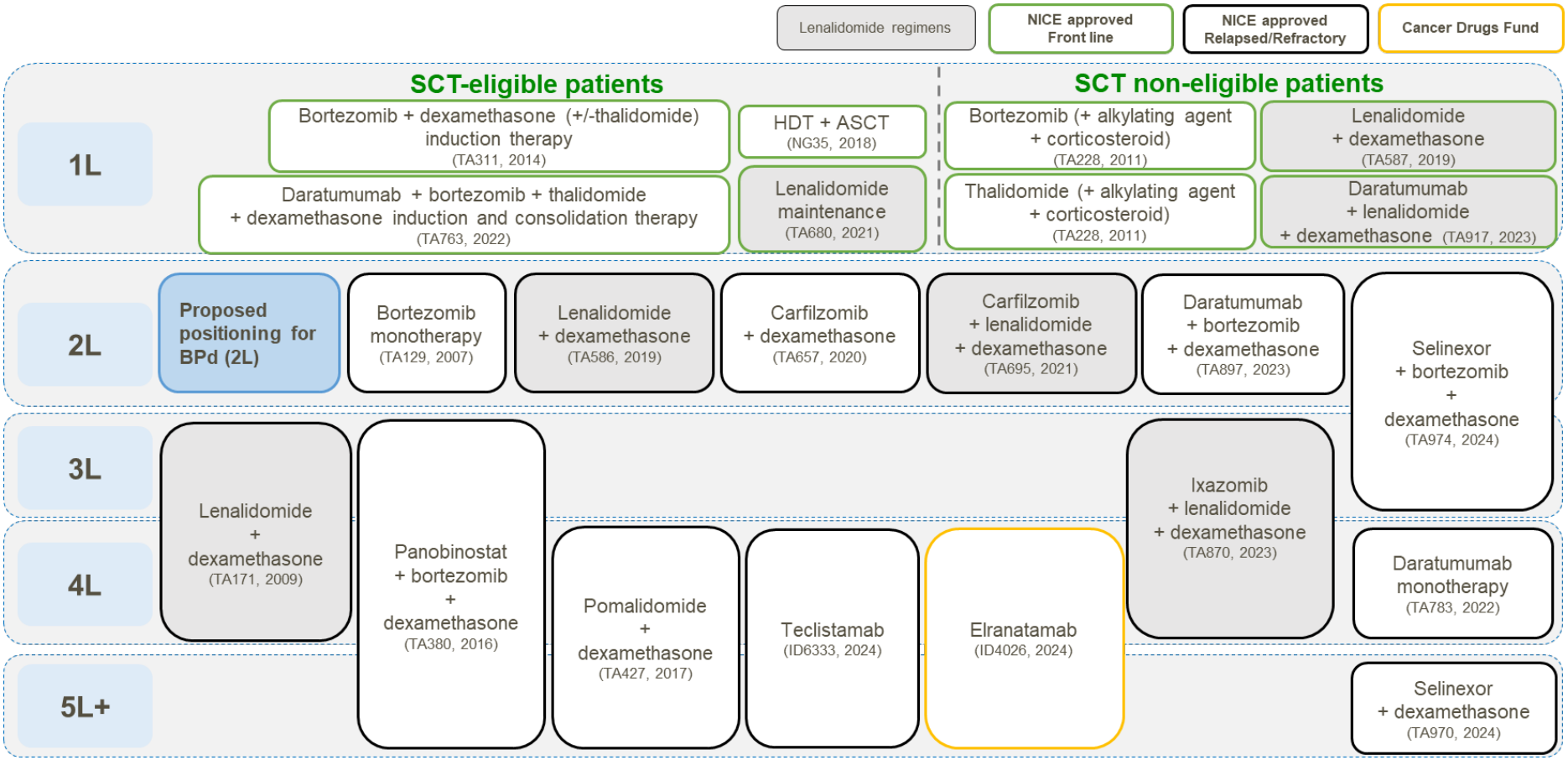
Source: CS, Figure 4

2.3 Company's overview of current service provision

The company has presented the current NHS treatment pathway for patients with RRMM and the proposed positioning of BPd, should BPd be recommended by NICE (CS, Figure 3). The company has positioned BPd as a second-line treatment for patients who are refractory to, or who are unsuitable for, treatment with lenalidomide (CS, p19).

Clinical advice to the EAG is that CS, Figure 3 is an accurate representation of the current NHS treatment pathway; however, some NHS patients who are eligible for autologous stem cell transplant (ASCT) choose not to receive lenalidomide maintenance treatment in the first-line setting. Possible reasons for refusing lenalidomide maintenance treatment include complications from, or poorly tolerated, ASCT and high dose therapy and/or would like a treatment break. However, lenalidomide might be considered an option at a later-line.

The company highlights (CS, p18) that belantamab mafodotin with bortezomib and dexamethasone (BVd) is currently being appraised by NICE (ID6212[9]) as a second-line treatment option for MM after one or more treatments. The first NICE Appraisal Committee meeting for BVd will be on 8th January 2025 and NICE expects guidance to be published on 5 March 2025.[9]



ASCT=autologous stem cell transplant; HDT=high-dose therapy; NICE=National Institute for Health and Care Excellence; NG=NICE Guideline; SCT=stem cell transplant; TA=technology appraisal
Source: CS, Figure 3

Figure 1 Company's overview of the treatment pathway for multiple myeloma

A description of first- and second-line treatments is presented in the CS (CS, Section B.1.3.2.2). The company highlights that treatment options at each line depend on prior treatments and that patients are not rechallenged with a previous treatment.

Second-line treatment options

The company has positioned BPd as a second-line treatment for patients with RRMM who have received one prior line of treatment including a lenalidomide-containing regimen and for whom lenalidomide is unsuitable (CS, p19). The currently available second-line lenalidomide-sparing treatments are bortezomib monotherapy, carfilzomib+dexamethasone (Kd), daratumumab+bortezomib+dexamethasone (DVd) and selinexor+bortezomib+dexamethasone (SVd). Clinical advice to the EAG is that:

- current first-line treatments for MM are new and early experience suggests that they are very effective; it is not clear which of the available second-line treatments will become standard of care (SoC) in the future
- in the NHS, daratumumab is currently widely used to treat patients in the first-line setting. Patients undergoing ASCT typically receive daratumumab plus bortezomib and thalidomide and dexamethasone as an induction treatment (6 cycles) and as consolidation treatment (2 cycles) [TA763[10]]; this can be followed by lenalidomide maintenance treatment [TA680[11]]. Thus, most patients who have had an ASCT will have been exposed to first-line daratumumab (but may not necessarily be refractory to it). Since 2023, patients who are ineligible for ASCT are offered treatment with daratumumab plus lenalidomide and dexamethasone. Consequently, on disease progression, ASCT-ineligible patients may be refractory to daratumumab
- in the first-line setting, 30% of ASCT-eligible NHS patients choose not to take up lenalidomide maintenance treatment
- clinical experience of prescribing SVd (a second-line lenalidomide-sparing treatment) is limited as SVd has only recently (2024) been recommended by NICE (TA974[12]).

2.4 Critique of the company's definition of the decision problem

A summary of the final scope[13] issued by NICE and the decision problem addressed by the company is presented in Table 2. More information regarding key issues is provided in Section 2.4.1 to Section 2.4.7.

Table 2 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Intervention	Belantamab mafodotin with pomalidomide and dexamethasone (BPd)	As per scope	As per scope
Population	People with relapsed or refractory multiple myeloma who have had at least 1 prior line of treatment including a lenalidomide-containing regimen	Adults (≥18 years) with RRMM who have had 1 line of treatment including a lenalidomide-containing regimen (second-line patients) and for whom lenalidomide is unsuitable. There is a considerable unmet need in current NHS practice at second-line for a new, more efficacious triplet regimen for patients who have had a prior lenalidomide containing regimen, and for whom lenalidomide is unsuitable.	The company has presented clinical effectiveness evidence from the DREAMM-8 trial. The DREAMM-8 trial included 302 patients who had all received at least one prior line of treatment, including a lenalidomide-containing regimen; 52.5% of DREAMM-8 trial patients had only received one prior line of treatment.
Comparator(s)	For people who have had 1 prior therapy: • bortezomib monotherapy • carfilzomib with dexamethasone (Kd) • daratumumab with bortezomib and dexamethasone (DVd) • selinexor with bortezomib and low-dose dexamethasone (SVd) [only if their condition is refractory to both daratumumab and lenalidomide] For people who have had ≥2 prior therapies, please see final scope issued by NICE. For people who have had any number of prior therapies: • conventional chemotherapy	For people who have had a prior lenalidomide containing regimen, and for whom lenalidomide is unsuitable: • Kd • DVd • SVd (for a subgroup of patients who are refractory to daratumumab and lenalidomide) In line with NICE Methods, the decision problem addresses only those comparators with the potential to affect prescribing decisions in England and Wales. As the standard practice in MM is to treat patients with several modalities in combination regimens, GSK do not consider bortezomib monotherapy to be a relevant comparator as it is rarely used in clinical practice	Clinical advice to the company and the EAG is that, for patients who had had a prior lenalidomide containing regimen in the first-line setting, the relevant second-line setting comparators are DVd, hKd* and SVd (for the subgroup of patients who are refractory to daratumumab and lenalidomide). Clinical advice to the company and the EAG is that bortezomib monotherapy is rarely used in the NHS as a second-line treatment and is not a relevant comparator. The company has not discussed the use of conventional chemotherapy regimens or BSC. Clinical advice to the EAG is that patients who are considered suitable for treatment with BPd in the second-line setting would not be offered conventional chemotherapy or BSC.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	regimens • best supportive care (BSC)		
Outcomes	• OS • PFS • Response rates • AEs of treatment • HRQoL	As per scope	Direct evidence The company has presented clinical effectiveness evidence for BPd versus PVd for all outcomes listed in the final scope issued by NICE. Indirect evidence The company undertook PFS and OS NMAs to compare the clinical effectiveness of BPd versus DVd, hKd and SVd. Due to issues relating to data inputs, the EAG considers that results from these analyses have weaknesses.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Economic analysis	The cost effectiveness of treatments should be expressed in terms of ICERs per QALY gained The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs should be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies should be taken into account. The availability and cost of biosimilar and generic products should be taken into account	As per scope	As per scope

* Carfilzomib with dexamethasone dose recommended in TA657[14]
AE=adverse event; BPd=belantamab mafodotin+pomalidomide+dexamethasone; BPD=belantamab mafodotin+bortezomib+dexamethasone; BSC=best supportive care; DVd=daratumumab+bortzomib+dexamethasone; EAG=external assessment group; hKd=high-dose carfilzomib+dexamethasone; HRQoL=health-related quality of life; Kd=carfilzomid+dexamethasone; ICER=incremental cost effectiveness analysis; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PVd=pomalidomide+bortezomib+dexamethasone; QALY=quality adjusted life year; RRMM=relapsed or refractory multiple myeloma; SVd=selinexor+bortezomib+dexamethasone
Source: CS, Table 1 and EAG comment

2.4.1 NHS treatment pathway

Clinical advice to the EAG is that the treatment pathway for NHS patients with RRMM is evolving. First-line daratumumab is proving effective and the impact of prior first-line treatment with daratumumab on OS is not known. Further, there is currently limited experience of treating patients who are refractory to first-line treatment with daratumumab and it is not clear which of the second-line treatment options will become standard of care in the future (see Section 2.3).

2.4.2 Source of direct clinical effectiveness data

The company has presented clinical effectiveness evidence for BPd from the DREAMM-8 trial. The DREAMM-8 trial is an ongoing (still recruiting[15]) international phase III, open-label, randomised controlled trial (RCT) that compares the efficacy and safety of belantamab mafodotin plus pomalidomide and dexamethasone (n=155) with pomalidomide plus bortezomib and dexamethasone (PVd, [n=147]) in patients with RRMM who have received ≥1 line of prior therapy, including lenalidomide. At the point of the primary analysis (data cut-off: 29 January 2024), the median DREAMM-8 trial follow-up was 21.8 months (CS, p24).

The comparator in the DREAMM-8 trial (PVd) is not recommended by NICE as the company did not provide an evidence submission (TA602[16]).

2.4.3 Population

In the final scope[13] issued by NICE, the population is described as patients who have received ≥1 line of prior therapy; the company has limited the population to patients who have only received one prior line of therapy that includes a lenalidomide-containing regimen and for whom lenalidomide is unsuitable.

The EAG highlights that:

- only 52.5% of DREAMM-8 trial patients had only received one prior line of therapy
- there is no robust clinical effectiveness evidence available from the DREAMM-8 trial for all patients who are unsuitable for treatment with lenalidomide
- only 25% of DREAMM-8 trial patients had received prior treatment with daratumumab. Clinical advice to the EAG is that this limits the generalisability of the trial to NHS patients as, moving forward, most NHS patients will receive daratumumab in the first-line setting. The impact of prior daratumumab exposure on the efficacy of BPd is not known

2.4.4 Intervention

The DREAMM-8 trial intervention is BPd; the DREAMM-8 trial BPd dosing regimen is provided in Table 1.

In December 2023, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP)[17] confirmed the initial recommendation not to renew the conditional marketing authorisation for belantamab mafodotin as a treatment for adults who had received ≥4 previous treatments and whose disease had not responded to treatment with at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and whose cancer has worsened since receiving the last treatment. The reason for not renewing the authorisation was that recent data had not confirmed the effectiveness of belantamab mafodotin; the CHMP[17] considered that the benefits of belantamab mafodotin no longer outweighed its risks.

The combination of belantamab mafodotin, pomalidomide and dexamethasone (BPd) does not currently have a marketing authorisation from the Medicines Healthcare products Regulatory Agency (MHRA) for use in patients with RRMM who have received ≥1 prior line of treatment including a lenalidomide-containing regimen. [redacted] (CS, Table 2).

In the anticipated MHRA marketing authorisation (CS, Table 2), it is stipulated that ophthalmic examinations, including assessment of visual acuity and slit lamp examination, must be performed before each of the first four doses of belantamab mafodotin and during treatment as clinically indicated. Clinical advice to the EAG is that the required ophthalmology checks could be burdensome for patients and could pose a substantial burden on NHS resources.

Clinical advice to the EAG is that ocular toxicity is a notable side effect of treatment with belantamab mafodotin. In the DREAMM-8 trial BPd arm, eye-related events led to belantamab mafodotin dose reductions (encompassing both the decrease in dose and the extension of dosing intervals), interruptions/delays, and discontinuations in [redacted]%, 86%, and 9% of patients, respectively.

2.4.5 Comparators

The final scope[13] issued by NICE lists comparators for patients who have had 1, 2 ,3, 4, 5 and >5 prior therapies. In line with the company's intended positioning of BPd as a second-line treatment, the company has only considered the treatments listed in the final scope[13] for patients who have received one prior line of treatment (including a lenalidomide-containing regimen) and for whom lenalidomide is unsuitable. The company has provided clinical effectiveness evidence for the comparison of BPd versus DVd, hKd (carfilzomib with dexamethasone dose recommended in TA657[14]) and SVd (for the subgroup of patients who are refractory to daratumumab and lenalidomide). Clinical advice to the company and the EAG is that bortezomib monotherapy is rarely used to treat NHS patients with RRMM and is not a

relevant comparator. The company has not discussed the use of conventional chemotherapy regimens or BSC; clinical advice to the EAG is that patients who are considered suitable for treatment with BPd in the second-line setting would not be offered conventional chemotherapy or BSC.

2.4.6 Outcomes

The company has provided DREAMM-8 trial (BPd versus PVd) results for all the outcomes listed in the final scope[13] issued by NICE, namely overall survival (OS), progression-free survival (PFS), response rates (including duration of response [DoR] and overall response rate [ORR]), adverse events (AEs) and health-related quality of life (HRQoL). Clinical advice to the EAG is that these are the most important outcomes for patients with RRMM.

DREAMM-8 trial data are immature; median PFS in the BPd arm has not been reached and median OS has not been reached in either trial arm.

The outcome data available from the DREAMM-8 trial are for the ITT population; results for second-line only patients have not been reported.

Due to the absence of head-to-head trials comparing BPd with relevant comparator treatments, the company carried out PFS and OS network meta-analyses (NMAs) to generate comparative data. Due to issues relating to data inputs, the EAG considers that results from these analyses are unreliable.

2.4.7 Economic analysis

As specified in the final scope[13] issued by NICE, the cost effectiveness of treatments was expressed in terms of incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained. Outcomes were assessed over a 34-year time horizon (which the company considered was equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

Belantamab mafodotin, carfilzomib, daratumumab, panobinostat, pomalidomide and selinexor treatments are available to the NHS at confidential Patient Access Scheme (PAS) prices. Only the confidential price of belantamab mafodotin is known to the company. Cost effectiveness results generated using the discounted prices for all drugs are presented in a confidential appendix. The EAG has used the pomalidomide current list price in all analyses.

The EAG agrees with the company that a severity weighting was not applicable for this appraisal (see CS, Section B.3.6 for details).

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company to support the use of BPd as a treatment option for patients with RRMM who have received one prior line of treatment (including a lenalidomide-containing regimen) and for whom lenalidomide is unsuitable.

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify and select BPd clinical effectiveness evidence. Full details of the company's methods are presented in the CS (CS, Appendix D). The company's literature searches were comprehensive and were completed <6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the Liverpool Reviews and Implementation Group (LR*i*G) in-house systematic review checklist is presented in Table 3. The EAG considers that the company's systematic review methods were appropriate.

Table 3 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.1, Table 1
Were appropriate sources searched?	Yes	CS, Appendix D.1.1 The company's literature searches were comprehensive and were completed <6 months before the company's evidence submission to NICE
Was the timespan of the searches appropriate?	Yes	Clarification response C2 The search period (2008-2024) was determined to be sufficient to capture all relevant trials due to the rapidly evolving multiple myeloma treatment patterns
Were appropriate search terms used?	Yes	CS, Appendix D.1.1
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.1, Table 1 The SLR eligibility criteria were broader than the decision problem criteria as the SLR was designed to summarise the efficacy and safety of RRMM treatments in clinical trials enrolling adult patients who had had ≥1 prior line of therapy
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.2
Were data extracted by two or more reviewers independently?	Yes	CS, Appendix D.1.3
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, p34 Assessment of the quality of the DREAMM-8 trial was carried out using the minimum criteria recommended by NICE.[18] CS, Appendix D.1.3 Assessment of the quality of trials included in the NMAs was carried out using the Cochrane RoB assessment tool for randomised trials (RoB2[19])
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix D.1.3
Were attempts to synthesise evidence appropriate?	Yes	The company carried out NMAs to generate clinical effectiveness evidence to compare BPd with DVd, hKd and SVd. The EAG's critique of the company's methods is presented in Section 3.6 of this report

CS=company submission; EAG=External Assessment Group; RoB=risk of bias; RRMM=relapsed or refractory multiple myeloma; SLR=systematic literature review
Source: LRiG in-house checklist

3.2 EAG summary and critique of clinical effectiveness evidence

3.2.1 Included trials

The company SLR identified one relevant trial, the DREAMM-8 trial. The DREAMM-8 trial is an ongoing, international, open-label, phase III RCT trial that provides evidence of the efficacy of BPd as a treatment for adult patients with RRMM who have received ≥1 prior line of treatment including a lenalidomide-containing regimen. The DREAMM-8 trial comparator treatment is PVd. As noted in Section 2.4.1, PVd is not recommended by NICE for use in the NHS.

The company conducted NMAs to compare the clinical effectiveness of BPd versus DVd, hKd and SVd. The EAG's summary and critique of the company's NMAs are presented in Section 3.6. Details of the trials that provided the data that were used in the company NMAs are available in the CS (CS, Appendix D).

3.2.2 Characteristics of the DREAMM-8 trial

A summary of the DREAMM-8 trial design is presented in the CS (Figure 4). The treatment regimens administered in the trial are shown in Table 4. Treatment is continued until disease progression (International Myeloma Working Group [IMWG] criteria) or unacceptable toxicity.

Table 4 DREAMM-8 trial treatment regimens

Treatment	Dose	Administration	Timing
BPd (Q4W)			
Belantamab mafodotin	2.5mg/kg (cycle 1) 1.9mg/kg thereafter	Intravenous	Day 1
Pomalidomide	4mg	Oral	Days 1 to 21
Dexamethasone	40mg	Oral	Days 1, 8, 15 and 22
PVd (Q3W)			
Bortezomib	1.3mg/m^2	Subcutaneous	Days 1, 4, 8, 11 of cycles 1 to 8 and days 1 and 8 thereafter
Pomalidomide	4mg	Oral	Days 1 to 14
Dexamethasone	40mg	Oral	The day of, and day after, subcutaneous bortezomib

Q3W=every 3 weeks; Q4W=every 4 weeks
Source: Adapted from CS, Figure 4

In the DREAMM-8 trial, randomisation was stratified by number of prior lines of treatment (1, 2/3 or ≥4), prior bortezomib treatment (yes or no) and prior anti-CD38 treatment (yes or no). Patients were originally stratified based on International Staging System (ISS) status but, in Protocol Amendment 1, ISS status was swapped for prior anti-CD38 treatment (CS, p.30). The trial enrolled no more than 50% of patients who had had ≥2 prior lines of treatment. The numbers of patients recruited to the BPd arm and PVd arms were 155 and 147, respectively.

Patients were recruited from 18 countries (Australia, Brazil, Canada, China, Czech Republic, France, Germany, Israel, Italy, Japan, South Korea, New Zealand, Poland, Russian Federation, Spain, Turkey, UK [five treatment centres] and the US). Treatment cross-over was not permitted in the DREAMM-8 trial.

3.2.3 Demographic and disease characteristics of DREAMM-8 trial patients

DREAMM-8 trial baseline patient demographic characteristics and baseline patient disease characteristics are provided in the CS (CS, Table 7). The EAG agrees with the company (CS, p40) that baseline characteristics were balanced between the trial arms. Clinical advice to the EAG is that DREAMM-8 trial patients are generally comparable to NHS patients, although patients in the trial are slightly younger (median ages: 67 years [BPd] and 68 years [PVd]) than NHS patients (average 70 years).

The company is positioning BPd as a treatment for patients with RRMM who have received one line of therapy, including a lenalidomide-containing regimen (second-line), and for whom lenalidomide is unsuitable. All DREAMM-8 trial patients had been previously treated with lenalidomide. Just over half (52.5%) of DREAMM-8 trial patients had received only one prior line of treatment. Some patients (33.8%) had received 2 or 3 prior lines of treatment, and a small proportion (13.6%) had received ≥4 prior lines of treatment. In response to clarification question A1, the company provided the demographic and disease characteristics of patients who had received only one line of previous treatment. The EAG is satisfied that the characteristics of patients who had received one previous line of treatment are similar to the characteristics of the overall trial population. Clinical advice to the EAG is that exposure to different treatment agents influences the evolution of the disease and, in general, patients who have had more lines of treatment are likely to have worse outcomes than patients who have had fewer lines of treatment.

Only 25% of DREAMM-8 trial patients had received prior treatment with daratumumab. Clinical advice to the EAG is that this limits the generalisability of the trial to NHS patients as, moving forward, most NHS patients will receive daratumumab in the first-line setting (see Section 2.3). The impact of limited prior daratumumab exposure on DREAMM-8 trial results is not known.

3.2.4 Quality assessment of the DREAMM-8 trial

The company conducted a quality assessment of the DREAMM-8 trial using the minimum criteria recommended by NICE.[18] The results of the company's assessment are presented in the CS (CS, Table 10). The EAG agrees with the company's assessment (CS, Table 10) and

considers that the DREAMM-8 trial is of good methodological quality and has a low risk of bias.

3.2.5 Statistical approach used to analyse the DREAMM-8 trial

Information relevant to the statistical approach taken by the company to analyse DREAMM-8 trial data has been extracted from the CS, the Clinical Study Report[20] (CSR), the trial statistical analysis plan[21] (TSAP) and the trial protocol.[22] A summary of the EAG checks of the pre-planned statistical approach used by the company is provided in Appendix 8.1. The EAG is confident that the company's statistical approach is appropriate.

3.3 DREAMM-8 trial results

The DREAMM-8 trial primary outcome is PFS. The data cut-off date for the PFS analysis reported in the CS was 29th January 2024; at this point, median follow-up was 21.8 months. The estimated DREAMM-8 trial completion date is 1 May 2029.[15] The DREAMM-8 trial schedule of planned analyses is event-driven (see Table 5).

Table 5 Planned DREAMM-8 trial analyses

Analysis	Purpose	Timing
IA1	Harm (inferior efficacy)	~35 PFS events (25% PFS information fraction)
IA2	Efficacy	~145 PFS events (~84% PFS information fraction)
IA3	Primary PFS analysis	[redacted]
IA4	Efficacy	[redacted]

IA=interim analysis; OS-overall survival; PFS=progression-free survival
Source: CS, p44

3.3.1 Key DREAMM-8 trial clinical effectiveness results

PFS and OS results

Key DREAMM-8 trial ITT population PFS and OS results are presented in Table 6. At the cut-off date of 29 January 2024, median PFS had not been reached in the BPd arm and median OS had not been reached in either of the trial arms.

Table 6 Key DREAMM-8 trial PFS and OS results

Endpoint	BPd (N=155)	PVd (N=147)
Progression-free survival		
Median, months	NR (95% CI: 20.6 to NR)	12.7 (95% CI: 9.1 to 18.5)
HR	0.52 (95% CI: 0.37 to 0.73), p<0.001	
Overall survival		
Median, months	NR (95% CI: 33.0 to NR)	NR (95% CI: 25.2 to NR)
Estimated HR	0.77 (95% CI: 0.53 to 1.14), p=0.095	

CI=confidence interval; NR=not reached; PFS=progression-free survival; OS=overall survival
Source: CS, Table 11, Table 12, Table 13

Subgroup analyses

The results of the DREAMM-8 trial PFS subgroup analyses are presented in the CS as a forest plot (CS, Figure 12). The EAG agrees with the company (CS, p62) that the treatment benefit of BPd is evidenced across all subgroups; however, many of the subgroup analysis results have been generated using data from a small number of patients.

The company has provided detailed PFS, OS and TTD information for the lenalidomide refractory and high-risk cytogenetic subgroups (CS, Appendix E).

DoR, MRD, ORR, TTD results

Key DREAMM-8 trial ITT population DoR, MRD, ORR and TTD results are presented in Table 7.

Table 7 DREAMM-8 trial summary of DoR, MRD, ORR and TTD results

Endpoint	BPd (N=155)	PVd (N=147)
Duration of response		
Median, months	NR (95% CI: 24.9 to NR)	17.5 (12.1 to 26.4)
Minimal residual disease		
sCR/CR, %	23.9 (95% CI: 17.4 to 31.4)	4.8 (95% CI: 1.9 to 9.6)
p-value	<0.001	
Overall response rate		
sCR+CR+VGPR+PR	77.0 (95% CI: 70.0 to 83.7)	72.0 (95% CI: 64.1 to 79.2)
Difference	[redacted]	
Time to treatment discontinuation (safety population)	**BPd** (N=150)	**PVd** (N=147)
Median, months	[redacted] (95% CI: [redacted] to [redacted])	[redacted] (95% CI: [redacted] to [redacted])

CI=confidence interval; CR=complete response; DoR=duration of response; NR=not reached; PR=partial response; sCR=stringent complete response; TTD=time to treatment discontinuation; VGPR=very good partial response
Source: CS, Table 11

Other outcomes

Time to progression, PFS2, minimum residual disease negativity, complete response rate, time to response, time to best response and time to next treatment results are presented in the CS (CS, Appendix N). The results all indicate a treatment benefit for BPd compared with PVd.

3.3.2 Real-world evidence: National Cancer Registration and Analysis Service

The company has reported (CS, Section B.2.7.3) results from analyses of NHS National Cancer Registration and Analysis Service (NCRAS)[23] data; data from patients in England who were diagnosed with RRMM between 1 January until 2013 and 31 December 2020 were included in these analyses. The study authors identified a cohort of patients (N=730) that were considered similar to patients enrolled in the DREAMM-8 trial (D8-like cohort), i.e., patients who had received ≥1 prior line of treatment that contained ≥2 cycles of lenalidomide, were not refractory to bortezomib, and had no prior treatment with pomalidomide or belantamab mafodotin or other anti-BCMA therapy. Outcomes for the subgroup of the D8-like cohort who had been treated with DVd in the second-line setting and who were refractory to lenalidomide (n=148) were assessed. Median time to next treatment or death was 10 months, median time to treatment discontinuation or death was 6.8 months and OS was 21.1 months (CS, p66).

3.4 DREAMM-8 trial health-related quality of life

In the DREAMM-8 trial, HRQoL data were collected using the EQ-5D-3L[24] questionnaire, the EORTC QLQ-C30[25] questionnaire and the EORTC QLQ-MY20[26] questionnaire (including the EORTC QLQ-IL52 disease symptoms questionnaire). Results are available for the ITT population only.

Results from the EQ-5D-3L questionnaire are reported in the CS (CS, Section B.2.6.1.7) and results from the remaining questionnaires are reported in the CS (CS, Appendix N2).

The EAG agrees with the company (CS, p61) that:

- across study visits, the EQ-5D-3L mean utility scores were 'broadly similar' between the BPd arm and the PVd arm (CS, Figure 10)
- the data (CS, Figure 11) show a gradual increase in utility scores in both trial arms from Week 13 and this increase becomes more marked from around Week 37 onwards
- within the period when most of the recorded EQ-5D-3L data were concentrated, mean utility scores were similar in the BPd arm and the PVd arm
- statistical analysis results suggest that, for patients who are progression-free and on treatment, compared with patients in the PVd arm, utility is statistically significantly better for patients in the BPd arm
- EORTC QLQ-C30, EORTC QLQ-MY20 and EORTC QLQ-IL52 questionnaire results align with EQ-5D-3L assessment results (CS, Appendix N)

3.5 DREAMM-8 trial safety and tolerability results

The DREAMM-8 trial safety results for the 295 patients who received at least one dose of BPd (n=150) or PVd (n=145) are summarised in Section 3.5.1 to Section 3.5.3. Median duration of treatment exposure (CS, Table 28) was longer in the BPd arm ([redacted]) than in the PVd arm ([redacted]). At data cut-off, more patients in the BPd arm (42%) than in the PVd arm (22%) remained on study treatment (CS, Table 5).

3.5.1 Summary of DREAMM-8 trial adverse events

A summary of the AEs reported in the DREAMM-8 trial is presented in Table 8. The company has included an analysis of AE incidence rates using exposure-adjusted incidence rate (EAIR) methodology. The EAIR methodology adjusts for time on treatment differences between the DREAMM-8 trial BPd and PVd arms (CS, p85) and the results are presented as incidence per 100 person-years. The EAIR-adjusted AE results are available in the CS (CS, Table 23).

The company highlights (CS, Section B.2.10) that the safety and tolerability of BPd in the DREAMM-8 trial is consistent with previous trials of single agent belantamab mafodotin in patients who had received >2 previous lines of treatment.[27,28] The company acknowledges (CS, p85) that eye-related AEs are known AEs associated with belantamab mafodotin.

Table 8 Summary of DREAMM-8 trial adverse events

	BPd (n=150) n (%)	PVd (n=145) n (%)
Any AE	149 (>99)	139 (96)
AE related to any study treatment	143 (95)	118 (81)
Grade 3/4 AE	136 (91)	106 (73)
Related to any study treatment	120 (80)	85 (59)
AEs leading to permanent discontinuation of any study treatment	22 (15)	18 (12)
AEs related to any study treatment leading to permanent discontinuation of any study treatment	19 (13)	9 (6)
Belantamab mafodotin discontinuation due to eye-related event	14 (9)	-
AEs leading to dose reduction	92 (61)	88 (61)
Belantamab mafodotin dose reduction due to eye-related event	88 (59)	-
AEs leading to dose interruption/delay	136 (91)	109 (75)
Belantamab mafodotin dose interruption / delay due to eye-related event	124 (83)	-
Any SAE	95 (63)	65 (45)
Related to any study treatment	45 (30%)	21 (14%)
Fatal SAEs	17 (11)	16 (11)
Related to any study treatment	3 (2)	0

AE=adverse event; SAE=serious adverse event
Source: CS, Table 23

3.5.2 DREAMM-8 trial treatment-emergent adverse events by system organ class

The treatment-emergent adverse events (TEAEs) experienced by ≥20% of patients in the BPd and PVd arms of the DREAMM-8 trial (by system organ class) are presented in Table 9. More information about AEs is presented in the CS (CS, Appendix F).

The overall incidence of TEAEs was similar between trial arms and the company stated that the TEAEs were as expected for each drug class. The rates of all eye-related events were 91% and 37% for the BPd and PVd arms, respectively, and rates of Grade ≥3 eye-related events were 48% and 6%, respectively. The eye-related AEs are described in detail in the CS (CS, Section B.2.10.3).

Table 9 DREAMM-8 trial treatment-emergent AEs by system organ class

	BPd (n=150) n (%)		PVd (n=145) n (%)	
	All	**Grade ≥3**	**All**	**Grade ≥3**
Any adverse event	**149 (>99)**	**141 (94)**	**139 (96)**	**110 (76)**
Blood and lymphatic system disorders, n (%)	**96 (64)**	**77 (51)**	**83 (57)**	**61 (42)**
Neutropenia	72 (48)	63 (42)	50 (34)	41 (28)
Thrombocytopenia	54 (36)	36 (24)	44 (30)	29 (20)
Anaemia	35 (23)	15 (10)	38 (26)	19 (13)
Infections and infestations, n (%)	**123 (82)**	**73 (49)**	**99 (68)**	**38 (26)**
Pneumonia	36 (24)	26 (17)	17 (12)	11 (8)
COVID-19	56 (37)	10 (7)	31 (21)	3 (2)
Upper respiratory tract infection	40 (27)	2 (1)	25 (17)	0
Eye-related event, n (%)	**136 (91)**	**72 (48)**	**54 (37)**	**9 (6)**
Vision blurred	119 (79)	26 (17)	22 (15)	0
Visual acuity reduced	34 (23)	20 (13)	8 (6)	1 (1)
Dry eye	91 (61)	12 (8)	14 (10)	0
Photophobia	66 (44)	5 (3)	6 (4)	0
Eye irritation	75 (50)	6 (4)	13 (9)	0
Foreign body sensation in eye	91 (61)	9 (6)	9 (6)	0
Eye pain	49 (33)	3 (2)	7 (5)	0
Cataract	40 (27)	9 (6)	15 (10)	6 (4)
Corneal epithelial microcysts	34 (23)	12 (8)	0	0
Punctate keratitis	34 (23)	9 (6)	1 (1)	1 (1)
Other, n (%)	**35 (23)**	**2 (1)**	**33 (23)**	**10 (7)**
Diarrhoea	11 (7)	1 (1)	34 (23)	4 (3)
Neuropathy peripheral	23 (15)	2 (1)	33 (23)	2 (1)
Constipation	40 (27)	9 (6)	32 (22)	7 (5)
Fatigue	35 (23)	2 (1)	33 (23)	10 (7)

Source: CS, Table 24

3.5.3 DREAMM-8 trial fatal and treatment-related fatal adverse events

DREAMM-8 trial fatal and treatment-related fatal AEs are presented in the CS (CS, Table 25). Of the 17 fatal SAEs in the BPd arm, 3 were treatment-related, and of the 16 fatal SAEs in the PVd arm, none were treatment-related.

3.5.4 Relative dose intensity of belantamab mafodotin

The relative dose intensity (RDI) of belantamab mafodotin is discussed in the CS (CS, Section B.2.10.4). The company states that most of the DREAMM-8 trial eye-related AEs were resolved with dose reductions, interruptions/delays, and discontinuations (in [redacted]%, 86%, and 9% of patients, respectively), resulting in a significantly lower RDI for patients in the BPd arm than in the PVd arm. The company also states that the efficacy of BPd was maintained even

with delays and dose reductions. The median RDIs for all treatments administered in the DREAMM-8 trial are presented in the CS, (CS, Table 28). The overall median belantamab mafodotin RDI across the trial was [redacted]. Based on analyses of the company's [redacted] belantamab mafodotin data and clinical advice to the company, the company considers that the magnitude of the DREAMM-8 trial belantamab mafodotin RDI will be reflected in NHS clinical practice.

3.5.5 EAG conclusions: safety and tolerability

The EAG highlights that Grade 3/4 AEs are high in both arms of the DREAMM-8 trial.

Clinical advice to the EAG cautions that the high level of eye-related events experienced by patients treated with belantamab mafodotin are of concern, particularly in older patients; however, the company stated that these AEs were manageable (CS, p97). Symptoms range from itchy, irritated eyes to change in Best Corrected Visual Acuity. These side effects are mostly reversible and manageable, with recovery typically occurring within weeks or months. Eye-related AEs impact patients' HRQoL and the ocular effects of the drug can continue even after treatment is stopped. Further, the requirement in the anticipated MHRA marketing authorisation (CS, Table 2), for patients to be seen by an ophthalmologist for the first 4 months of treatment could be burdensome for patients and could pose a substantial burden on NHS resources.

3.6 EAG summary and critique of the indirect comparisons

The decision problem addressed by the company focused on adult patients with RRMM who had received one line of treatment including a lenalidomide-containing regimen and for whom lenalidomide was unsuitable (i.e., second-line patients). The EAG agrees with the company that DVd, hKd and SVd are the relevant NHS comparators to BPd (see Section 2.4.5 of this EAG report). The company's SLR did not identify any head-to-head trials investigating the efficacy of BPd versus any of these comparators and therefore the company conducted NMAs (Section 2.4.5).

3.6.1 Summary of company's NMA approach

As described in the CS (CS, pp72-83 and CS, Table 19), to align with the decision problem, the company carried out the five NMAs listed in Table 10. The full set of (fixed effect and random effect) NMA results are available in the main body of the CS (CS, Section B.2.9.4.3 and B.2.9.4.4) and in CS, Appendix D.4.5; the EAG has focused on the NMAs that generated results that have been used in the company economic analyses (the lenalidomide-exposed PFS NMA and the lenalidomide-exposed plus ITT OS NMA). The company considered that PFS and OS were the only outcomes of interest to this appraisal.

Table 10 Primary and secondary NMA analyses conducted by the company

Analysis	Population	Endpoint	Treatment effect type	Number of included studies
Primary	Lenalidomide-exposed	PFS	Fixed-effects Random-effects	8
	Lenalidomide-exposed	OS	Fixed-effects Random-effects	4
Secondary	Lenalidomide-refractory	PFS	Fixed-effects Random-effects	8
	Lenalidomide-exposed plus ITT	OS	Fixed-effects Random-effects	12
	Lenalidomide-refractory plus ITT	OS	Fixed-effects Random-effects	12

ITT=intention-to-treat; NMA=network-meta-analysis; OS=overall survival; PFS=progression-free survival

3.6.2 Identification of trials for inclusion in the NMAs

SLR and feasibility assessment

In response to clarification question A3, the company provided further details about the SLR and feasibility assessment. The company SLR (a combination of original search, update1 and updated 2) identified 47 publications for possible inclusion in the NMAs. The following steps were taken to identify studies for inclusion in the NMAs:

- identifying studies that could be used to form a connected network: 17 studies remaining
- restricting the evidence to regimens approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and any treatments likely to be future HTA comparators to the BPd DREAMM-8 trial regimen: 12 studies[8,29-39] remaining

The connected network included BPd and the three relevant NHS treatments: DVd, hKd and SVd. As the selection of studies for inclusion in the NMAs was based on a global SLR, some of the 12 studies[8,29-39] included treatments that are not available to NHS patients.

The population in the decision problem addressed by the company was adult patients with RRMM who had received one line of treatment including a lenalidomide-containing regimen and for whom lenalidomide was unsuitable (second-line patients). None of the 12 studies included in the NMAs only enrolled patients receiving second-line treatment. All the studies included patients who had previously been treated with lenalidomide; however, not all studies reported PFS and OS results for patients who had been treated with lenalidomide. Key characteristics (patient demographics and prior lines of therapy) of the 12 studies[8,29-39] included in the NMAs are provided in the CS (Appendix D, Table 45 and Table 46).

3.6.3 Quality assessment of the trials included in the NMAs

Using the Cochrane Risk of Bias assessment tool[19] (RoB2), the company conducted quality assessments of all trials included in the NMAs, except for the GEM-KyCyDex[29] trial (there was insufficient GEM-KyCyDex[29] trial information available from the conference abstract to allow quality assessment to be carried out). The company's quality assessment results are available in the CS (CS, Appendix D, Section D3). Overall, the EAG agrees with the company's quality assessment conclusions; 6/11 trials were considered to have some concerns, and 5/11 trials were considered to have low risk of bias.

3.6.4 EAG summary and critique of company NMA methods

The EAG summary and critique of the company statistical approaches to the NMAs is presented in Table 11.

Table 11 EAG summary and critique of the company statistical approaches to the NMAs

Item	EAG assessment	Summary of company approach	EAG comments
Was a feasibility assessment carried out prior to conducting the NMAs?	NMA	The company SLR identified 70 relevant studies for inclusion in the NMAs; 47 studies were included in the NMA feasibility assessment. In total, the company identified 12 studies that formed a connected network. As part of the feasibility assessment, the company considered the similarity of the studies in terms of study design, patient populations, distribution of baseline characteristics that can modify relative effects, and outcome definitions, their measurement and duration of follow-up. Full details of the feasibility assessment, including data extraction tables, are presented in the CS (Appendix D.4.1). The company considered that there were no major imbalances across the included studies (CS, p84).	The company provided the Feasibility Assessment report as part of the clarification response (clarification question A3). However, the Feasibility Assessment report PFS and OS network descriptions do not always match the network descriptions described in the CS. In the (ITT population) tabulated comparisons presented by the company, several of the baseline patient characteristics varied widely across the studies. For example, the proportions of high-risk cytogenic patients ranged from 3.5%[37] to 24%[31] (CS, Appendix 10, Table 45); 1 prior line of treatment ranged from 0%[35] to 66%[37] (CS, Appendix D, Table 46); prior lenalidomide therapy ranged from 20%[39] to 100%[34] (CS, Appendix D, Table 46). The EAG agrees with the company that, as the reporting of baseline characteristics within the primary analysis populations (lenalidomide-exposed patients) was limited, there are challenges when fully assessing between-study heterogeneity.
Were NMAs conducted for all relevant outcomes?	Partly	The company presented PFS and OS NMAs (CS; Section B.2.9 and Appendix D.4).	The company did not conduct safety/tolerability or PRO NMAs. The EAG considers that it may not have been possible to conduct meaningful NMAs of these outcomes due to potential differences in assessment methods and lack of common outcome data across the included studies.
Were NMAs informed by relevant comparators?	Yes	The company conducted five constant HR NMAs to compare the relative efficacy of BPd versus relevant comparators. The three NHS comparators (DVd, hKd and SVd) listed in the final scope issued by NICE were included in the NMAs.	The EAG agrees that, in the absence of head-to-head trial data, it was appropriate to use NMAs to generate estimates of relative treatment effects of BPd and relevant comparators. The EAG notes the inclusion of several comparators in the NMAs that are not available to NHS patients.
Were the networks of comparators appropriate?	Yes	The company presented five separate networks: <u>Primary analysis:</u> 1. PFS for lenalidomide-exposed population (8 studies) (CS, Figure 17) 2. OS for lenalidomide-exposed population (4 studies) (CS, Figure 19) <u>Secondary analysis:</u> 3. PFS for lenalidomide-refractory population (8 studies) (CS, Figure 21) 4. OS for lenalidomide-exposed population (12 studies) (CS, Figure 23)	The EAG considers that the company PFS and OS NMA networks were appropriate and included all relevant NHS comparators.

Item	EAG assessment	Summary of company approach	EAG comments
		5. OS for lenalidomide-refractory population (12 studies) (CS, Figure 23)	
Was the PH assumption appropriately assessed within the PFS and OS NMAs?	Partly	The company assessed the DREAMM-8 trial PFS and OS PH assumptions using the Grambsch-Therneau test, log-log and Schoenfeld residual plots (CS, Appendix D.4.2). The company considered that it was reasonable to assume hazards were proportional. For the comparator trials, the company studied hazard plots and concluded that it was reasonable to assume that, for the studies that included relevant NHS comparators, PFS and OS hazards were proportional.	The EAG agrees with the company that there was no statistically significant evidence of violation of the PFS and OS PH assumptions for the DREAMM-8 trial. However, the EAG noted that, for the comparator trials, from the hazard functions presented (CS, Appendix D, Figures 6 and 7, it was not possible to be confident that PFS and OS hazards were constant over time; this means that for some of the trials in the networks, PFS and OS PH assumptions are/may not be valid (for example, PFS hazards in the IKEMA[31] trial do not appear to be proportional). The effect of non-proportionality on the NMA results is unknown.
Were transitivity and inconsistency appropriately addressed in the NMAs?	No	The company considered that the networks met the transitivity/congruence assumption as no major differences in the distribution of potential TEMs were observed. However, the company goes on to state that '…imbalances were identified in the distribution of patients with one prior line of therapy across the included studies' (CS, Section B.2.9.3). The company was unable to test the assumption of inconsistency in the NMAs as there were no closed treatment loops in the evidence networks.	The EAG considers that it was difficult to fully explore the extent to which the transitivity assumption was met. As stated by the company (CS, p84), "…the reporting of baseline characteristics within the primary analysis population was limited…which presents challenges in fully assessing the between-study heterogeneity". In addition, as the company acknowledged that there were some imbalances in the distribution of potential TEMs, it is likely that the assumption of transitivity was only partially met, and that all NMA results may not be reliable. The EAG considers that not being able to test for inconsistency in the NMAs (due to no closed loops) adds uncertainty to NMA results, potentially leading to unvalidated conclusions.
Were NMA methods appropriate?	Partly	The methods used in the company NMAs were described in the CS (Section B.2.9) and in CS, Appendix D.4. The company performed NMAs in a Bayesian framework. Stan was implemented through R (version 4.3.2) using the RStudio interface (version 2023.12.1) and the 'multinma' package (version 0.6.0.9000). The company carried out FE and RE PFS and OS NMAs to assess the relative effectiveness of BPd versus relevant comparators. Company goodness-of-fit summary statistics (CS, Table 22) showed that there was very little difference between the two models in terms of how well they fit the data.	The EAG considers that the NMAs have been correctly implemented. FE models were used in the base case analysis; there is very little difference between FE and RE NMA results. <u>TEMs</u> Clinical advice to the EAG (and the to the company) is that potentially important prognostic factors and TEMs exist. However, the company was unable to explore these TEMs due to data limitations. Therefore, the EAG has concerns that there may be residual confounding due to observed and unobserved differences in study populations (especially for prior line of treatment, ECOG PS and ISS stage). Failing to adjust for known TEMs that are likely to reduce the size of the treatment effect can lead to misleading results due to confounding (i.e., differences may be due to TEMs rather than the treatments), overestimation or

Item	EAG assessment	Summary of company approach	EAG comments
		TEMs The company explained that, for patients with RRMM, seven critical treatment effect modifiers had been identified via the published literature and discussions with experts. After carrying out exploratory PFS subgroup analyses, the company considered that the most important TEMs were likely to be prior line of treatment, ECOG PS and ISS stage. The company was unable to adjust for any of the seven TEMs that were identified as being important for patients with RRMM (prior line of treatment, prior immunomodulatory drugs exposure, ISS stage, ECOG PS, prior lenalidomide exposure, prior bortezomib use and cytogenic risk profile) (CS, Section B.2.9.2.2). Immature survival data The company cautioned that, as the DREAMM-8 trial OS data were immature, NMA updates would be required to enhance the interpretability of the posterior estimates.	underestimate of the treatment effect (in this case, might overestimate the treatment effect) and decreased external validity (NMA results may not be generalisable to broader patient populations). Immature survival data The EAG considers that if the company OS NMAs were re-run with more mature DREAMM-8 trial data, results might change.
Was the presentation of NMA results appropriate?	Yes	The company has provided a comprehensive set of NMA results for each of the five comparisons of BPd versus comparators. In the main body of the CS (Section 2.9.4), the company has presented narrative FE results alongside FE forest plots. In the CS (Appendix D4), the company has provided FE and RE PFS and OS rankograms, RE forest plots, DIC model comparisons, treatment rankings using SUCRA and league tables.	The EAG considers that, as most of the relevant comparisons (BPd versus NHS treatments) only include data from two studies, forest plots of relative treatment effects from the individual studies would have provided useful information.

CS=company submission, EAG=External Assessment Group; ECOG=Eastern Cooperative Oncology Group; FE=fixed-effect; HR=hazard ratio; ISS=multiple myeloma international staging system; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazard; PS=performance status; RRMM=relapsed and remitting multiple myeloma SUCRA=surface under the cumulative ranking; TEMs=treatment effect modifiers

3.6.5 Company NMA results

Results from the company fixed effects (FE) PFS and OS NMAs for BPd versus relevant NHS comparators for each population considered relevant by the company are presented in Table 12. Bold results are statistically significantly better for BPd versus the comparator. The full set of company FE and RE PFS and OS NMA results is available in the CS (Section 2.9.4 and Appendix D).

Table 12 Company fixed effects NMA results: BPd versus relevant NHS comparators

Company fixed effect NMA results	BPd vs DVd HR (95% CrIs)	BPd vs SVd HR (95% CrIs)	BPd vs hKD HR (95% CrIs)
Lenalidomide-exposed: PFS	[redacted]	[redacted]	[redacted]
Lenalidomide-exposed: OS	[redacted]	[redacted]	[redacted]
Lenalidomide-refractory: PFS	[redacted]	[redacted]	[redacted]
Lenalidomide-exposed+ITT: OS	[redacted]	[redacted]	[redacted]
Lenalidomide-refractory+ITT: OS	[redacted]	[redacted]	[redacted]

NB All results have been taken from the league tables presented in CS, Appendix D4. Results in bold are statistically significantly better for BPd versus the comparator. HR<1 suggests a lower probability of the outcome occurring when treated with BPd compared to the comparator
CrIs=credible intervals; HR=hazard ratio; NMA=network meta-analysis; PFS=progression-free survival; OS=overall survival
Source: CS, Appendix D

For the lenalidomide-exposed population, FE PFS NMA results showed that BPd was statistically significantly more effective than hKd and SVd; this PFS advantage was also experienced by lenalidomide-refractory patients treated with BPd compared to those treated with hKd.

The company's FE OS NMA results show no statistically significant differences between BPd and any of the comparators, no matter the population of interest. The FE OS NMA results showed a numerical advantage for patients treated with BPd compared to all comparators, however, all credible intervals were wide, which suggests high levels of uncertainty.

3.6.6 EAG comments on company NMAs: PFS (lenalidomide-exposed) NMA and OS (lenalidomide-exposed+ITT) NMA

PFS subgroup analysis: TEMs

As part of the NMA exercise, the company took considerable steps to identify all possible treatment effect modifiers (TEMs) that might affect outcomes for patients with RRMM. Of the seven TEMs identified (via discussions with clinical experts and targeted literature searching), the company concluded that prior line of treatment, ECOG PS and ISS stage were the three most important TEMs.

The company extracted PFS subgroup results from studies included in the NMAs for five of the seven TEMs considered important. Inspection of these results shows that, for the three most important TEMs identified by the company, where within-trial data were available, there were variations in point-estimates (HRs) (see CS, Appendix D, Table 49) and there were also overlapping credible intervals. For most of the studies, within-trial data were not available. The EAG considers that the company's NMA results may not be reliable as, due to lack of reported trial data, it was not possible to explore the impact of important TEMs.

NMA populations

It was possible to populate the company PFS (lenalidomide-exposed) NMA with data from lenalidomide-exposed patients; however, prior line of treatment was mixed, i.e., none of the eight studies[8,30-35,38] included in this PFS NMA only included patients treated in the second-line setting. In the DREAMM-8 trial, PFS results were similar for patients who had received one line of treatment and for patients who had received more than one line of treatment; however, the company did not present clinical trial evidence demonstrating that this result was also likely to occur in the other included studies.

Due to lack of publicly available trial data, it was not possible for the company to carry out an OS (lenalidomide-exposed) population NMA. Instead, the company carried out an NMA that included lenalidomide-exposed population OS data (n=4 studies[8,30,34,38]) and ITT population OS data (n=8 studies[29,31-33,35-37,39]); none of the 12 studies[8,29-39] included in this OS NMA only included patients treated in the second-line setting.

Only 25% of DREAMM-8 trial patients had received prior treatment with daratumumab. Of the other 11 studies[29-39] included in the NMAs, only two studies[31,33] reported that patients had been previously treated with daratumumab. Clinical advice to the EAG is that, moving forward, most NHS patients will receive daratumumab in the first-line setting and the impact of prior treatment with daratumumab on the effectiveness of later-line treatments is not known. The EAG considers that as it is not known how many patients in the studies included in the NMAs

had previously been treated with daratumumab, the company PFS and OS NMA results may not be relevant to the decision problem addressed by the company.

Immature survival data

The company cautioned that the DREAMM-8 trial OS data were immature. The EAG considers that if the company OS NMAs were re-run with more mature DREAMM-8 trial data, results might change.

Subsequent treatments

Clinical advice to the EAG is that MM is a heterogeneous disease and that the sequence of subsequent treatments in clinical trials and in NHS clinical practice is varied. In the NMAs, the effect on OS of the type and frequency of subsequent treatments in the included studies has not been considered. It is not known whether the subsequent treatments used in the trials that informed the NMAs are likely to represent the subsequent treatments available to NHS patients; this means that it is not clear whether NMA results are generalisable to NHS patients.

OS data inputs into the lenalidomide-exposed+ITT OS NMA

In response to clarification question C4, the company provided PFS and OS NMA data inputs. The OPTIMISMM trial OS HR used in the company NMAs was not the final (published) ITT analysis OS HR (HR=0.94; 95% CI: 0.77 to 1.15), rather, the HR had been sourced from an unpublished conference presentation[40] and had been generated from a preplanned exploratory analysis using a Cox PH model with subsequent therapy as a time-dependent covariate and adjusting for stratification factors (HR=0.76; 95% CI: 0.62 to 0.93). As the adjusted results are statistically significant and the ITT results are not statistically significant, the results from this exploratory analysis highlight the importance of the effect of subsequent treatments on OS results and that NMA results generated using trial ITT OS HRs are therefore not reliable.

3.6.7 EAG concluding remarks

Company PFS (lenalidomide-exposed) NMA

It was possible to populate the company PFS (lenalidomide-exposed) NMA with data from lenalidomide-exposed patients. However, prior line of treatment was mixed and due to lack of reported trial data, it was not possible to explore the impact of important TEMs. The EAG therefore considers that the company's PFS (lenalidomide-exposed) NMA results may not be reliable.

Company OS (lenalidomide-exposed plus ITT) NMA

Within and across the studies included in the company OS (lenalidomide-exposed plus ITT) NMA, populations were heterogeneous and the generalisability of these study results to NHS patients in the second-line setting who have previously been treated with lenalidomide is unclear. In addition, the EAG considers that (i) an inappropriate HR was used to link BPd with all the comparator treatments, and (ii) the company was unable to adjust for the impact of subsequent treatments on the effectiveness of comparator treatments. The EAG therefore considers that company OS NMA results should not be used to inform decision-making.

3.7 Conclusions of the clinical effectiveness section

The main source of BPd clinical effectiveness evidence is the DREAMM-8 trial; an ongoing (still recruiting) good quality, international, phase III, open-label RCT that compares the efficacy and safety of BPd (n=155) versus PVd (n=147) in adults with RRMM who have previously received ≥1 line of therapy including lenalidomide. The focus of the CS is on a subgroup of this population (adults with RRMM who have received one prior line of therapy including a lenalidomide-containing regimen and for whom lenalidomide is unsuitable); this subgroup is narrower than the population described in the final scope[13] issued by NICE.

Although all DREAMM-8 trial patients had previously received a lenalidomide containing regimen, only 52.5% had only received one prior line of therapy including a lenalidomide-containing regimen. No specific clinical trial evidence has been provided by the company for patients who are contraindicated to lenalidomide and who were therefore unsuitable for treatment with lenalidomide.

Only 25% of DREAMM-8 trial patients had received prior treatment with daratumumab. Clinical advice to the EAG is that this limits the generalisability of the trial results to NHS patients as, moving forward, most patients in the NHS will have received daratumumab in the first-line setting, either as a limited number of treatments (ASCT-eligible patients) or until disease progression (ASCT ineligible patients).

PVd is not a relevant comparator and therefore the company carried out NMAs to generate evidence to compare the clinical effectiveness of BPd versus DVd, hKD and SVd; clinical advice to the company and the EAG is that these are the relevant comparators.

The EAG highlights that it was not possible to explore the effect of TEMs on company NMA results and has the following concerns about the data used to conduct the company NMAs:

- DREAMM-8 trial data were immature (median OS had not been reached in either arm, and median PFS had only been reached in the PVd arm)
- none of the trials included only patients treated in the second-line setting
- in the OS NMAs, not all patients had been previously treated with lenalidomide
- where trial data were available, very few patients had been previously treated with daratumumab
- the OPTIMISMM trial (PVd vs Vd) HR used in the company OS NMAs was adjusted for subsequent treatment; however, all other HRs used in the analysis were not adjusted for subsequent treatments

The EAG therefore considers that company PFS NMA results may be unreliable, and the OS NMA results should not be used to inform decision-making.

The EAG highlights that Grade 3/4 AEs are high in both arms of the DREAMM-8 trial (BPd: 91%; PVd: 73%). Clinical advice to the EAG cautions that the high level of eye-related events experienced by patients treated with belantamab mafodotin are of concern, particularly in older patients and that the ophthalmology checks (performed before each of the first four doses of belantamab mafedotin and during treatment as clinically indicated), stipulated in the anticipated MHRA BPd marketing authorisation could be burdensome for patients and could pose a substantial burden on NHS resources.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of the use of BPd as a treatment option for patients with RRMM who have received one prior line of treatment including a lenalidomide-containing regimen and for whom lenalidomide is unsuitable. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft® Excel.

4.1 Company review of published cost effectiveness evidence

The company undertook SLRs to identify relevant cost effectiveness, cost, resource use and HRQoL data from the published literature. The purpose of the SLR was to generate evidence to inform the company cost effectiveness and budget impact models.

The SLR was conducted according to the NICE technology appraisal submission guidelines[41] and the Cochrane Handbook for Systematic Reviews of Interventions.[42] The review was first conducted in January 2023 and updated (using the same methodology) in January 2024 and April 2024. Electronic databases were searched from 2008 to present. The time span for the searches of health technology assessment (HTA) websites was 10 years and, for the grey literature searches, 3 years. Full details of the methods used by the company to identify and select relevant cost effectiveness evidence are presented in the CS (CS, Appendix G).

The company's SLR identified 70 studies that described RRMM cost effectiveness analyses. Twenty of these studies were conducted in UK settings (CS, Appendix G, Table 9). The models described in ten of these studies were partitioned survival models and one study used Markov and partitioned survival modelling approaches; the remaining studies described Markov models (n=4), other modelling approaches (n=4) or did not specify model structure (n=1).

4.2 EAG critique of the company's literature reviews

The EAG considers all the company's cost effectiveness evidence SLR methods were of a good standard (Table 13). The company's database searches were comprehensive and captured a wide range of studies relating to economic evaluations and HRQoL in patients with RRMM.

Table 13 EAG appraisal of systematic review methods (cost effectiveness, HRQoL and healthcare resource use/cost)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Extracted by one reviewer and checked by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	29 peer-reviewed publications were quality assessed
Were attempts to synthesise evidence appropriate?	Not applicable

EAG=External Assessment Group; HRQoL=health-related quality of life; LR*i*G=Liverpool Reviews and Implementation
Source: LR*i*G in-house checklist

4.2.1 EAG conclusion

The EAG considers the methods used by the company to conduct systematic reviews of cost effectiveness, HRQoL and healthcare resource use studies were of a good standard.

4.3 EAG summary and critique of the company's submitted economic evaluation

4.3.1 NICE Reference Case checklist and Drummond checklist

Table 14 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	The company has considered a population that is narrower than the population described in the final scope, namely patients with RRMM who have had one line of therapy including a lenalidomide-containing regimen (second-line) and for whom lenalidomide is unsuitable.
Comparators	As listed in the scope developed by NICE	Clinical advice to the EAG is that the three comparators (DVd, hKd and SVd) are the most appropriate for patients with RRMM who have had one line of therapy including a lenalidomide-containing regimen (second-line) and for whom lenalidomide is unsuitable.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓
Perspective on costs	NHS and PSS	✓
Type of economic evaluation	Cost utility analysis with fully incremental analysis	✓
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓
Synthesis of evidence on health effects	Based on systematic review	✓
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	✓
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	✓
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	✓
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓

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	✓
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓

EAG=External Assessment Group; EQ-5D=EuroQol 5 dimensions; NHS=National Health Service; NICE=National Institute for Health and Care; PSS=Personal Social Services; QALY=quality adjusted life year; RRMM=relapsed/refractory multiple myeloma
Source: EAG assessment of NICE Reference Case[41]

Table 15 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	Results from the company NMAs may be unreliable
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	The company should have used the current pomalidomide list price
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

EAG=External Assessment Group; NMA=network meta-analysis
Source: Drummond and Jefferson[43]

4.4 Model structure

The company developed a de novo cohort-based partitioned survival model in Microsoft® Excel. This structure is a standard in oncology HTA submissions. The model comprises four mutually exclusive health states:

- progression-free (PF) on treatment (on-tx)
- PF off treatment (off-tx)
- progressed disease (PD)
- death

An illustration of the model structure is presented in Figure 2. The proportion of patients occupying each health state is estimated using data from parametric distributions fitted to

DREAMM-8 trial data; the illustration shows how health state occupancy is calculated from these data.

In each weekly cycle, costs and QALYs are estimated based on health state membership. Costs and QALYs are accumulated over the model time horizon and then total costs and total QALYs are used to estimate ICERs per QALY gained (BPd versus each comparator).

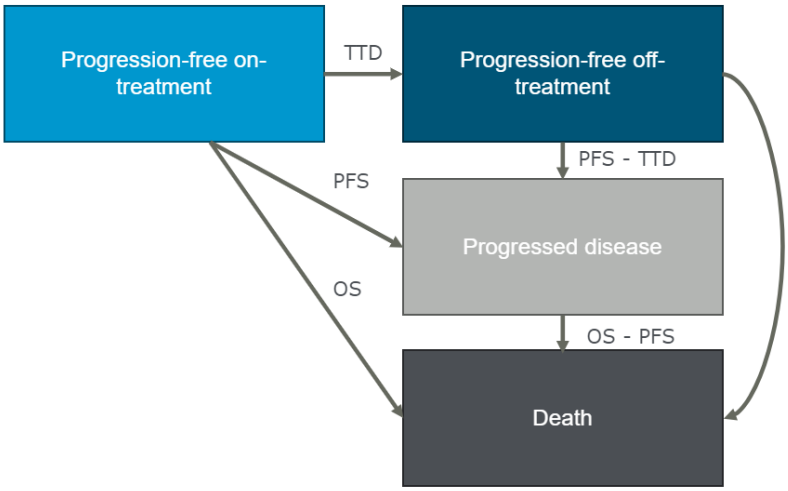


Figure 2 Structure of the company model

CS=company submission; OS=overall survival; PFS=progression-free state; TTD=time to treatment discontinuation
Source: CS, Figure 28

4.5 Population

The population entering the model is adult patients with documented MM, previously treated with one prior line of treatment (including a lenalidomide-containing regimen for at least two consecutive cycles) and with documented disease progression during or after their most recent therapy. The model baseline patient characteristics reflect the baseline characteristics of the DREAMM-8 trial ITT population (Table 16).

Table 16 Model population characteristics

Baseline characteristic	DREAMM-8 trial ITT population
Baseline mean age (years)	66.1
Baseline weight (kg)	[redacted]
Baseline body surface area (m^2)	[redacted]
% of males	60.0%*

* This value is higher than the value provided in response to clarification question A1 (second-line population only)
ITT=intention-to-treat
Source: CS, Table 29

4.6 Interventions and comparators

The modelled intervention was BPd. Belantamab mafodotin is available in 100mg vials which are administered via IV infusion. The company also presented cost effectiveness results based

on use of a 70mg vial; this size of vial is not currently available but is expected to be available by the end of this NICE appraisal process. In the company model, BPd was implemented in line with the DREAMM-8 trial protocol.

The company considered that the relevant comparators were: DVd, hKd and SVd. In the company model, the three comparator treatments were implemented in line with their respective marketing authorisations[44-46] and were given according to their licensed dosing regimens.

4.7 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). The model cycle length was 1 week. The model time horizon was 33.9 years and costs and outcomes were discounted at a rate of 3.5% per annum.

4.8 Treatment effectiveness and extrapolation

Estimates of the relative treatment effect of BVd versus comparators were generated using (fixed effects) PFS and OS NMA results (HRs). In the base case analysis, HRs were applied to DREAMM-8 trial PVd extrapolated outcomes. PVd, rather than BPd, was selected as the reference treatment as PVd hazard profiles were considered more similar to the hazard profiles of comparators than BPd hazard profiles. Unadjusted OS was used in the company base case analysis; this was considered a conservative approach. Model base case analysis clinical data inputs are presented in Table 17.

Table 17 Company model base case analysis clinical data inputs

Endpoint	Source of clinical effectiveness	
	BPd	Non-trial comparators (DVd, hKd, SVd)
PFS	Extrapolation of DREAMM-8 trial data	HRs vs PVd (from the lenalidomide exposed PFS NMA)
OS	Extrapolation of unadjusted DREAMM-8 trial data	HRs vs PVd (from the lenalidomide plus ITT OS NMA)
TTD	Extrapolation of DREAMM-8 trial data	PFS HRs vs PVd (from the lenalidomide-exposed PFS NMA) used as proxy for TTD HR

HR=hazard ratio; ITT=intention-to-treat; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation
Source: CS, Table 32

4.8.1 Parametric distribution selection

The process taken by the company to select parametric distributions to extrapolate DREAMM-8 trial PFS, OS and TTD data was in line with the process described in NICE TSD 14.[47] In brief:

- The use of parametric distributions was justified through assessment of the proportional hazards (PH) assumption (CS, Appendix O).

- Six standard parametric distributions (exponential, Weibull, Gompertz, log-logistic, lognormal and Generalised Gamma) were fitted to DREAMM-8 trial Kaplan-Meier data; Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores were used to assess goodness of fit.
- UK clinical experts and an external Health Economics expert assessed the clinical plausibility and visual goodness of fit of the parametric distributions to the DREAMM-8 trial data. In addition, the clinical experts identified the most plausible curves based on clinical plausibility or survival analysis diagnostics.[48]
- Comparator (DVd, hKd and SVd) PFS, and OS distributions were generated by applying NMA HRs for each comparator to the distributions used to extrapolate DREAMM-8 trial PVd data (base case); as it was not possible to carry out a TTD NMA, PFS NMA HRs were applied to DREAMM-8 trial PVd TTD data.

Information about the distributions used in the company base case analyses and the justification for these choices is presented in Table 18.

Table 18 Distributions used in the company base case analyses to extrapolate DREAMM-8 trial PFS, OS and TTD data

Endpoint	Curve selection	Brief justification	Comparison between extrapolation and DREAMM-8 trial data at 2 years
PFS	Weibull	Similar statistical fit between most curves. Good agreement between clinical expert for both interventions based on clinical plausibility of extrapolated outcomes, with a focus on the 5-year landmark estimates	[redacted]
OS	Exponential	Good statistical fit based on AIC and BIC, and unanimous distribution choice between clinical experts based on clinical plausibility of 5-,10-, and 20-year landmark estimates	[redacted]
TTD	Weibull	For BPd, clinical experts unanimously selected the exponential model, but the Weibull model was used in the base case due to the similarity of predicted values with exponential distribution, and consistency in the distribution choice with PVd For PVd, it was a unanimous distribution choice for Weibull between clinical experts based on the predicted 5- and 10-year estimates	[redacted]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation
Source: CS, Table 33

4.8.2 Adverse events

Grade ≥3 TEAEs that occurred in at least 5% of patients were included in the company model (Table 19).

Table 19 Incidence of Grade ≥3 AE reported in ≥5% of patients

Adverse event	BPd	hKd	SVd	DVd
Source	DREAMM-8 trial	Usmani 2023[49]	Bahlis 2018[50]	DREAMM-7 trial[51]
Neutropenia	0.42	0.07	0.19	[redacted]
Anaemia	0.10	0.16	0.04	[redacted]
Thrombocytopenia	0.24	0.16	0.31	0.35
Lymphopenia	[redacted]	0.07	-	[redacted]
Pneumonia	0.17	0.09	-	0.04
Peripheral neuropathy	[redacted]	0.01	-	[redacted]
Hypertension	[redacted]	0.18	-	[redacted]
Fatigue	0.06	0.05	0.23	[redacted]
Keratopathy	[redacted]	-	-	[redacted]
Blurred vision	0.17	-	-	[redacted]
Dry eyes	0.08	-	-	-

Source: CS, Table 42

4.9 Health-related quality of life

Health state utility values were derived from DREAMM-8 trial EQ-5D3L data. In the company base case analysis, PFS health state utility values were assumed to differ between treatments. The DREAMM-8 trial did not collect data for patients treated with hKd, SVd or DVd; the company has assumed that utility values for patients receiving these treatments are the same as the utility values for DREAMM-8 trial patients treated with PVd (Table 20).

Table 20 Progression-free and progressed disease treatment-specific health state utilities

Treatment	Utility	Source
PFS (on-treatment)	[redacted]	DREAMM-8 trial
BPd	[redacted]	DREAMM-8 trial
PVd	[redacted]	DREAMM-8 trial
hKd	[redacted]	Assumed to be equal to PVd
SVd	[redacted]	Assumed to be equal to PVd
DVd	[redacted]	Assumed to be equal to PVd
PFS (off-treatment)	[redacted]	Assumption
PD	[redacted]	DREAMM-8 trial

PD=progressed disease; PFS=progression-free survival
Source: company model

4.9.1 Adverse event disutilities

The impact of treatment-related AEs on HRQoL was incorporated in the model as a one-off QALY loss for each AE; disutilities were applied in the first model cycle. However, eye-related side effects (experienced by patients treated with BPd) are ongoing. The company considers that DREAMM-8 trial EQ-5D-3L results are likely to reflect the reduction in HRQoL associated with eye-related side effects and therefore only the costs associated with treating these side effects are included in the model (CS, Table 60). The AE disutilities used in the company model are presented in Table 21.

Table 21 Adverse event disutilities included in the company model

Adverse event	Disutility	Source
Neutropenia	0.15	TA695[52]
Anaemia	0.31	TA695[52]
Thrombocytopenia	0.31	TA695[52]
Lymphopenia	0.07	TA897[53]
Pneumonia	0.19	TA695[52]
Peripheral neuropathy	0.07	TA897[53]
Hypertension	0.00	TA695[52]
Fatigue	0.12	TA695[52]

TA=technology appraisal
Source: CS, Table 45

4.10 Resource use and costs

4.10.1 Drug acquisition and administration costs

Unit costs

Belantamab mafodotin (100mg vial) is available to the NHS at a discounted PAS price. This cost is used in the company model. In the analysis that considered a 70mg vial (which is not currently available to the NHS), the 70mg vial was assumed to cost 70% of the cost of the 100mg vial.

The patent for pomalidomide is due to expire in 2024. The company considered that expiry of the patent would lead to a drop in the price of pomalidomide as generic alternatives become available. Based on GSK intelligence and the observed price trends of lenalidomide after it became generic, the company has assumed that the availability of generic pomalidomide will reduce the current list price by [redacted]%.

All other drugs included in the company model were costed using list prices sourced from the British National Formulary (BNF[54]). Where multiple unit costs/sizes were available, the pack size/dose most aligned to the comparator dosing regimen was selected. If treatment costs were inconsistent across per mg prices, the pack size and dose most aligned to the

comparator dosing regimen was selected. Drug acquisition costs are provided in the CS (CS, Table 46).

Dosing

In the company base case analysis, belantamab mafodotin dose was based on DREAMM-8 trial individual patient data (IPD) (i.e., actual dose received) and wastage calculations were applied to all administrations. Details of the approach used are presented in the CS (CS, Section B.3.5.1.3). For all other drugs, dosing was based on the Summary of Product Characteristics (SmPC) label with RDI applied to account for dose reductions or delays. Details of dosing schedules (based on SmPC labels) are provided in the CS (CS, Table 47).

For all comparators, a constant RDI was used to capture the impact of dose alterations; this approach was not necessary for BPd as IPD data were used to estimate costs. For all comparators, RDI was sourced from publications of the key trials. RDIs are shown in Table 22.

Table 22 Relative dose intensities

Drug	RDI	Source
Belantamab mafodotin (100mg vial)	[redacted]	DREAMM-8 trial CSR[20]
Belantamab mafodotin (70mg vial)	[redacted]	
Bortezomib	[redacted]	
Dexamethasone*	[redacted]	
Pomalidomide	[redacted]	
Daratumumab	[redacted]	DREAMM-7 trial CSR[55]
High dose carfilzomib	90.7%	TA695[52]
Selinexor	78.9%	TA974[12]
Isatuximab	92.3%	ICARIA-MM trial[56]

* Dexamethasone RDI was estimated as the average of BPd and PVd regimens and assumed to be the same for all comparator treatments
CSR=Clinical Study Report; RDI=relative dose intensity
Source: CS, Table 48

Wastage

In the company base case analysis, wastage was applied to all administrations. For IV and SC drugs, method of moments calculations were used to derive the number of vials needed per cycle based on weight or body surface area (BSA). For oral treatments, the acquisition cost was 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.

Drug administration costs

NHS Cost collection costs (2021/2022[57]) (simple infusion, complex infusion and prolonged infusion) were used to estimate administration costs for IV and SC drugs. It was assumed that the cost of administering oral drugs was zero (Table 21).

Table 23 Drug administration method and cost per administration

Regimen	Drug	Administration method	Cost	NHS Cost collection 2021/22[57] code
BPd	Belantamab mafodotin	IV treatment: First administration in a treatment cycle (simple infusion)	£286.71	SB12Z
		IV treatment: subsequent administrations in a treatment cycle	£368.44	SB157
	Pomalidomide	Oral	£0.00	NA - assumption
	Dexamethasone	Oral	£0.00	NA - assumption
hKd	High dose carfilzomib	IV treatment: First administration in a treatment cycle (simple infusion)	£286.71	SB12Z
		IV treatment: subsequent administrations in a treatment cycle	£368.44	SB157
	Dexamethasone	Oral	£0.00	NA - assumption
SVd	Selinexor	Oral	£0.00	NA - assumption
	Bortezomib	SC: Specialist Nursing, Cancer Related, Adult, Face to face	£119.00	N10AF
	Dexamethasone	Oral	£0.00	NA - assumption
DVd	Daratumumab	SC: Specialist Nursing, Cancer Related, Adult, Face to face	£119.00	N10AF
	Bortezomib	SC: Specialist Nursing, Cancer Related, Adult, Face to face	£119.00	N10AF
	Dexamethasone	Oral	£0.00	NA - assumption

IV=intravenous; NA=not applicable; SC=subcutaneous
Source: CS, Table 50 and Table 51

Subsequent treatments included in the model

Subsequent treatment costs were applied as a one-off cost on disease progression. The one-off cost was estimated based on the cost of a basket of potential treatment options. The distribution of the subsequent treatment options was based on expert advice.

Costs, which were sourced from the BNF and captured for up to two lines of subsequent treatment. A median OS of 9 months was assumed for patients receiving third- and later-line treatments (this assumption was used in TA897[53]).

The company highlighted that the proportions of patients in both arms of the DREAMM-8 trial who went on to receive a first subsequent treatment were low and suggested that this might be due to data immaturity. Therefore, in the base case, the proportions of patients who received first- and second-lines of subsequent treatments were informed by published data (Raab[58]) and proportions were assumed to be the same for all treatments (first subsequent treatment: 81%; second subsequent treatment: 34%).

4.10.2 Health state costs and resource use

Health state costs

The company sought clinical advice to estimate the frequency of health care resource use in different model health states (PFS on-treatment, PFS off-treatment and PD). The three clinical experts provided similar estimates of health care resource use frequency and therefore average frequencies were used in the model. In all three health states, frequencies of haematologist visits, biochemistry protein electrophoresis, immunoglobin and serum free light change were the same for patients irrespective of treatment. Differences in resource use were:

- **full blood count**: resource use per model cycle was 0.25 for patients treated with BPd and 0.5 for patients treated with hKd, SVd or DVd
- **ophthalmologist**: resource use per model cycle was 0.33 for patients treated with belantamab mafodotin (for four treatment cycles) and zero for other treatments

Costs were sourced from NHS Cost Collection Costs 2021/22. Total health state resource use costs are presented in Table 24.

Table 24 Total health state resource use costs used in the company model

Health state	Treatment				Source of costs
	BPd	hKd	SVd	DVd	
PFS on-treatment	£54.45	£55.19	£55.19	£55.19	NHS Cost Collection Costs 2021/22[57]
PFS off-treatment	£36.43	£36.43	£36.43	£37.17	
PD	£45.60	£45.60	£45.60	£45.60	

CS=company submission; PD=progressed disease; PFS=progression-free survival
Source: CS, Table 57

4.10.3 Adverse events costs

The company has included treatment-related Grade ≥3 AEs in the model. AE incidence data for BPd were sourced from the DREAMM-8 trial and AE incidence data for the comparator treatments were sourced from their respective RCTs (identified by the clinical SLR). AE unit costs were sourced from the NHS Cost Collection Costs 2021/2022[57] and were applied as a one-off cost in the first model cycle.

Grade ≥3 eye-related AEs only affect patients treated with belantamab mafodotin. The eye-related side effects considered were keratopathy, blurred vision and dry eyes. The frequency

of ophthalmologist visits and artificial tear usage were assumed to be one for mild cases, one for moderate cases and five for severe cases (ID2701[59]). Total AE costs for each treatment are presented in Table 25.

Table 25 Total AE costs for each modelled treatment

	BPd	hKd	SVd	DVd
One-off cost	£1,883.17	£1,245.47	£1,254.76	£1,488.54

Source: CS, Table 61

4.10.4 End-of-life costs

The company applied a one-off cost of terminal care to the proportion of patients who died in each model cycle. The end-of-life cost was £12,397. This cost is the total average cost of care services in the last 12 months of life and was sourced from Unit Costs of Health and Social Care 2022.[60] It accounts for both hospital and social care costs (£7,979 and £4,418 respectively).

4.10.5 Severity modifier

The company considered that, based on expected total QALYs for the general population and expected total QALYs for those with the condition and living with current treatments, a severity weighting was not applicable.

5 COST EFFECTIVENESS RESULTS

The cost effectiveness results presented in the CS were generated using the PAS price for belantamab mafodotin, a predicted pomalidomide price and list prices for all other drugs. To conform with the NICE process, the EAG has presented cost effectiveness results using the PAS price for belantamab mafodotin and current list prices for all other drugs. The company has presented cost effectiveness results for two subpopulations (CS, p167):

- 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. Given that SVd is only approved by NICE in the 2L population for patient's refractory to both daratumumab and lenalidomide, SVd is not considered a relevant comparator for this subpopulation.
- 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 BPd cannot be compared against DVd (but can be compared against any other approved lenalidomide-sparing regimen, including SVd).

The company base case pairwise deterministic results are presented in Table 26 and company base case pairwise probabilistic results (200 model iterations) are presented in Table 27.

Table 26 DVd eligible subpopulation: company base case pairwise results (PAS price for belantamab mafedotin)

Treatment	Total		Incremental		ICER (£/QALY)	INHB at £30,000
	Costs	QALYs	Costs	Incremental QALYs		
Deterministic results						
BPd	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	96,639	[redacted]
DVd	[redacted]	[redacted]	[redacted]	[redacted]	213,229	[redacted]
Probabilistic results						
BPd	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	97,549	[redacted]
DVd	[redacted]	[redacted]	[redacted]	[redacted]	238,679	[redacted]

ICER=incremental cost effectiveness ratio; INHB=incremental net health benefit; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: company model

Table 27 DVd ineligible subpopulation: company base case pairwise results (PAS price for belantamab mafedotin)

Treatment	Total		Incremental		ICER (£/QALY)	INHB at £30,000
	Costs	QALYs	Costs	QALYs		
Deterministic results						
BPd	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	96,639	[redacted]
SVd	[redacted]	[redacted]	[redacted]	[redacted]	120,460	[redacted]
Probabilistic results						
BPd	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	97,549	[redacted]
SVd	[redacted]	[redacted]	[redacted]	[redacted]	133,274	[redacted]

ICER=incremental cost effectiveness ratio; INHB=incremental net health benefit; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: company model

5.1 Deterministic sensitivity analyses

The company varied individual parameter input values. The parameter inputs were varied by upper and lower confidence bounds or, if not available, +/-20%. The parameters that had the biggest impact on ICERs per QALY gained varied between comparator treatments. However, for all comparator treatments, OS HRs, TTD HRs and BPd utility were three of the five variables that had the biggest impact on the ICERs per QALY gained.

Table 28 The five variables that had the biggest impact on ICERs per QALY gained (BPd versus comparator)

Rank	Comparator to BPd		
	DVd	hKd	SVd
1	OS HR (vs PVd)	OS HR (vs PVd)	OS HR (vs PVd)
2	TTD HR (vs PVd)	TTD HR (vs PVd)	TTD HR (vs PVd)
3	DVd Daratumumab RDI	hKd carfilzomib RDI	SVd one-off first subsequent treatment cost
4	BPd treatment utility	Administration cos per treatment cycle hKd (treatment cycle 2+)	SVd first subsequent treatment, % patients
5	PFS HR (vs PVd)	BPd treatment utility	BPd treatment utility

HR=hazard ratio; OS=overall survival; PFS=progression-free survival; RDI=relative dose intensity; TTD=time to treatment discontinuation
Source: company model

5.2 Scenario analyses

The company ran 23 scenario analyses to explore the impact on cost effectiveness results of alternative model assumptions. All company scenario analysis results, for all treatments, showed that BPd was the most cost effective treatment.

5.3 Validation

The model developers validated the model using the TECH-VER[61] checklist and found no issues with the computational accuracy of the model.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for the comparison of BPd versus DVd, hKd and SVd for adults (≥18 years) with RRMM who have had **1 LoT** including a lenalidomide-containing regimen (2L patients) and for whom lenalidomide is unsuitable.

6.1 Overview of modelling issues identified by the EAG

The EAG reviewed the company model to check that algorithms were accurate and that the parameter values used in the model match the values presented in the CS. Two errors were identified:

- the company assumed that when the pomalidomide patent expires at the end of 2024, the price of pomalidomide would drop by [redacted]% and has used this price in their base case analysis; the current list price for pomalidomide should have been used in the company base case analysis
- the company incorrectly calculated the cost of bortezomib for patients treated with SVd by costing the average dose per m^2 rather than the average dose per mg; this error does not affect the company base case analysis as it is only evident when wastage is removed from the model

The EAG has generated corrected company base case cost effectiveness results.

A summary of the EAG's critique of the company cost effectiveness analysis is presented in Table 29.

Table 29 Summary of the EAG critique of the company cost effectiveness analysis

Aspect considered	EAG comment	Section of EAG report
Model structure	• The model structure and time horizon are appropriate	NA
Population and comparators	• The population and comparators are appropriate	NA
Overall survival	• The EAG has removed OS differences between BPd, hKd, SVd and DVd (**EAG revision 1**)	1.2
Progression-free survival	• The approach to modelling PFS is acceptable	NA
Time to treatment discontinuation	• The approach to modelling TTD is acceptable	NA
Drug costs	• Assuming 0% vial sharing for IV and SC medications is not realistic • The company should not have modelled wastage for medications taken as tablets (**EAG revision 2**) • In the absence of IPD dosing for all treatments, the company should have used RDI for all treatments to account for actual dosages received (**EAG revision 3**)	6.3 6.4 6.5

Aspect considered	EAG comment	Section of EAG report
Utility values	• In the PFS health state, utility values should not vary by treatment • The DREAMM-8 trial utility values for patients treated with BPd are likely to be overestimates. The EAG has generated cost effectiveness results using ENDEAVOUR trial PFS and PD health state utility values for all patients (**EAG revision 4**)	6.6
Modelled subsequent treatments	• The approach to modelling subsequent treatments is acceptable	NA
Healthcare resource use	• Appropriate costs and resource use values are correctly applied	NA
Adverse events	• The approach to modelling AEs is appropriate. The inclusion of AE disutility values may result in double counting; however, their inclusion has an insignificant impact on model QALYs	NA
Company severity modifier	• The EAG agrees with the company that a severity modifier should not be applied.	NA
PSA	• The company PSA has been correctly specified	NA

AE=adverse event; EAG=External Assessment Group; IPD=Individual patient data; NA=not applicable; IV=intravenous; OS=overall survival; PD=progressive disease; PF=progression-free; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year; RDI=relative dose intensity; SC=subcutaneous; TTD=time to treatment discontinuation

6.2 Overall survival

Overall survival estimates

The company's FE OS (lenalidomide-exposed+ITT) NMA results showed no statistically significant differences between BPd and any of the comparators, no matter the population of interest. The FE OS (lenalidomide-exposed+ITT) NMA results showed a numerical advantage for patients treated with BPd versus all comparators, however, all credible intervals were wide, which suggests high levels of uncertainty. In Section 3.6.7, due largely to a lack of data for the population of interest, the EAG concluded that company OS (lenalidomide-exposed plus ITT) NMA results should not be used to inform decision-making. Further, results from a pre-planned exploratory analysis of OPTIMISMM trial data with subsequent therapy as a time-dependent covariate and adjusting for stratification factors was used in this NMA to represent the effectiveness of PVd vs Vd. As the OPTIMISMM trial links BPd to all comparators, this compromises all OS (lenalidomide-exposed plus ITT) NMA results. If the published HR had been used in the network, this would have resulted in all HRs (versus BPd) being closer to 1. Therefore, the EAG has assumed that OS for patients treated with BPd, DVd, hKd and SVd does not differ. The EAG has implemented the assumption of no difference in OS by using the curve selected by the company to estimate OS for patients treated with BPd for patients treated with hKd, SVd and DVd.

Time on subsequent treatment

If OS does not vary by treatment, then as time in the PFS health state and on treatment is longer for patients treated with BPd than for patients treated with hKd, SVd or DVd, this may mean that time on subsequent treatments is shorter for patients treated with BPd than for patients treated with DVd, hKd or SVd. In the company base case analysis and in the EAG preferred base case, time on subsequent treatment has been assumed to be independent of second-line treatment; therefore, BPd total costs may be overestimated and/or DVd, hKd or SVd total costs may be underestimated.

6.3 Vial sharing

The company has assumed that there will be no vial sharing for any of the SC or IV medications and so wastage will be incurred for these treatments. Clinical advice to the EAG is that at least some vial sharing will take place, although the extent of sharing is not known. The company has run a scenario with full vial sharing (CS, Table 70). The actual ICER per QALY gained for patients treated with BPd and comparator treatments will lie somewhere between the ICER per QALY gained with and without wastage. The EAG has reproduced the company full vial sharing scenario (EAG revision S1) to allow easy comparison with the EAG preferred base case and to show the impact of the EAG revisions on this scenario.

6.4 Wastage of medications taken as tablets

When estimating costs of medications taken as tablets (pomalidomide, selinexor and dexamethasone), the company has included the cost of wastage. In the model, all medications taken as tablets come in tablet sizes that allow reductions from the recommended dose; therefore, doses can be lowered without wastage. The EAG considers that whilst there may be some wastage of tablets, for example, from patients forgetting to take medication, or tablets remaining when treatment is stopped, wastage should not be included in the cost effectiveness the analysis.

6.5 Estimating drug costs

The company has used DREAMM-8 trial individual patient data (IPD) to generate accurate estimates of belantamab mafodotin drug use. Drug usage for all other intervention and comparator drugs has been estimated using RDI. The EAG considers that IPD-based costs are more accurate than RDI-based costs and highlights that the two approaches can generate different costs. For example, using IPD-based, rather than RDI-based, belantamab mafodotin drug costs reduces the company base case total cost of BPd treatment by [redacted].

To allow a fair comparison of drug costs, the EAG has run a scenario in which, for the intervention and the comparators, all drug costs have been estimated using the RDI-based approach.

6.6 Utility values

In the company base case, it has been assumed that, compared to patients treated with DVd, hKd or SVd, there is a utility benefit in the PFS health state for patients treated with BPd. In the CS, the company stated that:

> *Given the regularity of eye-related side effects in the BPd arm of DREAMM-8, the QoL gathered in the trial are highly likely to account for the HRQoL impact associated with these events* (CS, p134)

However, the DREAMM-8 trial EQ-5D data are unlikely to capture the detriment to HRQoL caused by eye-related AEs as it has been established that the EQ-5D tool is not sensitive to changes in vision and a visual 'bolt on' (EQ-5D-V) has been developed to account for impact of visual changes on utility.[62] In the DREAMM-8 trial, 48% of patients treated with BPd had a Grade ≥3 eye-related AE. As any vision-related impacts from these events on HRQoL are unlikely to have been captured by the EQ-5D tool, utility values for patients treated with BPd are likely to have been overestimated.

The EAG considered alternative sources of model utility values. The DREAMM-8 trial pooled PFS and PD utility values are not appropriate as they include data from patients treated with BPd. The DREAMM-8 trial PVd utility values relate to a treatment that is not considered in the company model. The EAG has revised the company model by using ENDEAVOUR trial utility values; these values informed the NICE appraisal of DVd as a treatment option for adults with multiple myeloma who had had one previous line of treatment that included lenalidomide or lenalidomide was unsuitable as a second-line treatment (TA897,[53] CS, Table 46). The EAG highlights that the TA897[53] PD health state utility value is very similar to the DREAMM-8 trial PD utility value.

The utility values used in the company base case and in an EAG revision are presented in Table 30.

Table 30 Company base case and EAG PFS utility values

Treatment	Company base case		EAG revision	
	Value	Source: DREAMM-8 trial	Value	Source
PFS (on treatment)	[redacted]	Pooled value	0.737	TA897[53]
BPd	[redacted]	BPd arm	0.737	
PVd	[redacted]	PVd arm	0.737	
hKd	[redacted]	Assumed to be equal to PVd	0.737	
SVd	[redacted]	Assumed to be equal to PVd	0.737	
DVd	[redacted]	Assumed to be equal to PVd	0.737	
PFS (off treatment)	[redacted]	Assumption	0.737	
PD	[redacted]	Pooled value	0.665	

EAG=External Assessment Group; PD=progressed disease; PFS=progression-free survival
Source: CS, Table 44 and TA897[53]

6.7 Impact of EAG revisions on company base case cost effectiveness results

The EAG has made the following revisions to the company base case:

- DVd, hKd and SVd OS set equal to BPd OS (R1)
- No wastage for medications taken as tablets (R2)
- RDI-based costing all treatments (R3)
- Use ENDEAVOUR trial (TA897[53]) PFS and PD utilities (R4)

The EAG has also reproduced results from the company scenario that assumed 100% vial sharing (S1).

Details of how the EAG revised the company model are presented in Appendix 2, Section 8.2 of this EAG report. Deterministic cost effectiveness results are provided in Table 32 to Table 36. Probabilistic cost effectiveness results for the EAG preferred scenario and key scenarios are presented in Table 37 to Table 41. All results have been generated using list prices for all drugs except for belantamab mafodotin (PAS price).

All results tables have been replicated using the confidential commercial arrangements described in Table 31; these results are presented in the confidential appendix.

Table 31 The sources of prices used to generate the cost effectiveness results presented in the confidential appendix

Treatment	Price source/type of commercial arrangement
Belantamab mafodotin	PAS
Bortezomib	MPSC
Carfilzomib	PAS
Daratumumab	PAS
Dexamethasone	eMIT
Panobinostat	PAS
Pomalidomide	PAS
Selinexor	PAS

eMIT=electronic Market Information Tool; MPSC=Medicines Procurement Supply Chain; PAS=Patient Access Scheme

Table 32 Deterministic results for BPd versus DVd, PAS price for belantamab mafodotin

EAG revisions to company base case	BPd		DVd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) DVd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table 33 Deterministic results for BPd versus hKd, PAS price for belantamab mafodotin

EAG revisions to company base case	BPd		hKd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**BPd dominates**	[redacted]	
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1) hKd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

AE=adverse event; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table 34 Deterministic results for BPd versus SVd, PAS price for belantamab mafodotin

EAG revisions to company base case	BPd		SVd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**BPd dominates**	[redacted]	
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) SVd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY

AE=adverse event; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table 35 Deterministic fully incremental results for DVd eligible subpopulation, PAS price for belantamab mafodotin – EAG base case

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
DVd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Table 36 Deterministic fully incremental results for DVd ineligible subpopulation, PAS price for belantamab mafodotin – EAG base case

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
SVd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Table 37 Probabilistic results for BPd versus DVd, PAS price for belantamab mafodotin

EAG revisions to company base case	BPd		DVd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**BPd dominates**	[redacted]	
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1) DVd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table 38 Probabilistic results for BPd versus hKd, PAS price for belantamab mafodotin

EAG revisions to company base case	BPd		hKd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**BPd dominates**	[redacted]	[redacted]
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1) hKd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table 39 Probabilistic results for BPd versus SVd, PAS price for belantamab mafodotin

EAG revisions to company base case	BPd		SVd		Incremental		ICER per QALY gained	NMB*	NMB change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs			
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**BPd dominates**	[redacted]	[redacted]
A.1 EAG corrected company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R1) SVd OS set equal to BPd OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Removed wastage for medications taken as tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) RDI used for costing all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Used PFS and PD utilities from the ENDEAVOR trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG preferred base case (R1-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S1) 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2. EAG alternative base case (R1-R4 plus S1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Willingness to pay threshold=£30,000/QALY
EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; NMB=net monetary benefit; OS=overall survival; PAS=Patient Access Scheme; PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year; RDI=relative dose intensity

Table 40 Probabilistic fully incremental results for DVd eligible subpopulation, PAS price for belantamab mafodotin – EAG base case

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
DVd	[redacted]	[redacted]			
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Table 41 Probabilistic fully incremental results for DVd ineligible subpopulation, PAS price for belantamab mafodotin – EAG base case

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
SVd	[redacted]	[redacted]			
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BPd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

6.8 EAG cost effectiveness conclusions

Company base case deterministic and probabilistic cost effectiveness results showed that BPd dominates all comparator treatments (calculated using a [redacted]% discount applied to the pomalidomide list price). However, once the current list price for pomalidomide is used in the company base case (and all EAG) analyses, then BPd no longer dominates comparator treatments.

There is no robust evidence to differentiate between OS for patients treated with BPd and OS for patients treated with any of the comparators. Therefore, the EAG has set OS for all treatments to be the same. This revision had the biggest impact on cost effectiveness results.

Results are also sensitive to doses that patients receive and how wastage is incorporated into the company model.

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8 APPENDICES

8.1 Appendix 1 EAG assessment of the company's statistical approach

Table 42 EAG assessment of statistical approach used to analyse DREAMM-8 trial data

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	Analyses of the primary endpoint of PFS (IRC), and of the secondary endpoints, OS, DoR, MRD, ORR, CRR, VGPR, TTBR, TTR, TTP and PFS-2 were conducted in the ITT population (CS, Table 9). Analyses of the patient reported outcome (PRO) endpoints were conducted using the ITT population. The OSDI and FACT GP5 are based on the safety population (CSR, Section 4.3.5). Analyses of safety data were based on the 'safety population' which included all randomised patients who received at least 1 dose of allocated study treatment (CS, p44). The EAG is satisfied that these populations were clearly defined and pre-specified in the TSAP (TSAP, p23).
Was an appropriate sample size calculation pre-specified?	Yes	The planned sample size is approximately 302 participants. The trial is event driven. Assumptions used to generate the sample size and power calculations are presented in the CS (CS, p45). At 173 PFS events, the study has 90% power to detect a HR of 0.6 at a 1.0% (one-sided) significance level. The EAG is satisfied that the sample size is appropriate and was pre-specified in the TSAP (TSAP, p85)
Were all protocol amendments made prior to analysis?	Yes	The final amendment (Amendment) 4 was made on 28 September 2023, prior to the database lock (6 November 2023).
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	Primary and secondary efficacy endpoints are defined in CS (CS, Table 6). Definitions and analysis approaches for these endpoints were pre-specified in the TSAP (TSAP, Section 4.2 and Section 4.3).
Was the analysis approach for PROs appropriate and pre-specified?	Yes	Mean, SD, median, min-max of the actual value and change from baseline using the EORTC QLQ-C30 questionnaire, QLQ-MY20 and QLQ-IL52 were assessed as secondary outcomes (CS, p42). The analysis approach for this outcome is documented in the TSAP (TSAP Section 4.3.5). EQ-5D-3L outcomes were exploratory analyses. The analytical approach for the EQ-5D-3L data is described in the CS (CS, p133) and in a separate TSAP not available to the EAG (TSAP Section 4.4.3.2) Other exploratory outcomes were OSDI, PGIS and FACT GP5. The analytical approach for the OSDI and FACT GP5 are described in the TSAP (TSAP Section 4.4.3.1 and Section 4.4.3.4) The analytical approach for the PGIS is described in a separate TSAP not available to the EAG (TSAP Section 4.4.3.3).
Was the analysis	Yes	Safety was specified as a secondary endpoint. The analysis

Item	EAG assessment	Statistical approach with EAG comments
approach for AEs appropriate and pre-specified?		of AEs followed the approach that was pre-specified in the TSAP (TSAP Section 4.5).
Was a suitable approach employed for handling missing data?	Yes	Participants with missing data are treated as non-responders
Were all subgroup and sensitivity analyses pre-specified?	Yes	The subgroup analyses are prespecified in the TSAP (TSAP Table 11).

AE=adverse event; CS=company submission; CRR=complete response rate; CSR=Clinical Study Report; DoR=duration of response; EAG=External Assessment Group; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-3L=EuroQoL-5 Dimensions-3 Level; IRC=independent review committee; ITT=intention-to-treat; MRD=minimal residual disease; ORR=objective response rate; OS=overall survival; OSDI=ocular surface disease index; PFS=progression-free survival; PRO=patient reported outcome; QoL=quality of life; TSAP=trial statistical analysis plan; TTBR=time to best response; TTP=time to progression; TTR=time to response; VGPR=very good partial response

Source: CS, DREAMM-8 CSR,[20] DREAMM-8 TSAP,[21] DREAMM-8 trial protocol,[22]

8.2 Appendix 2: EAG revisions to the company model

This appendix contains details of the changes that the EAG made to the company model.

EAG revision	Implementation instructions
Set up EAG revision switches	**Insert sheet 'EAG revisions'** Set cell B3="R1" Name cell C3=EAG_R1" Set cell B4="R2" Name cell C4="EAG_R2" Set cell B5="R3" Name cell C5="EAG_R3" Set cell B6="C1" Set cell C6="EAG_C1" Set cell B7="R4" Name cell C7="EAG_R4" Set cell B8="S1" Name cell C8="EAG_S1"
EAG drug price corrections	**In sheet 'Cost inputs'** Set cell G108='Data Store'!H98 **In Sheet 'EAG revisions'** Set cell C6=1 **In Sheet 'Cost Inputs'** Set cell D36=IF(EAG_C1=1,0,'Data Store'!D79) Apply C1 to all subsequent revisions
R1) OS for patients treated with hKd, SVd and DVd set equal to BPd	**In Sheet 'EAG revisions'** Set cell C3=1 **In Sheet 'Clinical Inputs'** In cells D33 clear data validation Set cell D33=IF(EAG_R1=1,"B-Pd","P-Vd") **In sheet 'Clinical Inputs'** Set cell D50=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!D53,'Data Store'!G53)) Set cell D51=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!D54,'Data Store'!G54)) Set cell D53=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!D56,'Data Store'!G56)) Set cell E50=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data

EAG revision	Implementation instructions
	Store'!E53,'Data Store'!H53)) Set cell E51=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!E54,'Data Store'!H54)) Set cell E53=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!E56,'Data Store'!H56)) Set cell F50=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!F53,'Data Store'!I53)) Set cell F51=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!F54,'Data Store'!I54)) Set cell F53=IF(EAG_R1=1,1,CHOOSE('Data Store'!$K$51,'Data Store'!F56,'Data Store'!I56))
R2) Remove wastage for medications taken as tablets	**In Sheet 'EAG revisions'** Set cell C4=1 **In Sheet 'Cost Inputs'** Set cell H68 =IF(EAG_R2=1,IF(bpd_unit_size_pom_fs=0,0,bpd_dose_per_treatment_pom_fs/bpd_unit_size_pom_fs),IF(bpd_unit_size_pom_fs=0,0,ROUNDUP(bpd_dose_per_treatment_pom_fs/bpd_unit_size_pom_fs,0))) Set cell J68 =IF(EAG_R2=1,F68,IF(bpd_unit_size_pom_fs=0,0,ROUNDUP(bpd_dose_per_admin_pom_fs/bpd_unit_size_pom_fs,0)*bpd_admin_per_cycle_pom_fs)) Set cell L68 =IF(EAG_R2=1,H68,IF(bpd_unit_size_pom_fs=0,0,ROUNDUP(bpd_dose_per_admin_pom_fs/bpd_unit_size_pom_fs,0)*bpd_admin_per_cycle_pom_fs)) Set cell H69 =IF(EAG_R2=1,IF(bpd_unit_size_dexam_fs=0,0,bpd_dose_per_treatment_dexam_fs/bpd_unit_size_dexam_fs),IF(bpd_unit_size_dexam_fs=0,0,bpd_dose_per_treatment_dexam_fs/bpd_unit_size_dexam_fs)) Set cell J69 =IF(EAG_R2=1,F69,IF(bpd_unit_size_dexam_fs=0,0,ROUNDUP(bpd_dose_per_admin_dexam_fs/bpd_unit_size_dexam_fs,0)*bpd_admin_per_cycle_dexam_fs)) Set cell L69 =IF(EAG_R2=1,H69,IF(bpd_unit_size_dexam_fs=0,0,ROUNDUP(bpd_dose_per_admin_dexam_fs/bpd_unit_size_dexam_fs,0)*bpd_admin_per_cycle_dexam_fs)) Set cell F93 =IF(EAG_R2=1,IF(hkd_unit_size_dexamethasone_fs=0,0,hkd_dose_per_treatment_dexamethasone_fs/hkd_unit_size_dexamethasone_fs),IF(hkd_unit_size_dexamethasone_fs=0,0,ROUNDUP(hkd_dose_per_treatment_dexamethasone_fs/hkd_unit_size_dexamethasone_fs,0)))

EAG revision	Implementation instructions
	Set cell H93 =IF(EAG_R2=1,(IF(hkd_unit_size_dexamethasone_fs=0,0,hkd_dose_per_treatment_dexamethasone_fs/hkd_unit_size_dexamethasone_fs)),(IF(hkd_unit_size_dexamethasone_fs=0,0,ROUNDUP(hkd_dose_per_treatment_dexamethasone_fs/hkd_unit_size_dexamethasone_fs,0)))) Set cell J93 =IF(EAG_R2=1,F93,IF(hkd_unit_size_dexamethasone_fs=0,0,ROUNDUP(hkd_dose_per_admin_dexamethasone_fs/hkd_unit_size_dexamethasone_fs,0)*hkd_admin_per_cycle_dexamethasone_fs)) Set cell L93 =IF(EAG_R2=1,H93,IF(hkd_unit_size_dexamethasone_fs=0,0,ROUNDUP(hkd_dose_per_admin_dexamethasone_fs/hkd_unit_size_dexamethasone_fs,0)*hkd_admin_per_cycle_dexamethasone_fs)) Set cell F115 =IF(EAG_R2=1,IF(svd_unit_size_selinexor_fs=0,0,svd_dose_per_treatment_selinexor_fs/svd_unit_size_selinexor_fs),IF(svd_unit_size_selinexor_fs=0,0,ROUNDUP(svd_dose_per_treatment_selinexor_fs/svd_unit_size_selinexor_fs,0))) Set cell H115 =IF(EAG_R2=1,F115,IF(svd_unit_size_selinexor_fs=0,0,ROUNDUP(svd_dose_per_admin_selinexor_fs/svd_unit_size_selinexor_fs,0)*svd_admin_per_cycle_selinexor_fs)) Set cell F117 =IF(EAG_R2=1,IF(svd_unit_size_dexamethasone_fs=0,0,svd_dose_per_treatment_dexamethasone_fs/svd_unit_size_dexamethasone_fs),IF(svd_unit_size_dexamethasone_fs=0,0,ROUNDUP(svd_dose_per_treatment_dexamethasone_fs/svd_unit_size_dexamethasone_fs,0))) Set cell H116 =IF(EAG_R2=1,F116,Bortez_MOM1_units) Set cell H117 =IF(EAG_R2=1,F117,IF(svd_unit_size_dexamethasone_fs=0,0,ROUNDUP(svd_dose_per_admin_dexamethasone_fs/svd_unit_size_dexamethasone_fs,0)*svd_admin_per_cycle_dexamethasone_fs)) Set cell F143 =IF(EAG_R2=1,IF(dvd_unit_size_dexamethasone_fs=0,0,dvd_dose_per_treatment_dexamethasone_fs/dvd_unit_size_dexamethasone_fs),IF(dvd_unit_size_dexamethasone_fs=0,0,ROUNDUP(dvd_dose_per_treatment_dexamethasone_fs/dvd_unit_size_dexamethasone_fs,0))) Set cell H143 =IF(EAG_R2=1,IF(dvd_unit_size_dexamethasone_fs=0,0,dvd_dose_per_treatment_dexamethasone_fs/dvd_unit_size_dexamethasone_fs),IF(dvd_unit_size_dexamethasone_fs=0,0,ROUNDUP(dvd_dose_per_treatment_dexamethasone_fs/dvd_unit_size_dexamethasone_fs,0)))

EAG revision	Implementation instructions
	Set cell L142=IF(EAG_R2=1,F142,Bortez_MOM1_units) Set cell N142=IF(EAG_R2=1,H142,Bortez_MOM1_units) Set cell L143 =IF(EAG_R2=1,F143,IF(dvd_unit_size_dexamethasone_fs=0,0,ROUNDUP(dvd_dose_per_admin_dexamethasone_fs/dvd_unit_size_dexamethasone_fs,0)*dvd_admin_per_cycle_dexamethasone_fs)) Set cell N143 =IF(EAG_R2=1,H143,IF(dvd_unit_size_dexamethasone_fs=0,0,ROUNDUP(dvd_dose_per_admin_dexamethasone_fs/dvd_unit_size_dexamethasone_fs,0)*dvd_admin_per_cycle_dexamethasone_fs))
R3) RDI used for costing all treatments	**In Sheet 'EAG revisions'** Set cell C5 =1 **In Sheet 'Cost Inputs'** In cell D60 clear data validation Set cell D60=IF(EAG_R3=1,"No","Yes")
R4) PFS and PD utilities from the ENDEAVOR trial	**In Sheet 'EAG revisions'** Set cell C7=1 **In Sheet 'Quality of Life Inputs'** In cells D9 and D10 clear data validation Set cell D9=IF(EAG_R4=1,"No","Yes") Set cell D10=IF(EAG_R4=1,"TA897","DREAMM-8")
S1) Vial sharing 100%	**In Sheet 'EAG revisions'** Set cell C8=1 **In Sheet 'Cost Inputs_others'** In cell D10 clear data validation Set cell D10=IF(EAG_S1=1,"No","Yes")

Single Technology Appraisal

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

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 22 October 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.

Issue 1 Significant process errors with EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG have made incorrect statements and reached multiple erroneous conclusions regarding topics which could easily have been resolved at the clarification question stage.	The following Issues should be entirely removed from the EAG report: • Generalisability of DREAMM-8 trial results to NHS patients • Limitation of the company PFS and OS NMA, including lack of evidence to support different OS modelling • RDI used for costing all treatments • Use of alternative utility values For any Issue which is not removed from the report, the Company should be allowed to provide a brief response at ACM (i.e. on Committee slides) to outline their objections to the EAG's position, as would have been detailed in their clarification questions responses. This will help minimise the committee's time spent	NICE PMG36 Section 5.6.3 states that "If the company evidence submission is incomplete or the decision problem is not specified appropriately, the technical lead consults with the EAG and sends a letter of clarification and any requests for additional analyses to the company within 21 days of receiving the submission" The clear meaning of this Section is that if the EAG do not ask questions on a topic it is because they view the evidence submission as being complete. The purpose of conducting the appraisal in this way is to avoid wasting Committee time on issues which can easily be resolved, and to avoid prejudicially biasing the Committee against the intervention by providing a one-	The EAG considers that the four issues raised by the company are matters of opinion, not factual inaccuracies. No changes have been made to the EAG report. The EAG highlights that the purpose of the clarification letter is to clarify issues that have not been fully explained in the CS. The EAG considers that it was not necessary to seek clarification on any of the four bulleted issues raised by the company.

	on addressing potential misunderstandings.	sided assessment of the evidence. Failure to follow their own processes undermines NICE's principle of being accountable for the decisions that they make, and leaves NICE open to an appeal by industry or patient groups. We note that notwithstanding the above, the Company did oblige an off-process request for additional information sent more than 21 days after receiving the submission in the interests of helping the Committee reach an informed decision. The Company would be happy to work with the Technical Team to similarly resolve the highlighted issues.	
The EAG have used the wrong comparator in their assessment	Any reference to the trade name of branded pomalidomide ('Imnovid®') should be removed from the report. The EAG should use generic pomalidomide in all comparisons.	The Scope specifies that the comparator used in combination with belantamab mafodotin should be 'pomalidomide', not the branded equivalent. By the time of the Committee's deliberations, the EAG agrees	The EAG has used the correct comparator. However, as requested, the following words have been removed from the EAG report: *"(brand name: Imnovid™)"*

	In addition, the following statement should be removed from Page 66, Section 6.1: *"the current list price for pomalidomide should have been used in the company base case analysis"*, since this refers to branded Imnovid® not generic pomalidomide	that generic alternatives to pomalidomide will be available (page 58, Section 4.10.1 of the EAG Report states "the patent for pomalidomide is due to expire in 2024"). This point is further corroborated by clinical expert opinion (see clinical notes attached to reference pack for appendix M), and is confirmed by NICE appraisal committee in TA658 (1). This has major implications for the affordability of the BPd combination (see below), since the correct list price to use in the appraisal is the list price associated with the lowest-price generic alternative to branded Imnovid®.	
The EAG have obfuscated their choice of comparator by describing it as an 'error correction'	A new Issue should be created, titled 'Assumed price of generic pomalidomide'. The Committee should be given an opportunity to discuss their preferred approach to this assumption. The description of the EAG replacing the wholesale price of	This is a significant process error because the EAG have acted beyond their remit, and taken a decision which should have been reserved for the Committee. The major source of uncertainty in the appraisal is the assumed price of generic pomalidomide	This is not a process error. It is stated in the NICE Guide to the Methods of Technology Appraisal 2022 (Section 4.4.4) that 'Reference-case analyses should be based on prices that reflect as closely as

	generic pomalidomide with the branded Imnovid® list price in the model as an 'error correction' should be removed.	(that is, whether the Committee should conservatively consider the lowest generic price which is available to the NHS at the time of Committee meeting or whether the Committee can accept the Company's argument that the eventual final discount can be predicted with fair accuracy). It is not appropriate for EAGs to describe their preferred approach to this uncertainty as an 'error correction'. This obfuscates matters of expert judgement behind a claim that the EAG are merely making a technical change or error correction. This denies external stakeholders, including patient groups, the opportunity to understand why a decision has been made about their care. The Company notes parenthetically that the EAG's proposed 'error correction' is actually itself incorrect – it uses the list price of branded pomalidomide ('Imnovid®') when	possible the prices that are paid in the NHS for all evaluations.' The costing approach used by the EAG was adopted following discussion with the NICE technical team. NICE decisions are made using drug prices that are accurate at the time of meetings.

		as discussed above the NHS will not be paying this for pomalidomide at the point of approval.	

Issue 2 Generalisability of DREAMM-8 trial results to NHS patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 11, Section 1.3 The decision problem: summary of the EAG's key issues. *"No clinical effectiveness evidence has been provided by the company for patients who lenalidomide is unsuitable"* **Page 25, Section 2.4.3 Population.** *"there is no robust clinical effectiveness evidence available from the DREAMM-8 trial for patients who are unsuitable for treatment with lenalidomide"*	The Company proposes the removal of these statements from Sections 1.3, Section 2.4.3 and Section 3.7.	It is factually inaccurate to say that no evidence has been provided on the effectiveness of the intervention on patients for whom lenalidomide is unsuitable. By definition, patients who are refractory to lenalidomide will find lenalidomide to be an unsuitable treatment. This is not the only reason why lenalidomide might be unsuitable for a patient, but it is an important one. The ITT population for DREAMM-8 is 81% lenalidomide refractory, and therefore lenalidomide is unsuitable for at least 81% of patients in the DREAMM-8 trial. The remaining 19% of patients in the ITT population are	For clarity, the EAG has amended the text as follows: **Page 11** *"No clinical effectiveness evidence has been provided by the company for **all** patients for who lenalidomide is unsuitable"* **Page 25** *"there is no robust clinical effectiveness evidence available from the DREAMM-8 trial for **all** patients who are unsuitable for treatment with lenalidomide"*

Page 48, Section 3.7 Conclusions of the clinical effectiveness section *"No specific clinical trial evidence has been provided by the company for patients who were unsuitable for treatment with lenalidomide"*		lenalidomide exposed, and clinical expert opinion is that this often results in lenalidomide being an unsuitable treatment option in the 2L (2). Therefore, by any measure it is reasonable to describe the ITT population of DREAMM-8 as 'predominantly unsuitable for treatment with lenalidomide' The evidence presented for the effectiveness of BPd in this population is robust and specific. The significant PFS benefit of BPd versus PVd in the ITT population (HR:0.52 [0.37,0.73], p <0.001) demonstrates its effectiveness. Additionally, in the specific subgroup of lenalidomide-refractory patients (who are 100% lenalidomide-unsuitable, as described above), the PFS benefit is even more pronounced (HR:0.45 [0.31,0.65]). Specifically, the mPFS for lenalidomide refractory patients is 24.0 months (17.6 – NR) for BPd compared to 9.2 months (7.2 – 12.5) for PVd. The Company notes it would have been happy to share this	**Page 48** *"No specific clinical trial evidence has been provided by the company for patients who* ***are contraindicated to lenalidomide and who were therefore*** *unsuitable for treatment with lenalidomide"*

		information with the EAG had they asked about the issue during clarification questions.	
Page 11, Section 1.3 The decision problem: summary of the EAG's key issues; **Page 25, Section 2.4.3 Population;** **Page 31, Section 3.2.3 Demographic and disease characteristics of DREAMM-8 trial patients;** **Page 45, Section 3.6.6 EAG comments on company NMAs: PFS (lenalidomide-exposed) NMA and OS (lenalidomide-exposed+ITT) NMA** **Page 48, Section 3.7 Conclusions of the clinical effectiveness section.**	This statement should be amended to read, '*25% of DREAMM-8 trial patients had received prior treatment with daratumumab, which is approximately in line with current NHS prescribing patterns'*	The statement, "most NHS patients currently receive daratumumab in the first-line setting," is factually inaccurate. Therefore, to draw conclusion "that this limits the generalisability of the trial result to NHS patients" is also inaccurate. As of 2024, the majority of the NHS patients in 2L are still receiving treatments that were approved prior to DRd's approval in October 2023. Implementation of the DRd regimen in the NHS will take time (for example, standard practice with a NICE appraisal is for a three month window to be assumed before a hospital is ready to provide any new treatment) (3). Data from the MAIA trial shows DRd extended mPFS; after a median follow up of 56.2 months, the mPFS is still not reached (95% CI 54.8–NR) (4).	For clarity, the EAG has amended the text as follows: *"Only 25% of DREAMM-8 trial patients had received prior treatment with daratumumab. Clinical advice to the EAG is that this limits the generalisability of the trial results to NHS patients as,* ***moving forward****,* ***most NHS patients will receive*** *daratumumab in the first-line setting. The impact of limited prior daratumumab exposure on DREAMM-8 trial results is not known"*

All sections mentioned above refer to the same point from the EAG on patients previously treated with daratumumab: *"Only 25% of DREAMM-8 trial patients had received prior treatment with daratumumab. Clinical advice to the EAG is that this limits the generalisability of the trial results to NHS patients as most NHS patients currently receive daratumumab in the first-line setting. The impact of limited prior daratumumab exposure on DREAMM-8 trial results is not known"*		Therefore, while more patients will receive the DRd regimen in 1L going forward, due to the regimen's long mPFS, daratumumab refractoriness in the 2L setting will remain low in the near term (3–5 years), maintaining the relevance of the DREAMM-8 trial results for NHS patients. This is confirmed by clinical validation, indicating that approximately 10% or fewer patients are currently refractory to daratumumab. This proportion is expected to rise to 15-20% in 2025 and 50-60% in 2027 (2). In general, the Company notes that the precedent amongst NICE Committees is to disregard highly speculative arguments about what treatment pathways might look like several years into the future. The Company further notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions.	

Issue 3 Lack of evidence to support modelling different overall survival for the intervention and comparator treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13, Section 1.5 The cost effectiveness evidence: summary of the EAG's key issues *"In the company model, it is assumed that OS for patients treated with BPd is longer than OS for patients treated with any of the comparator treatments". However, none of the company OS NMA results showed that OS for patients treated with BPd was statistically significantly different from OS for patients receiving the comparator treatments. Further, the EAG considers that company OS NMA results are unreliable and should*	The statements should be amended to read: *"In the company model, it is assumed that OS for patients treated with BPd is longer than OS for patients treated with any of the comparator treatments. This is confirmed by the results of their NMA, which demonstrated an OS increase of vs all relevant comparators: BPd over DVd [redacted] SVd and hKd "* The company further proposes that the EAG preferred base case is revised to align with the company base case, using OS and PFS input from the respective NMAs The Company notes that it is conventional to highlight when the	It is incoherent (and therefore factually inaccurate) to talk about the 'statistical significance' of a Bayesian NMA. Furthermore, it is bad statistical inference to accept the null hypothesis as literally true just because it cannot be rejected - even if the Company **had** run a frequentist NMA the EAG would still be incorrect in their application of statistics on this point. The Company notes that NICE guidelines emphasise the importance of considering all relevant evidence to ensure robust decision-making, and not relying purely on statistical tests without interpretation. In this submission, major sources of evidence which the company have presented and which	The EAG acknowledges that it was incorrect to use the term 'statistically significant' but highlights that the conclusion drawn by the company (CS, p96) was: "BPd showed favorable results for OS, although not statistically significant, compared to hKd, DVd, and SVd." The EAG has amended the wording of the text as follows: *"In the company model, it is assumed that OS for patients treated with BPd is longer than OS for patients treated with any of the comparator*

not be used to inform decision-making (see Issue 2)" **Page 13, Section 1.5 The cost effectiveness evidence: summary of the EAG's key issues** *Assume that OS for patients treated with BPd, DVd, hKd and SVd is the same*	output of a Bayesian NMA crosses one, and sometimes to colloquially describe this as being 'statistically significant' or not. Therefore, we have not highlighted other instances where this inaccuracy occurs; only where it clearly affects the EAG's statistical interpretation	support an OS improvement for BPd include: • The uncertainty surrounding the OS HRs is accounted for in the model through probabilistic sensitivity analysis, which provides an unbiased, probabilistic interpretation of results (i.e., distribution of ICERs) incorporating this uncertainty. • The company's submitted surrogacy report (Appendix O.4 of the original submission) demonstrates a clear relationship between the strong PFS result and OS extrapolations (5). • Evidence from the DREAMM-7 trial, where Blenrep in combination with a different adjunct treatment does demonstrate a statistically significant OS benefit	*treatments". **However, the company OS NMA credible intervals all crossed 1.** Further, the EAG considers that company OS NMA results are unreliable and should not be used to inform decision-making (see Issue 2)"* The information provided in the surrogacy report and from the DREAMM-7 trial do not provide evidence for the comparison of BPd versus DVd, hKd or SVd. The EAG emphasises that uncertainty around point estimates is not resolved by PSA when the mean PSA ICER per QALY gained is used to inform decision making.

		Therefore, the company's position is that the EAG's alternative approach of assuming equal OS between comparators is an extreme scenario, supported neither by adequate statistical practice nor other supportive data, and should not be considered in the base case. The Company notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions. The Company further notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions.	

Issue 4 Limitation of company PFS and OS NMAs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, Section 1.4 The clinical effectiveness evidence: summary of EAG's key issues. *"only the OPTIMISMM trial (PVd vs Vd) HR used in the company OS (lenalidomide-exposed+ITT) NMA was estimated using a Cox proportional hazard model with subsequent therapy as a time-dependent covariate and adjusting for stratification factors"* **Page 48, Section 3.7 Conclusions of the clinical effectiveness section** *"the OPTIMISMM trial (PVd vs Vd) HR used in the company OS NMAs was adjusted for subsequent treatment; however, all other HRs used in the analysis were not adjusted for subsequent treatments"*	Amend the text on Page 12 to the following: *"a Cox proportional hazard model with subsequent therapy as a time-dependent covariate and adjusting for stratification factors **was only required** for OPTIMISMM trial (PVd vs Vd) HR used in the company OS (lenalidomide-exposed+ITT)"* Remove the text on Page 48, given HR adjustment for subsequent treatments was only required for the OPTIMISMM trial and appropriate to do so.	The EAG's statement inaccurately implies that the non-usage of this technique in other trials was an error or omission by the company. In fact, this fails to take into account the high rates of unintended cross-over of patients from their assigned interventions (PVd and Vd) in the parallel group OPTIMISMM trial. The unintended cross-over was unique to OPTIMISMM among other trials in the OS lenalidomide-exposed plus ITT network, based on publicly available evidence. At the time of the final OS analysis of OPTIMISMM, 79.1% of patients in the Vd arm and 68.3% in the PVd arm had received at least one subsequent therapy (6). Crucially, more than two thirds	This is not a factual inaccuracy. As the PVd vs Vd HR was sourced from an unpublished conference presentation, only limited details of the methods used to generate this HR are available. The information available from the conference presentation does not mention 'cross over', rather subsequent therapy. The information provided in the published conference abstract does not include the HR used in the company lenalidomide-exposed OS NMA. No changes have been made to the EAG report.

		of patients in the Vd arm received pomalidomide as subsequent treatment (6). Preplanned OS analysis using a Cox proportional hazard model with subsequent therapy as a time-dependent covariate and adjusting for stratification factors produces a more accurate estimate of the relative effect of PVd vs Vd. This method appropriately addresses the trial's efficacy question. Therefore, using the adjusted OS HR for OPTIMISMM in the corresponding NMA is appropriate. It is an essential methodological consideration rather than a flaw. The Company notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions.	

Page 12, Section 1.4 The clinical effectiveness evidence: summary of EAG's key issues. *"The EAG therefore considers that company PFS NMA results may be unreliable, and the company OS NMA results should not be used to inform decision-making"*	Remove the quoted text	It is unclear what the EAG are arguing in this section, but it cannot be that the Company PFS NMA results are 'unreliable' in the technical statistical sense, as the longer time to reach mPFS in the BPd arm suggests that patients are experiencing prolonged benefits, which is a positive outcome reflecting BPd's effectiveness. This is unrelated to the amount of random error which might be embedded in the NMA process and therefore unrelated to reliability. As a result, the Company believes the statement is either factually inaccurate (and referring to a concept other than reliability) or entirely unsupported (since the EAG argument does not support their claims) and either way should be cut from the report.	This is a matter of opinion, not a factual inaccuracy. No changes have been made to the EAG report.

		The Company asks the Committee to note responses they have already provided on daratumumab and generalisability (**Issue 2, Row 3)** and adjusted OS HRs for the OPTIMISMM trial (**Issue 3, Row 1)** as supporting a positive case for the reliability of the DREAMM-8 data and NMA. Based on the above, the company disagrees with the EAG position and proposes that the statement for the PFS and OS NMAs is amended accordingly to speak on the validity of the NMAs. The Company notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions.	
Page 42, Section 3.6.4 EAG summary and critique of company NMA methods *"The EAG agrees with the company that there was no statistically significant evidence of*	The EAG statement: "*for some of the trials in the networks, PFS and OS PH assumptions are/may not be valid…"*	The Company notes the lack of confidence in the EAG statement on whether the PFS and OS hazards are constant over time for certain comparator trials presented in	This is not a factual inaccuracy. No changes have been made to the EAG report.

violation of the PFS and OS PH assumptions for the DREAMM-8 trial. However, the EAG noted that, for the comparator trials, from the hazard functions presented (CS, Appendix D, Figures 6 and 7, it was not possible to be confident that PFS and OS hazards were constant over time; this means that for some of the trials in the networks, PFS and OS PH assumptions are/may not be valid (for example, PFS hazards in the IKEMA(7) trial do not appear to be proportional). The effect of non-proportionality on the NMA results is unknown"	Should be amended to: "*for some of the trials in the networks, PFS and OS PH assumptions **are probably** valid…"* The EAG statement: "*The effect of non-proportionality on the NMA results is unknown".* Should be cut	the CS (Appendix D, Figures 6 and 7). Despite this, the EAG then make statements indicating high certainty that these assumptions are in fact violated. One of these two positions must be factually inaccurate, as both positions together are incoherent. The company believes that the lack of confidence in the EAG position regarding the hazard functions for the comparator trials precludes a definitive statement for violation of the PH assumption. Therefore, the company propose that the two highlighted statements are amended accordingly.	
Page 46, Section 3.6.6 EAG comments on company NMAs: PFS (lenalidomide-exposed) NMA and OS (lenalidomide-exposed + ITT) NMA	The company propose that the following text is cut: *"As the adjusted results are statistically significant and the ITT results are not statistically*	The use of adjusted OS HRs only for the OPTIMISMM trial with subsequent treatment as a time-dependent covariate was justified and appropriate.	This is not a factual inaccuracy. No changes have been made to the EAG report.

"The OPTIMISMM trial OS HR used in the company NMAs was not the final (published) ITT analysis OS HR (HR=0.94; 95% CI: 0.77 to 1.15), rather, the HR had been sourced from an unpublished conference presentation[40] and had been generated from a preplanned exploratory analysis using a Cox PH model with subsequent therapy as a time-dependent covariate and adjusting for stratification factors (HR=0.76; 95% CI: 0.62 to 0.93). As the adjusted results are statistically significant and the ITT results are not statistically significant, the results from this exploratory analysis highlight the importance of the effect of subsequent treatments on OS results and that NMA results generated using trial ITT OS HRs are therefore not reliable"	*significant, the results from this exploratory analysis highlight the importance of the effect of subsequent treatments on OS results ~~and that NMA results generated using trial ITT OS HRs are therefore not reliable~~"*	This rationale and methodology, discussed in in **Issue 3, Row 1,** ensures that analysis accurately reflects the impact of the unintended cross-over of trial patients. Consequently, it is factually inaccurate to say that "the results from this exploratory analysis highlight… that the NMA results generated using trial ITT OS HRs are therefore not reliable" The statement fails to take into account the high rates of unintended cross-over of patients from their assigned interventions that were unique for the OPTIMISMM trial, among other trials in the company's OS lenalidomide-exposed plus ITT network. The Company maintains its position that the use of the adjusted OS HR was appropriate and applicable only in the case of OPTIMISMM, based on publicly available evidence. If	

		the Company is correct then the results generated **are** reliable, and therefore this exploratory analysis can neither confirm nor disconfirm the reliability of the approach; the argument is circular. The Company notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions.	
Page 47, Section 3.6.7 EAG concluding remarks *(ii) the company was unable to adjust for the impact of subsequent treatments on the effectiveness of comparator treatments.*	The company propose that the statement is amended to: "In both the absence of publicly available patient-level data and lack of requirement to adjust for the impact of subsequent treatments on the effectiveness of comparator treatments, the company did not conduct such analysis"	It is factually incorrect to say that the company was 'unable' to adjust for the impact of subsequent treatments. Firstly, the Company can only analyse such data as actually exists. Secondly, even if such data was made available it would not be appropriate statistical practice to conduct such analysis. Of all studies in the respective OS network, OPTIMISMM was unique in having the characteristics of an unintended cross-over study (as discussed in in	This is not a factual inaccuracy. No changes have been made to the EAG report.

		Issue 3, Row 1). Hence, such analysis was warranted in this case and the Company appropriately used the published results of this analysis in the respective NMA. The Company notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions.	
Page 48, Section 3.7 Conclusions of the clinical effectiveness section *"the OPTIMISMM trial (PVd vs Vd) HR used in the company OS NMAs was adjusted for subsequent treatment; however, all other HRs used in the analysis were not adjusted for subsequent treatments"*	The OS HRs used as inputs in the company's OS lenalidomide-exposed plus ITT NMAs were based on published data for the trials included in the corresponding network. The company would like to highlight that data for unintended cross-over were only available for the OPTIMISMM trial. Therefore, the impact of subsequent treatments on the efficacy of comparator treatments was taken into account when the corresponding evidence were publicly available.	The high rates of unintended cross-over in the parallel group OPTIMISMM trial were unique among the trials included in the company's OS lenalidomide-exposed plus ITT NMA based on publicly available evidence. The company maintains its position that the use of the adjusted OS HR was appropriate and applicable only in the case of OPTIMISMM.	This is a matter of opinion, not a factual inaccuracy. The company did not fully discuss the rationale for using the adjusted OPTIMISMM trial OS HR when the EAG questioned the source of this adjusted HR. No changes have been made to the EAG report.

	The company propose that this statement is removed from the list of concerns about the data used to conduct the company's NMAs.		

Issue 5 RDI used for costing all treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Section 1.5 The cost effectiveness evidence: summary of the EAG's key issues *"The company has used DREAMM-8 trial individual patient data to estimate the cost of belantamab mafodotin and used RDI to estimate the cost of all other drugs. This is problematic as the two approaches can generate different*	The company suggest the following changes to the sections critiquing the use of IPD data: • Revision of the EAG preferred base-case to use IPD RDI for belamaf, aligning with the previous EAG statement that IPD is the more accurate method. • Commentary on the magnitude to which IPD methodology versus mean RDI is likely to alter comparator treatment costs (DVd, SVd, hKd) to inform a balanced argument on	Throughout the EAG report, there is a distinct lack of consistency around preferences for use of IPD RDI versus mean RDI between BPd and comparators to inform treatment costs. At least one of these approaches must be factually inaccurate, as they are contradictory. Rationale for the EAG's preferred assumptions lacks adequate justification to make a factually accurate critique of fair and appropriate choice of methodology. The issues identified are the following: 1. The EAG has failed to identify key differences in dosage	The term IPD-RDI is not used in the CS. The terminology used in the EAG report is consistent with the terminology used by the company in the CS. No changes have been made to the EAG report. The EAG reiterates their view that the same approach should be used to estimate RDI for all treatments. Ultimately, the NICE Appraisal Committee will select their

costs. For example, using IPD-based, rather than RDI-based, belantamab mafodotin drug costs reduces the company base case total cost of BPd treatment by £57,079 (36.7%).” **Page 66, Section 6.1 Overview of modelling issues identified by the EAG, Table 29** *“In the absence of IPD dosing for all treatments, the company should have used RDI for all treatments to account for actual dosages received (**EAG revision 3**)”* **Page 68, Section 6.5 Estimating drug costs** *“The EAG considers that IPD-based costs*	choosing appropriate methodology. • Correction of terminology throughout to IPD-RDI; Use of IPD is another more accurate form of RDI. The language used in the report seem to imply IPD as a separate methodology, instead of an alternate measure of RDI dispersion, conceptually comparable to mean or median RDI. • Removal of the sentence “*This is problematic as the two approaches can generate different costs”, g*iven appropriate rationale is required as to why differing costs are problematic when considering two different measures of dispersion. • Removal of the sentence “*For example, using IPD-based, rather than RDI-based, belantamab mafodotin drug costs reduces the company base case total cost of BPd*	between BPd and comparators to drive fair choice of methodology. 2. The EAG has stated that ignoring these differences and assuming the same method for all comparators (mean RDI) is a ‘fair comparison’. 3. The EAG state the differing methodology (mean RDI versus IPD RDI) as problematic due to ‘differing costs’ without substantiation. 4. The recommendations by the EAG are contrary to their previous statement that the IPD RDI is more accurate. Regular dose modification due to eye-related side effects is a unique characteristic of treatment with belamaf. Using the mean RDI approach for belamaf would artificially inflate the costs by assuming time varying trends identified in belamaf dosing do not exist. It does not account for trends clearly shown in the trial data of increasing dose reductions and	preferred approach to estimating drug costs. No changes have been made to the EAG report.

are more accurate than RDI-based costs and highlights that the two approaches can generate different costs" **Page 69, Section 6.5 Estimating drug costs** *"To allow a fair comparison of drug costs, the EAG has run a scenario in which, for the intervention and the comparators, all drug costs have been estimated using the RDI-based approach"*	*treatment by £57,079 (36.7%)*". Drug costs depicted in the model align with the DREAMM-8 trial, and as such this language implies this setting unjustifiably reduces costs rather than making them more accurate (as agreed with by the EAG). • Removal or revision of the sentence *"In the absence of IPD dosing for all treatments, the company should have used RDI for all treatments to account for actual dosages received (**EAG revision 3**)"*, given actual dosages received in DREAMM-8 is estimated by the IPD RDI methodology, and given the significant differences in biological rationale for RDI between treatments • Removal or revision of the sentence *"To allow a fair comparison of drug costs, the EAG has run a scenario in which, for the intervention and the comparators, all drug*	delays over time. Use of mean RDI also skews towards the earlier points in follow-up where more patients are on-treatment and the dose intensity is higher. For comparator treatments, RDI was relatively high ([redacted] [Daratumumab], 90.7% [Carfilzomib], 78.9% [Selinexor]) and so time variation of dosage is unlikely to impact treatment costs. In addition, the model estimates patients are on BPd treatment for longer than comparators (At 3 years; BPd:29%, hKd: 6%, SVd: 8%, DVd: 20%). Time varying trends would have a much higher bearing on the treatment costs of belamaf than comparators and thus ignoring these unfairly biases cost impacts for the BPd arm versus comparator. Lastly, NICE guidelines prefer using IPD for subgroups when feasible, according to their methods (8). A fair comparison of treatment costs involves the use of suitable methodologies for appropriate treatments. The use of IPD for	

	costs have been estimated using the RDI-based approach" given mean RDI inappropriately biases treatment costs in favour of comparator treatments versus BPd. If the EAG are to retain their preferred base case, they should be required to provide sufficient clinical and statistical justification as to why dosage of belamaf is likely to be far higher in UK clinical practice than dosage seen in the DREAMM-8 trial.	belamaf and the use of RDI for other treatments ensures an equitable comparison of treatments, which is reflective of real-world practice in the UK. The Company notes it would have been happy to share this information with the EAG had they asked about the issue during clarification questions.	

Issue 6 Use alternative utility values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Section 1.5 The cost effectiveness evidence: summary of the EAG's key issues *"DREAMM-8 trial data suggest that patients who are progression-free and treated with BPd experience a better health-*	The statement should be amended to: *"DREAMM-8 trial data suggest that patients who are progression-free and treated with BPd experience a better health-related quality of life than patients treated with PVd. ~~Given the ocular toxicity~~*	The proposed position of the EAG is significantly outside NICE's ordinary processes. EQ-5D is clearly specified by NICE as the most appropriate measure of HRQoL, and the method of eliciting the EQ-5D is not criticised by the EAG. The EAG has taken the unusual position that the EQ-	This is a matter of opinion, not a factual inaccuracy. Ultimately, the NICE Appraisal Committee will select their preferred utility values. No changes have been made to the EAG report.

related quality of life than patients treated with PVd. Given the ocular toxicity experienced by patients treated with BPd, clinical advice to the EAG is that this difference in health-related quality of life may be unrealistic"	~~*experienced by patients treated with BPd, clinical advice to the EAG is that this difference in health-related quality of life may be unrealistic*~~*"*	5D is insensitive to ocular outcomes and that therefore the HRQoL measured in the trial is not a good proxy for HRQoL as actually experienced by NHS patients. Disregarding data which patients generate about themselves is paternalistic and contrary to NICE's stated principles. This notwithstanding, the company would like to highlight that eye related side effects have been accounted for in the utility analysis of EQ-5D-3L from DREAMM-8 trial, as provided in CS section B.3.4.3, page 134. Despite these side effects being included in the utility analysis, patients who are progression-free and treated with BPd experience a better health-related QoL than patients treated with PVd. It is important to note that not all eye-related side effects are symptomatic, which further supports this. The Company notes it would have been happy to share this information with the EAG had they	

		asked about the issue during clarification questions.	
Page 67, Section 6.1 Overview of modelling issues identified by the EAG, Table 29 *"In the PFS health state, utility values should not vary by treatment. The DREAMM-8 trial utility values for patients treated with BPd are likely to be overestimates. The EAG has generated cost effectiveness results using ENDEAVOUR trial PFS and PD health state utility values for all patients (EAG revision 4)"* **Page 67, Section 6.1 Overview of modelling issues identified by the EAG, Table 29** *"The DREAMM-8 trial utility values for patients treated*	The statement should be amended to read: *"In the PFS health state, utility values should not vary by treatment. ~~The DREAMM-8 trial utility values for patients treated with BPd are likely to be overestimates.~~ The EAG has generated cost effectiveness results using ENDEAVOUR trial PFS and PD health state utility values for all patients (EAG revision 4)"* In addition, the Company suggest that the EAG preferred base case is revised to the align with utility values presented by the company at clarification question stage.	As per the Company's response to the above issue, the EAG provide no evidence supporting the assumption that BPd utility values are overestimated. Furthermore, the position directly contradicts trial data and NICE's own stated preferences. Ignoring the DREAMM-8 trial data marginalises the patient voice and should only be done under exceptionally unusual circumstances. The Company notes that the EAG use this position to support a further position of treatment-independent utilities. Utilising non-treatment specific utility values from an older trial (primary completion year: 2014) fails to capture the current health benefits of BPd (9). This approach also contradicts NICE guidance, which clearly favours directly measured utility values as the optimal method for capturing health effects if available.	This is a matter of opinion, not a factual inaccuracy. Ultimately, the NICE Appraisal Committee will select their preferred utility values. No changes have been made to the EAG report.

with BPd are likely to be overestimates"			

Issue 7 Minor factual inaccuracies and typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18, Section 2.3 Company's overview of current service provision *"The first NICE Appraisal Committee meeting for BVd will be on **12th December 2024** and NICE expects guidance to be published on 5 March 2025"*	The company propose that the statement is modified to: *"The first NICE Appraisal Committee meeting for BVd will be on **8th January 2025** and NICE expects guidance to be published on 5 March 2025"*	The date of the first NICE appraisal Committee meeting for BVd should be corrected (10).	Thank you. The EAG report has been updated accordingly.
Page 20, Section 2.3 Company's overview of current service provision *"in the NHS, daratumumab is currently widely used to treat patients in the first-line setting"* **Page 20, Section 2.3 Company's overview of current service provision**	The company propose that the statement is removed.	Please see **Issue 2, Row 2**. The amendment is proposed as the statement is not factually correct and to reflect expert clinical opinion and evidence the company provided in the CS.	These are not factual inaccuracies. No changes have been made to the EAG report.

"Consequently, on disease progression, ASCT-ineligible patients may be refractory to daratumumab"			
Page 20, Section 2.3 Company's overview of current service provision *"Since 2023, patients who are ineligible for ASCT are offered treatment with daratumumab plus lenalidomide"*	The statement should read: *"Since October 2023, patients who are ineligible for ASCT* ***have the option of*** *treatment with daratumumab in combination with lenalidomide* ***and dexamethasone****"*	The amendment correctly reflects TA917 by including adjunct dexamethasone in the combination (11). In addition, it is more correct to say that DRd is a treatment option, but not mandatory for patients to receive.	Thank you for the correction. We have updated the EAG report to: *"Since October 2023, patients who are ineligible for ASCT are offered treatment with daratumumab plus lenalidomide and dexamethasone"*
Page 26, Section 2.4.4 Intervention *"The company did not provide an anticipated date for MHRA approval (clarification question C1)"*	The company has informed NICE that 'the regulatory submission for DREAMM-8 was made in [redacted] in the CS Doc B. The company has also informed NICE of the 2L indication estimated approval date which is [redacted]. The company propose that the statement is removed.	The company has provided an anticipated date for MHRA approval.	This statement has been deleted from the EAG report.

Page 26, Section 2.4.4 Intervention *"Clinical advice to the EAG is that the required ophthalmology checks could be burdensome for patients and could pose a substantial burden on NHS resources"* **Page 38, Section 3.5.5 EAG conclusions: safety and tolerability** "Further, the requirement in the anticipated MHRA marketing authorisation (CS, Table 2), for patients to be seen by an ophthalmologist for the first 4 months of treatment could be burdensome for patients and could pose a substantial burden on NHS resources"	These statements should read: *"Patients on treatment with belamaf may be required to receive regular ophthalmology checks and in the absence of NHS system readiness preparation, there is potential that this could pose a sizeable impact on NHS resources."* and *"Further, the requirement in the anticipated MHRA marketing authorisation (CS, Table 2), for patients to be seen by an ophthalmologist for the first 4 months of treatment could be* ***arduous for patients and in the absence of NHS system readiness preparation, there is potential that this could pose a sizeable impact*** *on NHS resources"*	These amendments are proposed based on clinical validation meetings and GSK intention to offer a patient support programme (PSP) to facilitate the launch of belamaf on the NHS.	This is not a factual inaccuracy. The statements in the EAG report reflect clinical advice given to the EAG. No changes have been made to the EAG report.
Page 38, Section 3.5.5 EAG conclusions: safety and tolerability	The company would like to emphasise that the statement that eye-related side effects were manageable was made by clinical expert opinion and not	These amendments are proposed to correctly attribute statements made about the intervention	**Page 38** The amended wording suggested by the company was not

"Clinical advice to the EAG cautions that the high level of eye-related events experienced by patients treated with belantamab mafodotin are of concern, particularly in older patients; however, the company stated that these AEs were manageable (CS, p97)" **Page 49, Section 3.7 Conclusions of the clinical effectiveness section** *"Clinical advice to the EAG cautions that the high level of eye-related events experienced by patients treated with belantamab mafodotin are of concern, particularly in older patients and that the ophthalmology*	the company. Please see appendix M, page 8 and associated clinical expert notes in the reference pack for the appendix. The company proposes the following amendments: *"Clinical advice to the EAG cautions that the high level of eye-related events experienced by patients treated with belantamab mafodotin are of concern, particularly in older patients;* ***however, expert clinical opinion provided to the company stated that these AEs were manageable*** *(CS, p97)"* and *"Clinical advice to the EAG cautions that the high level of eye-related events experienced by patients treated with belantamab mafodotin are of concern, particularly in older patients;* ***however, expert***		provided in the CS. No changes have been made to the EAG report. **Page 49** This is not a factual inaccuracy. No changes have been made to the EAG report.

checks (performed before each of the first four doses of belantamab mafedotin and during treatment as clinically indicated), stipulated in the anticipated MHRA BPd marketing authorisation could be burdensome for patients and could pose a substantial burden on NHS resources"	***clinical opinion provided to the company stated that these AEs were manageable*** *(CS, p97). Ophthalmology checks (performed before each of the first four doses of* ***belantamab mafodotin*** *and during treatment as clinically indicated), stipulated in the anticipated MHRA BPd marketing authorisation could be* ***arduous for patients and in the absence of NHS system readiness preparation, there is potential that this could pose a sizeable impact on NHS resources****"*		
Page 38, Section 3.5.5 EAG conclusions: safety and tolerability *"Symptoms range from itchy, irritated eyes to a substantial deterioration in sight. Time to recovery depends on where the damage occurs and can be weeks or months"*	The statement should be amended to: *'Symptoms range from itchy, irritated eyes to change in Best Corrected Visual Acuity (BCVA). These side effects are mostly reversible and manageable, with recovery typically occurring within weeks or months.'*	The EAG should be careful with their use of language to avoid confusion with other unrelated conditions, and to avoid inappropriate catastrophization of a symptom in public documents that might be read by patients. Use of the term 'deterioration in sight' and 'damage'	The EAG has amended their report to include the company suggested wording.

		inaccurately describes the nature of the eye-related side effects and could mislead by implying permanent injury and progressively worsening symptoms. This language is not patient friendly as it catastrophizes a reversible symptom, making it inappropriate for a public document that might be read by patients. According to the DREAMM-8 trial, the BPd arm (N=150), out of the patients with normal baseline vision (20/25 or better in ≥ 1 eye), who experienced worsening of Best Corrected Visual Acuity (BCVA): • 92% (47/51) of those whose vision deteriorated to 20/50 saw their first event resolve in a median of 29 days • 100% (2/2) of those whose vision	

		deteriorated to 20/200 saw their first event resolve in a median of 25.2 days Furthermore, the DREAMM-8 trial results showed that although ocular events occurred in 89% of the patients who received BPd, only 9% of patients discontinued treatment due to eye-related side effects. This demonstrates that these side effects are largely manageable through dose adjustment or delay. These findings align with expert clinical opinion obtained during Clinical validation meetings. Additionally, across the entire DREAMM clinical trial programme, there is no evidence of permanent vision loss in patients treated with belamaf.	

Page 38, Section 3.5.5 EAG conclusions: safety and tolerability *"Eye-related AEs impact patients' HRQoL and the ocular effects of the drug can continue even after treatment is stopped"*	This statement should be removed.	The eye related side-effects are reversible and manageable (as confirmed by DREAMM-8 trial results and clinical expert opinion) and as discussed in **Issue 7, Row 8.** There is no evidence supporting the assumption that eye-related side effects associated with BPd impact HRQoL of patient or that the eye related side effect is permanent. The mean utility score, based on EQ-5D-3L, were broadly similar between the two treatment arms across the study visits, as addressed in Doc B, B.2.6.1.7, page 61. Additionally, PROs from the global health status and QoL domains of the EORTC QLQ-C30 showed no clinically meaningful change from baseline in either treatment group over time (12) The Company notes it would have been happy to share	This is not a factual inaccuracy. No changes have been made to the EAG report.

		this information with the EAG had they asked about the issue during clarification questions.	
Page 31, Section 3.2.3 Demographic and disease characteristics of DREAMM-8 trial patients *"Some patients (33.5%) had received 2 or 3 prior lines of treatment, and a small proportion (8.5%) had received ≥4 prior lines of treatment"*	The sentence should read: *"Some patients **(34.8%)** had received 2 or 3 prior lines of treatment, and a small proportion **(12.0%)** had received ≥4 prior lines of treatment"*	Minor transcription error	Based on information provided in CS, Table 7, the EAG report has been amended as follows: *"Some patients (**33.8%**) had received 2 or 3 prior lines of treatment, and a small proportion (**13.6%**) had received ≥4 prior lines of treatment"*
Page 26, Section 2.4.4 Intervention *"it is stipulated that ophthalmic examinations, including assessment of visual acuity and slit lamp examination, must be performed before each of the first four doses of belantamab mafedotin and during treatment as clinically indicated"*	The statement should read: *"it is stipulated that ophthalmic examinations, including assessment of visual acuity and slit lamp examination, must be performed before each of the first four doses of **belantamab mafodotin** and during treatment as clinically indicated"*	Spelling error	Thank you. This typographical error has been corrected.

Page 55, Section 4.8 Treatment effectiveness and extrapolation *"PVd, rather than BPd, was selected as the reference treatment as PVd hazard profiles were considered more similar to the hazard profiles of comparators than **BVd** hazard profiles"*	The sentence should read: *"PVd, rather than BPd, was selected as the reference treatment as PVd hazard profiles were considered more similar to the hazard profiles of comparators than **BPd** hazard profiles"*	Spelling error	Thank you. This typographical error has been corrected.
Page 31, Section 3.2.3 Demographic and disease characteristics of DREAMM-8 trial patients *"The company is positioning BPd as a second-line treatment for patients who have received lenalidomide-based first-line treatment, and/or for whom lenalidomide is unsuitable"*	The sentence should read: *"The company is positioning BPd as a second-line treatment for relapsed or refractory multiple myeloma (RRMM) patients who have received **at least one prior line of treatment including lenalidomide-containing regimen and for** whom lenalidomide is unsuitable"*	The company suggests using the description of the population addressed in the CS as provided in the decision problem, section B1.1, page 8, table 1.	The re-wording suggested by the company reflects the population described by NICE in the final scope rather than the population described by the company in the CS (Table 1), namely, "*Adults (≥18 years) with RRMM who have had **1 LoT** including a lenalidomide-containing regimen (2L patients) and for whom lenalidomide is unsuitable."* Changes have been made in line with the

			company wording in the CS (Table 1).
Page 50, Section 4 Cost effectiveness evidence, *"This section provides a summary of the economic evidence submitted by the company in support of the use of BPd as a treatment option for patients with RRMM who have received one prior line of treatment including a lenalidomide-containing regimen"*	The statement should read: *"This section provides a summary of the economic evidence submitted by the company in support of the use of BPd as a treatment option for patients with RRMM who have received one prior line of treatment including a lenalidomide-containing regimen* ***and for whom lenalidomide is unsuitable****"*	The company suggests using the description of the population addressed in the CS as provided in the decision problem, section B1.1, page 8, table 1.	**Page 50** The EAG has made the changes suggested by the company. However, please note that the wording used in the company's summary of cost effectiveness analysis (CS, p99) is: *"…in adult patients with RRMM who have had one prior therapy, and whose disease had progressed on the last therapy."* **Page 52 (checklist) and Page 66** The EAG has made the change in line with the population described by the company in the CS
Page 52, Section 4.3.1 NICE Reference Case Checklist and Drummond checklist, Table 14. *"i.e., limited to lenalidomide-exposed patients treated in the second-line setting"*	The sentence should read: *"i.e., for patients with RRMM who have had at least one line of prior treatment including a lenalidomide-containing regimen and for whom lenalidomide is unsuitable"*	The company suggests using the description of the population addressed in the CS as provided in the decision problem, section B1.1, page 8, table 1.	
Page 52, Section 4.3.1 NICE Reference Case Checklist and Drummond checklist, Table 14.	The sentence should read: *"Clinical advice to the EAG is that the three comparators*	The company suggests using the description of the population addressed in the CS as provided in the	

"Clinical advice to the EAG is that the three comparators (DVd, hKd and SVd) are the most appropriate for lenalidomide-exposed patients in the second-line setting"	*(DVd, hKd and SVd) are the most appropriate* ***for patients with RRMM who have had at least one line of prior treatment including a lenalidomide-containing regimen and for whom lenalidomide is unsuitable****"*	decision problem, section B1.1, page 8, table 1.	(Table 1), namely *"Adults (≥18 years) with RRMM who have had* ***1 LoT*** *including a lenalidomide-containing regimen (2L patients) and for whom lenalidomide is unsuitable."*
Page 66, Section 6 EAG critique of company economic model *"The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for the comparison of BPd versus DVd, hKd and SVd for lenalidomide-exposed patients treated in the second-line setting"*	The sentence should read: *"The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for the comparison of BPd versus DVd, hKd and SVd* ***for patients with RRMM who have had at least one line of treatment including a lenalidomide-containing regimen and for whom lenalidomide is unsuitable****"*	The company suggests using the description of the population addressed in the CS as provided in the decision problem, section B1.1, page 8, table 1.	

Confidential markings

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr><td>Page 33, Section 3.3.1 Key DREAMM-8 trial analyses, Table 7</td><td>The results for the difference of ORR should be marked confidential</td><td><table><tr><th colspan="3">Overall response rate</th></tr><tr><td>sCR+CR+VGPR+PR</td><td>77.0 (95% CI: 70.0 to 83.7)</td><td>72.0 (95% CI: 64.1 to 79.2)</td></tr><tr><td colspan="3">Difference [redacted]</td></tr></table></td><td>Thank you. This omission has been corrected.</td></tr>
</table>

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