29 May 2025
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

of an orphan medicinal product submitted for marketing authorisation application

Blenrep (belantamab mafodotin)
Treatment of multiple myeloma
EU/3/17/1925

Sponsor: GlaxoSmithKline Trading Services Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F
Other name	--
International Non-Proprietary Name	Belantamab mafodotin
Tradename	Blenrep
Orphan condition	Treatment of multiple myeloma
Sponsor's details:	GlaxoSmithKline Trading Services Limited Riverwalk 12 Citywest Business Campus Dublin 24 D24 YK11 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	GlaxoSmithKline Trading Services Limited
COMP opinion	7 September 2017
EC decision	16 October 2017
EC registration number	EU/3/17/1925
Post-designation procedural history	
Sponsor's name change	Name change from GlaxoSmithKline Trading Services Limited to GlaxoSmithKline (Ireland) Limited – EC letter of 1 April 2020
Transfer of sponsorship	Transfer from GlaxoSmithKline (Ireland) Limited to GlaxoSmithKline Trading Services Limited – EC decision of 10 June 2024
COMP opinion on review of orphan designation at the time of marketing authorisation	29 July 2020
Marketing authorisation start date	25 August 2020
Non-renewal of marketing authorisation	29 February 2024
Transfer of sponsorship	Transfer from GlaxoSmithKline (Ireland) Limited to GlaxoSmithKline Trading Services Limited – EC decision of 10 June 2024
NEW Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johanna Lähteenvuo / Edward Laane
Applicant	GlaxoSmithKline Trading Services Limited
Application submission	28 June 2024
Procedure start	18 July 2024
Procedure number	EMA/H/C/006511
Invented name	Blenrep

Therapeutic indication	Blenrep is indicated in adults for the treatment of relapsed or refractory multiple myeloma: • in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; and • in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide. Further information on Blenrep can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep-0
CHMP opinion	22 May 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Evangelia Giannaki / Jana Mazelova
Sponsor's report submission	24 February 2025
COMP discussion and adoption of list of questions	13-15 May 2025
Oral explanation	11 June 2025
Sponsor's removal request	12 June 2025
Removal from the Register	13 June 2025

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F was considered justified based on preliminary clinical data showing responses in treated patients with relapsing or refractory multiple myeloma;
- the condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a median survival of approximately 6 years;
- the condition was estimated to be affecting less than 4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised monoclonal antibody targeting B-cell maturation antigen conjugated with

maleimidocaproyl monomethyl auristatin F will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in heavily pretreated relapsed/refractory patients who have responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F, as an orphan medicinal product for the orphan indication: treatment of multiple myeloma.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation (not renewed)

The COMP opinion on the review of the orphan medicinal product designation in 2020 was based on the following grounds:

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of multiple myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating, in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Blenrep is of significant benefit for the subset population of the orphan condition as defined in the granted therapeutic indication still holds;
- the sponsor has provided clinical data that demonstrate the efficacy of Blenrep in heavily pretreated multiple myeloma patients who were refractory to several classes of products;
- for patients who have progressed after at least four prior therapies and who are refractory to at least one immunomodulatory drug, one proteasome inhibitor, and one anti-CD38 antibody treatment options become very limited and the available clinical data support improved efficacy of Blenrup compared to those options;
- the Committee considers that this constitutes a clinically relevant advantage;

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Blenrep, humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin

F, for treatment of multiple myeloma (EU/3/17/1925) is not removed from the Community Register of Orphan Medicinal Products.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Multiple myeloma (MM; also known as plasma cell myeloma) is a heterogeneous hematological B-cell malignancy characterized by dysregulated proliferation of plasma cells that clonally expand and accumulate in the bone marrow and/or at extramedullary sites, with potential for uncontrolled growth causing destructive osseous bone lesions, acute kidney injury, anemia, and hypercalcemia. The disease accounts for about 10-18% of all hematologic malignancies (Moreau et al., 2017; Siegel et al., 2020) and primarily affects older individuals (Howlader et al., 2020). The median age at onset of MM is around 72 years. The incidence rates increase with age, particularly after the age of 40 years, and are higher in men than in women with a ratio of around 3:2. The disease is often asymptomatic for a long time and therefore advanced at the time of diagnosis (Rajkumar et al., 2014).

The clonal plasma cells that cause MM are derived from post-germinal center B-cells. In a healthy individual, following antigen exposure (e.g., viral or bacterial infections), naive B-cells normally proliferate and subsequently undergo somatic hypermutation of the immunoglobulin (Ig)H and IgL VDJ sequences. This process produces long-lived plasma cells (a subset of plasma cells that provide long-lasting, sustained antibody production) that reside in the bone marrow and are an important component of humoral immunity. The development of an abnormal clonal plasma cell population mimics these normal biological processes but results in excessive amounts of intact immunoglobulins. In almost all patients, MM begins as an asymptomatic pre-malignant stage termed monoclonal gammopathy of unknown significance (MGUS), a clonal plasma cell dyscrasia present in 3% to 5% of people older than 65 years and in 10% of those older than 80 years. MGUS is associated with progression to active (symptomatic) MM, at a rate of approximately 1% to 2% per year, with a 20-year risk of progression to MM of approximately 18%. Only a few patients develop MM from the more advanced pre-malignant stage referred to as smouldering multiple myeloma (SMM). The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine and may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. The level of M-protein in plasma serves as a reflection of the disease burden over time.

Among patients newly diagnosed with MM, approximately 3.3% present with extramedullary disease. Approximately 10% to 15% of patients with MM are diagnosed with concurrent immunoglobulin light chain amyloidosis during the course of their disease.

Approximately 86% of people with MM reveals a monoclonal protein in the serum protein electrophoresis, defined as the presence of an atypical antibody in the blood. A 24-hour urine protein test to quantify Bence-Jones protein is important to document the presence of baseline proteinuria and evaluate for evidence of secondary light-chain amyloidosis, which often manifests as nephrotic range

proteinuria. CT or PET-CT are preferred for diagnosis of MM and should be used to evaluate patients with SMM when the clinical suspicion for MM is high (Cowan*, JAMA. 2022; 327(5): 464-477*).

The approved therapeutic indication:

"Blenrep is indicated in adults for the treatment of relapsed or refractory multiple myeloma:

in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; and

in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide''

falls within the scope of the designated orphan condition "Treatment of multiple myeloma".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The sponsor discussed the life-threatening and the chronically debilitating nature of the condition. The prognosis of MM varies due to its heterogenous manifestations and the response to the various possible treatments. In 2022, there were 187 952 new cases of MM and 121 388 related deaths globally [Ferlay, 2024]. The median survival (OS) for patients diagnosed with MM is approximately 5 years [Girvan, 2022; Leleu, 2023; Lopez-Muñoz, 2023; Ruotsalainen, 2024]. Survival is impacted by patients' characteristics and other factors. Median survival is longer for patients with vs. without stem cell transplant [Rosenberg, 2019; Leleu, 2023], decreases with increasing age, and is slightly longer for female patients [Durer, 2020; Leleu, 2023]. Longer survival was also found to be associated with lower International Staging System stages [Tandon, 2017].

MM is incurable. Despite the availability of multiple treatment options and improved survival outcomes over the last few years, most patients with MM will still experience relapses and become refractory [Verelst, 2018; Gandhi, 2019]. The duration of remission declines dramatically with each line of treatment, and patients who become refractory to the major classes of available therapies have very poor prognosis and limited therapeutic options [Kumar, 2017; Costa, 2022].

In addition to specific drug refractoriness risks, certain patient characteristics are associated with increased risk of progression; these include age, frailty, high-risk cytogenetics, renal impairment, comorbidities, and EMD [Jeryczynski, 2021]. Older and frail patients generally experience poorer outcomes compared to younger and fitter patients. These outcomes include increased risk of organ dysfunction and decreased resilience to treatment-related toxicity which renders them ineligible for certain treatments, such as CAR-Ts and bispecifics [Jeryczynski, 2021]. Renal disease is among the most frequent MM-presenting symptom, but it is also associated with disease progression. Failure to achieve renal response during treatment has been widely reported as a significant risk factor of progression [Yadav, 2016; Jeryczynski, 2021].

MM has a substantial patient burden, with both symptoms and treatments impacting QoL. Patients with MM report more symptoms and poorer quality of life (QoL) than non-MM patients [Kamal, 2021], and QoL scores decrease as treatment lines increase [Nielsen, 2017; Despiégel, 2019; Hatswell, 2019; Engelhardt, 2021]. In a cross-sectional, multicenter study in patients with MM, EORTC QLQ-C30 and QLQ MY20 scores decreased significantly with treatment line [Despiégel, 2019]. In particular, all patient functioning domains (i.e., physical, role, emotional, cognitive, social) statistically significantly worsened as the line of therapy increased from first line to fourth or greater

The COMP has previously accepted that MM is chronically debilitating due to the development of hypercalcemia, renal insufficiency, anaemia and/or bleeding, frequent infections, and bone lesions, and life-threatening in nature due to the poor survival of patients with relapsed or refractory (r/r) disease. The seriousness of MM earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

At the time of the orphan designation in 2017 and the initial orphan maintenance in 2021 (which was not renewed), the COMP concluded that the condition was estimated to be affecting less than 4 in 10,000 persons in the European Union (EU). The sponsor provides updated calculations and proposes now a figure of 3.86 in 10,000 persons.

To estimate MM prevalence in Europe, a systematic literature review was conducted, focusing on recent European studies and registries from 2019 to 2024. Three methods were used to derive prevalence estimates: 5-year and 10-year partial prevalence (weighted by country populations), and complete prevalence calculated from incidence and disease duration (median overall survival). Key data sources included the European Cancer Information System (ECIS), GLOBOCAN, and the Global Burden of Disease (GBD) study, each offering age-standardized and crude incidence and prevalence rates. Preference was given to data standardized to the European population, as these better reflect regional demographics.

5-year prevalence

Based on the most recent 2020 age-standardized data from the ECIS, the 5-year partial prevalence of MM in the European Union (EU) is estimated at 2.30 cases per 10,000 persons, with a range from 0.63 per 10,000 in Bulgaria to 3.04 per 10,000 in France. These figures were derived using population-adjusted data across EU and European Economic Area (EEA) countries, excluding Liechtenstein, for which French prevalence data was substituted. While ECIS reports prevalence for plasma cell cancers rather than MM alone, MM constitutes over 80% of these cases and therefore meets the inclusion criteria for MM-specific analysis [ECIS; Ferlay, 2024; Fend, 2023].

According to GLOBOCAN data using ICD code C90 for MM, the 5-year partial prevalence in the EU in 2022 was estimated at 2.34 cases per 10,000 persons, ranging from 0.92 per 10,000 in Bulgaria to 3.54 per 10,000 in Denmark. This estimate was derived by converting crude prevalence proportions per 100,000 into rates per 10,000 and multiplying by country-specific population estimates from the UN Population Division. Data was available for all EU countries except Liechtenstein, for which France's prevalence rate was used. When including both EU and EEA countries, the prevalence was slightly higher at 2.35 per 10,000 persons [Ferlay, 2024].

10-year partial prevalence

The number of prevalent cases of MM and the 10-year age-standardized partial prevalence of MM for individual countries in the EU and EEA were obtained from the ECIS database. Population estimates were also obtained from the ECIS database with the exception of Liechtenstein, where this was added from the UN Population Division. Based on the latest age-standardized (to the 2013 European standard population) ECIS data from 2020 (with the 10-year prevalence covering 2011 to 2020), MM was estimated to affect 3.30 per 10 000 persons in the EU (ranging from 0.88 per 10 000 in Bulgaria to 4.23 per 10 000 in Italy). The prevalence remained the same when considering countries in both the EU and the EEA.

Complete prevalence

Complete prevalence of MM was estimated by multiplying the latest annual incidence rates by the median disease duration, assuming both remained stable over time. Most countries reported MM incidence below 1 per 10,000, with slight increases over the past decade, except Germany, which saw a decrease from 0.51 to 0.44 per 10,000 between 2014 and 2022. Median OS, used as a proxy for disease duration, was derived from a literature review, with a value of 5.3 years selected based on a large, nationally representative French study (14,309 patients, 2013–2019). Incidence estimates were drawn from national registries, ECIS, GLOBOCAN, and GBD, and complete prevalence was calculated by multiplying incidence with OS and adjusting for population size using UN data.

Using the most recent age-standardized incidence data from the ECIS (2022), the complete prevalence of MM in the EU was estimated at 3.86 per 10,000 persons, rising slightly to 3.88 per 10,000 when including EEA countries. According to the sponsor, these estimates are considered the most reliable due to their recency and adjustment to the 2013 European standard population, aligning closely with current European demographics. In contrast, prevalence estimates from GLOBOCAN — standardized to the global population — were notably lower, while those from the GBD, though comprehensive, relied on modelled data that incorporated extrapolation to fill data gaps, potentially reducing their accuracy and representativeness for the EU population.

The sponsor also contacted sensitivity analyses based on the prognostic factors of age, sex, and stem cell transplant (SCT) status which reported lower prevalence estimates than the overall complete prevalence. Using a median OS of 5.1 years and the 2013 European age-standardized incidence rates for 2022 obtained from the ECIS database, the prevalence of MM in the sensitivity analyses based on age, sex and SCT status were estimated to be 3.72 for both age and sex and 3.47 for SCT status for the EU.

In the below table the estimated figures from the 3 different methodologies are presented.

Table 1. Summary of prevalence calculations for MM in the EU and EEA using 3 different methodologies with the most robust data

	EU-27			**EU-27 and EEA**		
Method (partial prevalence)	2020 population estimate	Prevalence proportion per 10 000	2020 prevalent cases	2020 population estimate	Prevalence proportion per 10 000	2020 prevalent cases
5-year prevalence (using ECIS)	447 300 000	2.30	109 765	453 090 630	2.30	157 604
10-year partial prevalence (using ECIS)	447 300 000	3.30	155 472	453 090 630	3.30	157 604
Method (complete prevalence)	Incidence from ECIS 2022 (per 10 000)	Prevalence proportion per 10 000	2022 prevalent cases (ECIS)	Incidence from ECIS 2022 (per 10 000)	Prevalence proportion per 10 000	2022 prevalent cases (ECIS)
Complete prevalence (using median OS 5.3 years)	0.73	3.86	172 504a	0.73	3.88	175 205

Abbreviations: ECIS=European Cancer Information System; EEA= European Economic Area; EU=European Union; MM=multiple myeloma; OS=overall survival
a 2022 incidence estimate from the ECIS (age-standardised to the 2013 European standard population)

The COMP considered that, given that the condition is an incurable disease, with increasing relapses over time, the complete prevalence (and not any partial prevalence referring to limited time from diagnosis) is the appropriate index to report the number of affected individuals for the orphan framework. The COMP concluded that the prevalence seems to be underestimated. The sponsor should recalculate the prevalence by using the crude incidence reported in ECIS and not the age-standardized incidence. In addition, the sponsor is requested to provide a sensitivity analysis on the prognostic factor of ISS Stage.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The new patient population which Blenrep will be approved for is the following:

Blenrep is indicated in adults for the treatment of relapsed or refractory multiple myeloma:

- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; and

- in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide.

The table below presents the medicinal products authorised for multiple myeloma. In the last column of the table, it is mentioned whether the authorised medicinal products for multiple myeloma should be considered as satisfactory methods or not based on their authorised indication.

Table 2. Current approved treatments for multiple myeloma in Europe

Active Ingredients	Name	Indication(s)	Satisfactory method
daratumumab	DARZALEX	DARZALEX is indicated: • in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. • in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. • in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. • as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.
elranatamab	ELREXFIO	ELREXFIO is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy	No, since Elrexfio covers subsequent lines of treatment.
bortezomib	VELCADE BORTEZOMIB ACCORD BORTEZOMIB FRESENIUS KABI BORTEZOMIB HOSPIRA BORTEZOMIB SUN	Bortezomib as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation. Bortezomib in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (HSCT). Bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.	No since for the population who received at least 1 prior line of treatment, bortezomib has the restriction with the HSCT and high-dose chemo.

Active Ingredients	Name	Indication(s)	Satisfactory method
doxorubicin	ZOLSKETIL PEGYLATED LIPOSOMAL CELDOXOME PEGYLATED LIPOSOMAL CAELYX PEGYLATED LIPOSOMAL	Doxorubicin pegylated liposomal is indicated: • In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.	No, since for the population who received at least 1 prior line of treatment, it has the restriction with the bone marrow transplant
isatuximab	SARCLISA	SARCLISA is indicated: • in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. • in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. • in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.
ciltacabtagene autoleucel	CARVYKTI	CARVYKTI is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.	No, since Carvykti is for patients with MM who have demonstrated disease progression on the last therapy and are refractory to lenalidomide. Blenrep covers also the patients who are not refractory to lenalidomide, therefore it has a broader indication.
thalidomide	THALIDOMIDE BMS ; THALIDOMIDE CELGENE ; THALIDOMIDE PHARMION THALIDOMIDE LIPOMED	Thalidomide in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy. Thalidomide is prescribed and dispensed according to the Thalidomide Pregnancy Prevention Programme (see section 4.4).	No since thalidomide is for untreated MM.

Active Ingredients	Name	Indication(s)	Satisfactory method
pomalidomide	IMNOVID; generics	Imnovid in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. Imnovid in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.
dexamethasone	NEOFORDEX	Neofordex is indicated in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products.	Yes, since the indication for dexamethasone is very broad.
talquetamab	TALVEY	TALVEY is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy	No, since Talvey covers subsequent lines of treatment.
carfilzomib	KYPROLIS	Kyprolis in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see section 5.1).	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.
ixazomib	NINLARO	NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.
idecabtagene vicleucel	ABECMA	Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	No, since Abecma covers subsequent lines of treatment.
elotuzumab	EMPLICITI	Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy (see sections 4.2 and 5.1). Empliciti is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy (see sections 4.2 and 5.1).	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.

Active Ingredients	Name	Indication(s)	Satisfactory method
panobinostat	FARYDAK	Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent	No, since Farydak covers subsequent lines of treatment.
melphalan flufenamide	PEPAXTI	Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation (see section 4.4)	No, since Pepaxti covers subsequent lines of treatment.
teclistamab	TECVAYLI	TECVAYLI is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	No, since Tecvayli covers subsequent lines of treatment.
selinexor	NEXPOVIO	NEXPOVIO is indicated: • in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. • in combination with dexamethasone 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 two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.
lenalidomide	REVLIMID LENALIDOMIDE KRKA D.D. NOVO MESTO LENALIDOMIDE ACCORD LENALIDOMIDE MYLAN	Lenalidomide as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Lenalidomide as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.	Yes, since there is overlap with the indications covering patients who had received at least one prior line of therapy.

Active Ingredients	Name	Indication(s)	Satisfactory method
melphalan	PHELINUN	High-dose of PHELINUN used alone or in combination with other cytotoxic medicinal products and/or total body irradiation is indicated in the treatment of: • multiple myeloma, • …[…]… • - mammary adenocarcinoma.	Yes, since the indication for melphalan is very broad.

The recently updated European Hematology Association (EHA) and European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up of MM describe recommended treatment options available for r/r MM patients in the third- and later lines setting (Dimopoulos, Ann Oncol. 2021; 32(3): 309-322). The EHA-ESMO guidelines distinguishes between treatment of elderly patients in the non-transplant setting, and younger or more fit patients in good clinical condition who are eligible for autologous stem-cell transplantation (ASCT) in the transplant setting. Treatments are discussed as regards to front-line treatment, consolidation, maintenance, and r/r disease. According to the guidelines, the selection of a suitable regimen in third- or subsequent lines of therapy for any given patient depends on several parameters such as prior exposure, refractoriness, and sensitivity to specific agents or classes of agents in prior lines of therapy.

Significant benefit

The sponsor received EMA protocol assistance dated January 2019 (EMEA/H/SA/3559/2/FU/2/2018/PA/HTA/PR/III) with regards to the evidence needed to justify significant benefit of belantamab mafodotin over existing treatments used for the treatment of patients who have received at least one prior therapy and for the ones who have received at least one prior therapy including lenalidomide.

The efficacy and safety of belantamab mafodotin in combination with bortezomib and dexamethasone (BVd) were investigated in a multicentre, randomised (1:1), open-label, Phase 3 study conducted in patients with MM who had relapsed following treatment with at least one prior line of therapy.

In the BVd arm (N = 243), patients received belantamab mafodotin 2.5 mg/kg by intravenous infusion every 3 weeks on day 1 of each cycle; bortezomib 1.3 mg/m2 (subcutaneously) on days 1, 4, 8, and 11 of cycles 1 to 8 (21 day cycles); and dexamethasone 20 mg (intravenous infusion or orally) on the day of and the day after bortezomib treatment. In the daratumumab, bortezomib, and dexamethasone (DVd) arm (N = 251), patients received daratumumab 16 mg/kg (IV) in 21day cycles: every week for cycles 1 to 3 and every 3 weeks for cycles 4 to 8. Patients were stratified by the Revised International Staging System (R-ISS), prior exposure to bortezomib, and the number of prior lines of therapy.

The key eligibility criteria for the study were having a confirmed diagnosis of MM as defined by International Myeloma Working Group (IMWG) criteria, having previously been treated with at least 1 prior line of MM therapy, and having had documented disease progression during or after their most recent therapy. Patients were excluded if they were intolerant to bortezomib, refractory to twice weekly bortezomib, previously treated with BCMA-targeted therapy, had ongoing ≥ Grade 2 peripheral neuropathy or neuropathic pain, or had current corneal epithelial disease except for mild punctate keratopathy.

The primary efficacy outcome measure was progression-free survival (PFS) as evaluated by a blinded Independent Review Committee (IRC) based on the IMWG criteria for MM.

A total of 494 patients were evaluated for efficacy in DREAMM-7. In the BVd arm, 90% of patients received prior proteasome inhibitor therapy (bortezomib, carfilzomib, ixazomib), 81% of patients received prior immunomodulator therapy (lenalidomide, thalidomide, pomalidomide), and 67% of patients previously received autologous stem cell transplantation (ASCT). 9% of patients were refractory to proteasome inhibitor therapy and 39% of patients refractory to immunomodulator therapy.

The efficacy and safety of belantamab mafodotin in combination with pomalidomide and dexamethasone (BPd) were investigated in a multicentre, randomised (1:1), open-label, Phase 3 study

conducted in patients with MM who had relapsed following treatment with at least one prior line of therapy, including lenalidomide.

In the BPd arm (N = 155), patients received belantamab mafodotin 2.5 mg/kg by intravenous infusion once on day 1 in cycle 1 (28-day cycle) followed by belantamab mafodotin 1.9 mg/kg by intravenous infusion every 4 weeks on day 1 of cycle 2 onwards (28-day cycles); pomalidomide 4 mg (orally [PO]) administered on days 1 to 21; and dexamethasone 40 mg PO on days 1, 8, 15, and 22 in all cycles (28-day cycles). In the pomalidomide, bortezomib, and dexamethasone (PVd) arm (N = 147), pomalidomide 4 mg PO was administered every 3 weeks on days 1 to 14 in all cycles (21-day cycles); bortezomib 1.3 mg/m2 was administered subcutaneously on days 1, 4, 8, and 11 in cycles 1 to 8, and on days 1 and 8 in cycle ≥ 9 (21-day cycles). Patients were stratified by the number of prior lines of treatment, prior exposure to bortezomib, prior anti-CD38 treatment, and International Staging System (ISS) status.

The key eligibility criteria included having confirmed diagnosis of MM as defined by IMWG criteria, having previously been treated with at least 1 prior line of MM therapy, including lenalidomide, and having had documented disease progression during or after their most recent therapy. Patients were excluded if they received prior treatment with or intolerant to pomalidomide, were previously treated with BCMA-targeted therapy, or had current corneal disease except for mild punctate keratopathy.

The primary efficacy outcome measure was PFS as evaluated by a blinded IRC based on the IMWG criteria for MM.

A total of 302 patients were evaluated for efficacy in DREAMM-8. In the BPd arm, 100% of patients received prior immunomodulator therapy (lenalidomide, thalidomide), 90% of patients received prior proteasome inhibitor therapy (bortezomib, carfilzomib, ixazomib), 25% of patients received prior anti-CD38 therapy (daratumumab, isatuximab), and 64% of patients previously received ASCT. 82% of patients were refractory to immunomodulator therapy, 26% of patients refractory to proteasome inhibitor therapy, and 23% of patients refractory to anti-CD38 therapy.

Efficacy results regarding the PFS at the time of the first interim analysis (data cut-off 2 October 2023) and from the second interim analysis data cut-off (7 October 2024) are presented in Table 3.

Table 3. Summary of PFS by IRC-assessed response (primary efficacy endpoint, ITT Population): DREAMM-7 and DREAMM-8

PFS	**DREAMM-7 (IA1 DCO: 02 October 2023)**		**DREAMM-7 (IA2 DCO: 07 October 2024)**		**DREAMM-8 (IA2 DCO: 29 January 2024)**		**DREAMM-8 (Post hoc analysis DCO: 07 October 2024)**	
	BVd N = 243	DVd N = 251	BVd N = 243	DVd N = 251	BPd N = 155	PVd N = 147	BPd N = 155	PVd N = 147
Number of participants, n (%)								
Progressed or died (event)	91 (37%)	158 (63%)	109 (45%)	167 (67%)	62 (40%)	80 (54%)	68 (44%)	89 (61%)
Disease progression	67 (28%)	139 (55%)	81 (33%)	147 (59%)	46 (30%)	66 (45%)	51 (33%)	74 (50%)
Death	24 (10%)	19 (8%)	28 (12%)	20 (8%)	16 (10%)	14 (10%)	17 (11%)	15 (10%)
Estimates for time variable (months)[a]								
Median (95% CI)	36.6 (28.4, -)	13.4 (11.1, 17.5)	33.8 (28.4, 45.8)	13.4 (11.1, 17.5)	- (20.6, -)	12.7 (9.1, 18.5)	32.6 (21.1, -)	12.5 (9.1, 17.6)
Hazard ratio (95%CI)[b]	0.41 (0.31, 0.53)		0.46 (0.35, 0.59)		0.52 (0.37, 0.73)		0.49 (0.35, 0.68)	
P-value[c]	<0.00001		-		<0.001		-	
Progression-free survival rate								
Time-to-event endpoint at 6 months (95% CI)	0.88 (0.83, 0.91)	0.77 (0.71, 0.82)	0.88 (0.83, 0.91)	0.77 (0.71, 0.82)	0.82 (0.75, 0.87)	0.72 (0.64, 0.79)	0.82 (0.75, 0.87)	0.72 (0.64, 0.79)
Time-to-event endpoint at	0.78 (0.72, 0.83)	0.53 (0.47, 0.60)	0.78 (0.72, 0.83)	0.53 (0.47, 0.60)	0.71 (0.63, 0.78)	0.51 (0.42, 0.60)	0.71 (0.63, 0.78)	0.51 (0.41, 0.59)

PFS	DREAMM-7 (IA1 DCO: 02 October 2023)		DREAMM-7 (IA2 DCO: 07 October 2024)		DREAMM-8 (IA2 DCO: 29 January 2024)		DREAMM-8 (Post hoc analysis DCO: 07 October 2024)	
12 months (95% CI)								
Time-to-event endpoint at 18 months (95% CI)	0.69 (0.62, 0.75)	0.43 (0.36, 0.49)	0.69 (0.62, 0.75)	0.43 (0.36, 0.49)	0.62 (0.54, 0.70)	0.43 (0.34, 0.52)	0.63 (0.54, 0.70)	0.41 (0.32, 0.50)
Time-to-event endpoint at 24 months (95% CI)	-	-	0.65 (0.58, 0.71)	0.34 (0.28, 0.41)	-	-	-	-

Abbreviations: BPd=belantamab mafodotin in combination with pomalidomide and dexamethasone; BVd=belantamab mafodotin in combination with bortezomib and dexamethasone; CI=confidence interval; DCO=data cutoff; DVd=daratumumab in combination with bortezomib and dexamethasone; HR=hazard ratio; IA=interim analysis; IRC=Independent Review Committee; ITT=intent to treat; IVRS=interactive voice response system PFS=progression-free survival; PVd=pomalidomide in combination with bortezomib and dexamethasone; R-ISS=Revised-International Staging System

[a] CIs were estimated using the Brookmeyer-Crowley method.

[b] DREAMM-7: HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes), and R-ISS at screening (I vs. II/III), with a covariate of treatment; DREAMM-8: HRs were estimated using a Cox Proportional Hazards model stratified by number of lines of prior therapy and prior bortezomib use assessed according to the IVRS strata with a covariate of treatment.

[c] DREAMM-7: P-value from 1-sided stratified log-rank test; DREAMM-8: P-value from 1-sided stratified log-rank test stratified by number of lines of prior therapy and prior bortezomib use assessed according to the IVRS strata with a covariate of treatment.

Regarding secondary endpoints and the overall survival (OS) at the planned interim analysis with a DCO date of 02 October 2023 (IA1), DREAMM-7 showed a strong and clinically meaningful OS benefit that favoured the BVd group vs. the DVd group with an HR of 0.57 (95% CI: 0.40, 0.80; p-value=0.00049). In DREAMM-8, at the planned interim analysis with a DCO date of 29 January 2024 (IA2), there was an OS trend in favour of the BPd group with an HR of 0.77 (95% CI: 0.53, 1.14; p-value=0.095) (Table 4).

Table 4. Summary of overall survival (secondary efficacy endpoint, ITT Population): DREAMM-7 and DREAMM-8

OS	**DREAMM-7 (IA1 DCO: 02 October 2023)**		**DREAMM-7 (IA2 DCO: 07 October 2024)**		**DREAMM-8 (IA2 DCO: 29 January 2024)**	
	BVd (N = 243)	DVd (N = 251)	BVd (N = 243)	DVd (N = 251)	BPd (N = 155)	PVd (N = 147)
Number of participants, n (%)						
Died (event)	54 (22%)	87 (35%)	68 (28%)	103 (41%)	49 (32%)	56 (38%)
Estimates for time variable (months)[a]						
Median (95% CI)	- (-, -)	- (-, -)	- (-, -)	- (41.0, -)	- (33.0, -)	- (25.2, -)
Hazard ratio (95% CI)[b]	0.57 (0.40, 0.80)		0.58 (0.43, 0.79)		0.77 (0.53, 1.14)	
P-value[c]	0.00049[d]		0.00023[e]		0.095	
Overall survival rate						
Time-to-event endpoint at 6 months (95% CI)	0.91 (0.87, 0.94)	0.89 (0.84, 0.92)	0.91 (0.87, 0.94)	0.89 (0.84, 0.92)	0.93 (0.88, 0.96)	0.88 (0.81, 0.92)
Time-to-event endpoint at 12 months (95% CI)	0.87 (0.81, 0.90)	0.81 (0.75, 0.85)	0.87 (0.81, 0.90)	0.81 (0.75, 0.85)	0.83 (0.76, 0.88)	0.76 (0.68, 0.82)
Time-to-event endpoint at 18 months (95% CI)	0.84 (0.79, 0.88)	0.73 (0.67, 0.78)	0.84 (0.79, 0.88)	0.73 (0.67, 0.78)	0.76 (0.69, 0.82)	0.69 (0.61, 0.76)
Time-to-event endpoint at 24 months (95% CI)	-	-	0.79 (0.73, 0.84)	0.67 (0.61, 0.73)	-	-
Time-to-event endpoint at 36 months (95% CI)	-	-	0.74 (0.68, 0.79)	0.60 (0.54, 0.66)	-	-

Abbreviations: BPd=belantamab mafodotin in combination with pomalidomide and dexamethasone; BVd=belantamab mafodotin in combination with bortezomib and dexamethasone; CI=confidence interval; DCO=data cutoff; DVd=daratumumab in combination with bortezomib and dexamethasone; HR=hazard ratio; IA-interim analysis; ITT=intent to treat; IVRS=interactive voice response system; OS=overall survival; PVd=pomalidomide in combination with bortezomib and dexamethasone; R-ISS=Revised-International Staging System

[a] CIs were estimated using the Brookmeyer-Crowley method.

[b] DREAMM-7: HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes), and R-ISS at screening (I vs. II/III), with a covariate of treatment; DREAMM-8: HRs were estimated using a Cox Proportional Hazards model stratified by number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no) assessed according to the IVRS strata with a covariate of treatment.

[c] DREAMM-7: P-value from 1-sided stratified log-rank test; DREAMM-8: P-value from 1-sided stratified log-rank test stratified by number of lines of prior therapy and prior bortezomib use assessed according to the IVRS strata with a covariate of treatment.

[d] Nominal p-value

[e] At 171 actual events (48.2% OS Information Fraction), OS declared significant if P-value <0.00112.

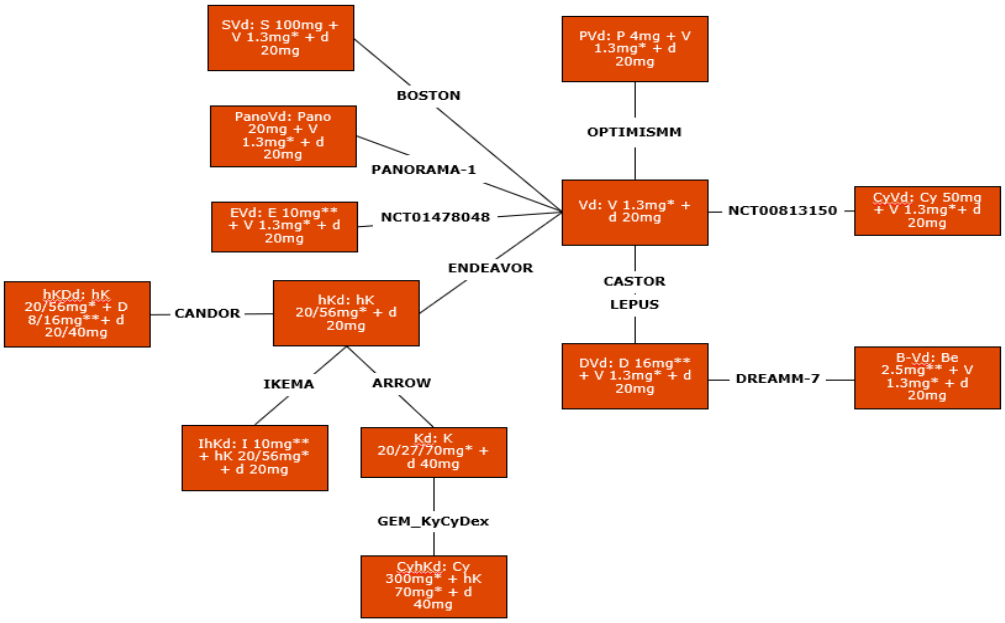
The arguments for the significant benefit of belantamab mafodotin were based on a clinically relevant advantage in terms of improved efficacy and safety and major contribution to patient care in the target patient population.

Significant benefit of belantamab mafodotin vs. comparators (daraturumab, isatuximab, carfilzomide, selinexor, ixazomib, elotuzumab and pomalidomide)

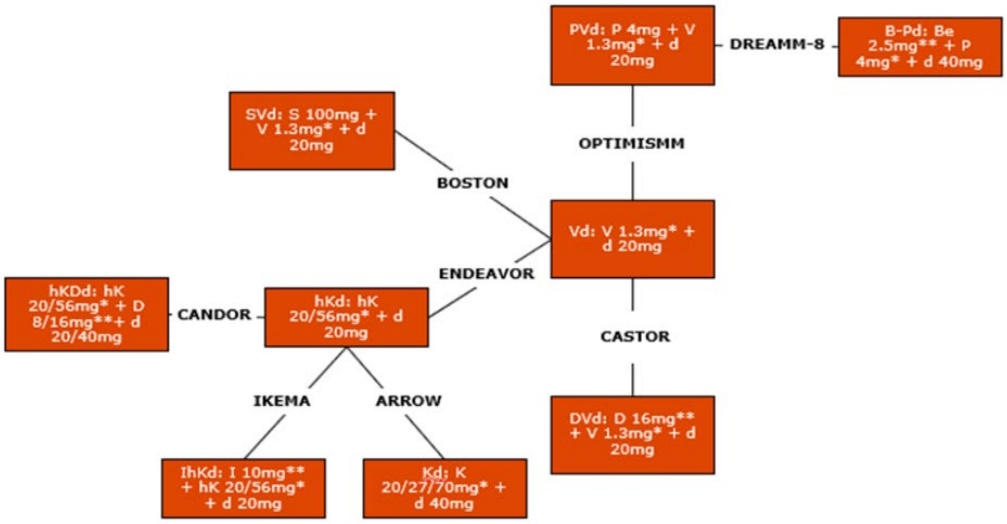
In the absence of a direct head-to-head comparison of belantamab mafodotin vs. all relevant comparators, a network meta-analysis was conducted by the sponsor to address the lack of direct evidence available comparing belantamab mafodotin to other existing treatments in the second line (2L) treatment landscape (daraturumab, isatuximab, carfilzomide, selinexor, ixazomib, elotuzumab and pomalidomide). The comparators included in the network meta-analysis have been selected based on their relevance to this treatment landscape and the heterogeneity in the patient populations of trials assessing each intervention. The comparators were identified through a systematic literature review of treatment for RRMM in adult patients with at least 1 prior line of therapy. The restricted network of evidence was based on the final studies identified in the systematic literature review for each of the DREAMM-7 and DREAMM-8 studies and is shown in Figure 1.

Figure 1. Connected Network of Evidence Based on Studies Identified in the Systematic Literature Review for DREAMM-7 and DREAMM-8

DREAMM-7



DREAMM-8



Abbreviations: B-Pd=belantamab mafodotin + pomalidomide + dexamethasone; B-Vd=belantamab mafodotin + bortezomib + dexamethasone; CyhKd=cyclophosphamide + high dose carfilzomib + daratumumab + dexamethasone; CyVd=cyclophosphamide + bortezomib + dexamethasone; DVd=daratumumab + bortezomib + dexamethasone; EVd=Elotuzumab + bortezomib + dexamethasone; hK=high dose carfilzomib; hKd=high dose carfilzomib + dexamethasone; hKDd=high dose carfilzomib + daratumumab + dexamethasone; IhKd=isatuximab + high dose carfilzomib + daratumumab; Kd=carfilzomib + dexamethasone; PanoVd=Panobinostat + bortezomib + dexamethasone; PVd=pomalidomide + bortezomib + dexamethasone; SVd=elinexor + bortezomib + dexamethasone; Vd=bortezomib + dexamethasone.
*=mg/m^2; **=mg/kg

According to the sponsor, the DREAMM-7 network meta-analyses [GSK DREAMM-7, 2024] consistently demonstrated that BVd is more efficacious compared with all comparators, for all populations, and in all assessed outcomes (PFS, OS, and ORR). Results were statistically significant for most comparisons, highlighting the clinical benefit of BVd in RRMM, and the large unmet need (Table 5).

The DREAMM-8 network meta-analyses [GSK DREAMM-8, 2024] demonstrated that BPd is more efficacious compared to all comparators when assessing PFS in both lenalidomide-exposed and lenalidomide-refractory analyses. Results were statistically significant for some fixed-effect comparisons, highlighting the clinical benefit of BPd in RRMM. The results were consistent regarding treatment effect of BPd vs. all comparators; however, they were not consistent across models in terms of statistical significance compared to individual treatments (Table 5).

Table 5. Summary of results from the network meta-analysis indirect comparisons

Drug (active substance)	Combination	Study	Justification of significant benefit	
			BVd vs. comparators	BPd vs. comparators
Daratumumab	Daratumumab monotherapy	SIRIUS	DREAMM-7 demonstrates benefit of BVd over DVd combination therapy. Similarly, the DREAMM-8 network meta-analysis demonstrates the benefit of BPd over DVd. Given the establishment of benefit over daratumumab combination therapy, the benefit of BVd and BPd over daratumumab monotherapy is considered to have also been demonstrated.	
	Daratumumab in combination with bortezomib and dexamethasone (DVd)	CASTOR LEPUS	Head-to-head superiority in PFS and OS demonstrated in DREAMM-7	Network meta-analysis indirect PFS HR = 0.73 (0.43, 1.25)
	Daratumumab in combination with carfilzomib and dexamethasone (DKd)	CANDOR	Network meta-analysis indirect PFS HR = 0.38 (0.24, 0.61)	Network meta-analysis indirect PFS HR = 0.86 (0.46, 1.62)
	Daratumumab in combination with lenalidomide and dexamethasone (DRd)	POLLUX	DRd not suitable for patients who are refractory to lenalidomide. BVd is suitable for these patients, as it does not contain lenalidomide. Furthermore, 34% of patients in DREAMM-7 were lenalidomide refractory.	DRd not suitable for patients who are refractory to lenalidomide. BPd is suitable for these patients as it does not contain lenalidomide. In addition, 78% of patients in DREAMM-8 were lenalidomide refractory.
Isatuximab	Isatuximab in combination with carfilzomib and dexamethasone (IsaKd)	IKEMA	Network meta-analysis indirect PFS HR = 0.42 (0.26, 0.69)	Network meta-analysis indirect PFS HR = 0.73 (0.36, 1.47)
Carfilzomib	Carfilzomib in combination with dexamethasone (Kd)	ENDEAVOUR	Network meta-analysis indirect PFS HR = 0.36 (0.23, 0.56)	Network meta-analysis indirect PFS HR = 0.58 (0.34, 1.01)
	Carfilzomib in combination with lenalidomide and dexamethasone (KRd)	ASPIRE	KRd not suitable for patients who are refractory to lenalidomide. BVd is, as it is lenalidomide-sparing. 34% of patients in DREAMM-7 were lenalidomide refractory.	KRd not suitable for patients who are refractory to lenalidomide. BPd is suitable for these patients as it does not contain lenalidomide. 78% of patients in DREAMM-8 were lenalidomide refractory.

Drug (active substance)	Combination	Study	Justification of significant benefit	
Selinexor	Selinexor in combination with bortezomib and dexamethasone (SVd)	BOSTON	Network meta-analysis indirect PFS HR = 0.19 (0.12, 0.29)	Network meta-analysis indirect PFS HR = 0.46 (0.26, 0.83)
Ixazomib	Ixazomib in combination with lenalidomide and dexamethasone (IxaRd)	TOURMALINE-MM1	IxaRd not suitable for patients who are refractory to lenalidomide. BVd is, and 34% of patients in DREAMM-7 were lenalidomide refractory.	IxaRd not suitable for patients who are refractory to lenalidomide. BPd is, as it does not contain lenalidomide and 78% of patients in DREAMM-8 were lenalidomide refractory.
Elotuzumab	Elotuzumab in combination with lenalidomide and dexamethasone (ERd)	ELOQUENT-2	ERd not suitable for patients refractory to lenalidomide. BVd is, and 34% of patients in DREAMM-7 were lenalidomide refractory.	ERd not suitable for patients refractory to lenalidomide. BPd is, as it does not contain lenalidomide and 78% of patients in DREAMM-8 were lenalidomide refractory.
Pomalidomide	Pomalidomide in combination with bortezomib and dexamethasone (PVd)	OPTIMISMM	Network meta-analysis indirect PFS HR = 0.23 (0.16, 0.34)	Head-to-head superiority in PFS and OS demonstrated in DREAMM-8

Network meta-analyses are typically considered to be methodologically preferable to naïve cross-trial comparisons of studies because they preserve randomization [Dias, 2014].
Note that the DREAMM-8 network meta-analysis was restricted to trials reporting data specifically in patients who were previously exposed to lenalidomide in alignment with the DREAMM-8 trial and proposed indication statement for BPd. In contrast, this restriction was not applied for DREAMM-7.

- *Significant benefit of belantamab mafodotin vs. idecabtagene vicleucel and ciltacabtagene autoleucel*

There are currently no head-to-head trials nor indirect treatment comparisons between belantamab mafodotin and CAR-T therapies, such as idecabtagene vicleucel and ciltacabtagene autoleucel.

The sponsor claimed that the 2 CAR-T therapies, recently approved for patients with RRMM after 2 or more lines of therapy, present with challenges such as eligibility, access, supply, and safety concerns such as cytokine release syndrome (CRS) and neurotoxicity, and early survival detriment in real-world settings.

The sponsor also discussed the safety of the CAR-T cells. The CAR-T toxicity profile limits its utility outside of very selected, fit populations. These toxicities include life-threatening or fatal immune, neurologic, hematologic, and hepatic toxicities (e.g., CRS, encephalopathy and ICANS, hypogammaglobulinemia, elevated alanine aminotransferase, hepatitis B viral reactivation leading to hepatic failure, parkinsonism, HLH/MAS, and Guillain-Barré syndrome), as well as susceptibility to opportunistic infections. These dangers are highlighted by the initial survival decrement observed in the registrational trial of ciltacabtagene autoleucel, attributed to drug-related toxicity as well as the inherent delay of CAR-T therapy required by its bespoke nature.

Where available, belantamab mafodotin remains a viable off-the-shelf anti-BCMA option that does not require access to tertiary care centers and may be particularly valuable for patients who cannot tolerate the adverse effects of CAR-T therapy, and for those patients who cannot wait for access to CAR-T therapy. CAR-T therapy is also associated with multiple supply challenges, including manufacturing (e.g., limited slots, high costs, prolonged manufacturing times), storage, and transportation [Rendo, 2022; Zhang, 2023; Carvykti SmPC, 2024].

Belantamab mafodotin is an off-the-shelf BCMA targeting ADC delivered in the out-patient setting via a 30-minute infusion without the need for any of these procedures to administer the treatment. Also, very few deaths are associated with treatment with belantamab mafodotin and the most frequent AE of ocular toxicity is not life-threatening and is manageable with dose and schedule modifications without impacting efficacy. As evidenced in the DREAMM 7 clinical trial, belantamab mafodotin has also demonstrated a significant OS benefit that clearly demonstrates the clinically meaningful benefit as well as the safety profile. It is also noteworthy that real-world studies of patients treated with belantamab mafodotin outside of clinical trials achieved comparable outcomes to those within clinical trials [Hultcrantz, 2021; Alegre, 2023], demonstrating the real-world clinical utility of belantamab mafodotin.

COMP discussion

The COMP considered that there are some methodological issues with the network analysis which need to be clarified:

First, it is not clear why 2 networks were used, given that the network of studies for DREAMM8 seems to be a subnetwork of the network for DREAMM7. The sponsor should provide a justification for this choice. Otherwise, the sponsor should provide one network constructed with all studies, which could be built by adding the BPd box with an edge to the PVd box in the network of DREAMM7.

In addition, given the complexity of the networks (e.g. the network of DREAMM7 includes 13 treatments), the sponsor should provide details on the specific statistical models used for the network meta-analyses, as well as the underlying assumptions and discuss their plausibility. The sponsor is also invited to discuss heterogeneity of the included studies.

- *Significant benefit of belantamab mafodotin vs. daraturumab*

Based on the above the significant benefit of belantamab mafodotin vs. daratumumab is considered justified based on the head-to-head comparison and the results of DREAMM7 study. The PFS assessed by IRC showed a statistically significant PFS benefit with BVd compared to DVd, as demonstrated by an HR of 0.41 (95% CI: 0.31, 0.53; p <0.00001). The median PFS was longer in the BVd group at 36.6 months (95% CI: 28.4, NR) vs. 13.4 months (95% CI: 11).1, 17.5) in the DVd group. A statistically significant OS benefit favoured the BVd group vs. the DVd group with an HR of 0.58 (95% CI: 0.43, 0.79; p-value=0.00023), in updated OS data based on DCO date of 07 October 2024 (IA2).

The COMP considers that this data can justify the significant benefit of belantamab mafodotin vs. daratumumab.

- *Significant benefit of belantamab mafodotin vs. isatuximab*

The sponsor claimed that based on the DREAMM7 and the DREAMM8 network meta-analysis the indirect PFS HR was 0.42 (0.26, 0.69) and 0.73 (0.36, 1.47), respectively. The results suggest there's no convincing evidence of significant benefit of BPd vs isatuximab with the upper limit of the 95% confidence interval being 1.47.

However, all the methodological issues highlighted above are applicable.

- *Significant benefit of belantamab mafodotin vs. carfilzomib*

The sponsor claimed that based on DREAMM7 and the DREAMM8 network meta-analysis the significant benefit of belantamab mafodotin vs. carfilzomib is justified.

Carfilzomib is authorised for the treatment of MM in combination with lenalidomide and dexamethasone (and the use of lenalidomide in lenalidomide-refractory patients is not recommended). However, it is also authorised in combination with daratumumab and dexamethasone.

The sponsor claimed that based on the DREAMM7 and the DREAMM8 network meta-analysis the indirect PFS HR was 0.38 (0.23, 0.56) and 0.58 (0.34, 1.01), respectively. The results suggest there's no convincing evidence of significant benefit of BPd vs carfilzomib (in the daratumumab / carfilzomib / dexamethasone combination regimen) with the upper limit of the 95% confidence interval being 1.01.

Similar to isatuximab, all the methodological issues highlighted above are applicable.

- *Significant benefit of belantamab mafodotin vs. selinexor*

The sponsor claimed that based on the DREAMM7 and the DREAMM8 network meta-analysis the significant benefit of belantamab mafodotin vs. selinexor is justified.

However, all the methodological issues highlighted above are applicable.

- *Significant benefit of belantamab mafodotin vs. ixazomib*

The sponsor claimed that based on DREAMM7 and the DREAMM8 network meta-analysis the significant benefit of belantamab mafodotin vs. ixazomib is justified since ixazomib is registered to be used in combination with lenalidomide and dexamethasone and lenalidomide is not suitable for patients who are refractory to lenalidomide and both DREAMM7 and DREAMM8 included lenalidomide-refractory patients. However, the indication for the BVd triplet is not limited to lenalidomide-refractory patients only.

In addition, all the methodological issues highlighted above are applicable.

- *Significant benefit of belantamab mafodotin vs. elotuzumab*

The sponsor claimed that based on DREAMM7 and the DREAMM8 network meta-analysis the significant benefit of belantamab mafodotin vs. elotuzumab is justified since elotuzumab (registered to be used in combination with lenalidomide and dexamethasone) is not suitable for patients who are refractory to lenalidomide and both DREAMM7 and DREAMM8 included lenalidomide-refractory patients. However, the indication for the BVd triplet is not limited to lenalidomide-refractory patients only.

In addition, all the methodological issues highlighted above are applicable.

- *Significant benefit of belantamab mafodotin vs. pomalidomide*

The sponsor claimed that based on the DREAMM7 network meta-analysis the indirect PFS HR was 0.23 (0.16, 0.34) and that in DREAMM-8 head-to-head superiority in PFS and OS was demonstrated. However, as DREAMM-8 study compared combination regimens belantamab / pomalidomide / dexamethasone versus bortezomib / pomalidomide / dexamethasone, this study does not provide any relevant data on comparative efficacy of belantamab mafodotin versus pomalidomide.

In addition, all the methodological issues highlighted above are applicable.

- *Significant benefit of belantamab mafodotin vs. melphalan*

The sponsor did not discuss the significant benefit of belantamab mafodotin versus melphalan.

According to the Table 2 melphalan is considered as satisfactory method since it has a broad indication. However, according to the ESMO guidelines (M.A. Dimopoulos, 2021), melphalan in combination with bortezomib/melphalan/prednisone is recommended only for first line multiple myeloma therefore the significant benefit can be justified.

- *Significant benefit of belantamab mafodotin vs. lenalidomide*

The sponsor did not discuss the significant benefit of belantamab mafodotin versus lenalidomide.

However, since lenalidomide refractory patients were included in both DREAMM-7 and DREAMM-8 studies (34% and 78% respectively) and these patients responded to treatment with belantamab mafodotin, the significant benefit is considered justified.

- *Significant benefit of belantamab mafodotin vs. dexamethasone*

The sponsor did not discuss the significant benefit of belantamab mafodotin versus dexamethasone.

However, dexamethasone is indicated for the treatment of symptomatic multiple myeloma in combination with other medicinal products. According to the summary of product characteristics (section 5.1), in controlled studies, combination treatment with dexamethasone consistently showed better outcomes in terms of survival and response than single agent dexamethasone.

4. COMP list of issues

- Prevalence

The COMP concluded that the prevalence is underestimated. The sponsor should recalculate the prevalence by using the crude incidence reported in ECIS and not the age-standardized incidence. In addition, the sponsor is requested to provide a sensitivity analysis on the prognostic factor of ISS Stage.

- Significant benefit

The COMP considered that the significant benefit of belantamab mafodotin over the medicinal products isatuximab, carfilzomib, selinexor, ixazomib, elotuzumab, pomalidomide is not considered justified.

The sponsor should discuss the methodological issues of the network meta-analyses provided to compare belantamab mafodotin over the above-mentioned medicinal products.

The sponsor should present a subgroups analysis of the responses observed in both DREAMM-7 and DREAMM-8 studies based on the type of prior lines of treatment (including the name of the products the patient received and not only the drug class).