SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Blenrep 100 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Belantamab mafodotin is an antibody-drug conjugate (ADC) that contains belantamab, an afucosylated humanised monoclonal IgG1k antibody specific for B cell maturation antigen (BCMA), produced using recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary) that is conjugated with maleimidocaproyl monomethyl auristatin F (mcMMAF).

One vial of powder contains 100 mg of belantamab mafodotin.

After reconstitution with 2 mL of sterile water for injection, each mL of solution contains 50 mg belantamab mafodotin.

Excipient with known effect

Each vial of reconstituted withdrawable solution contains 0.2 mg polysorbate 80 per mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

Lyophilised white to yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Blenrep in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
Blenrep 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

4.2 Posology and method of administration

Treatment with Blenrep should be initiated and monitored by physicians experienced in the treatment of multiple myeloma.

Recommended supportive care

Patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional before each of the first 4 doses of Blenrep, and as clinically indicated thereafter (see section 4.4).

Physicians should encourage patients to inform them of any ocular symptoms. Additionally, physicians should advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment as this may reduce ocular symptoms (see section 4.4).

For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.

Posology

Administration of Blenrep is to be continued according to the recommended schedule until disease progression or unacceptable toxicity. Blenrep is administered in combination with other treatments (see Table 1). For dosing instructions of agents administered in combination with Blenrep, see section 5.1 or refer to the corresponding Summary of Product Characteristics for the combination products, as appropriate.

Blenrep in combination with bortezomib and dexamethasone

When combined with bortezomib and dexamethasone, Blenrep is administered as a 30-minute infusion. Blenrep is administered once every 3 weeks with a starting dose of 2.5 mg/kg. Blenrep is administered from Cycle 1 until completion of treatment, while bortezomib and dexamethasone are administered for the first 8 Cycles. Each 21-day period is considered one treatment cycle.

Blenrep in combination with pomalidomide and dexamethasone

When combined with pomalidomide and dexamethasone, Blenrep is administered as a 30-minute infusion. Blenrep is administered once every 4 weeks with a starting dose

of 2.5 mg/kg given once in Cycle 1. From Cycle 2 and onwards, Blenrep is dosed at 1.9 mg/kg. Each 28-day period is considered one treatment cycle.

Dose modifications

The dosage of Blenrep should be individualised for each patient. Dose reduction levels for Blenrep are provided in Tables 1 and 2. Recommended modifications to manage adverse reactions are provided in Tables 3 and 4.

Table 1: Dose reduction schedule for Blenrep in combination with bortezomib and dexamethasone (BVd) (3-week cycle dosing regimen)[a]

Dose Levels	**Schedule**
Recommended starting dose schedule	2.5 mg/kg every 3 weeks
Reduced dose level 1	1.9 mg/kg every 3 weeks
Reduced dose level 2	NA

NA = Not applicable.

[a] Extended dosing intervals were observed during the clinical studies (see section 5.1, Table 10).

Table 2: Dose reduction schedule for Blenrep in combination with pomalidomide and dexamethasone (BPd) (4-week cycle dosing regimen)[a]

Dose Levels	**Schedule**
Recommended starting dose schedule	2.5 mg/kg once for Cycle 1 followed by 1.9 mg/kg once every 4 weeks starting with Cycle 2
Reduced dose level 1	1.9 mg/kg every 8 weeks
Reduced dose level 2	1.4 mg/kg every 8 weeks

NA = Not applicable.

[a] Extended dosing intervals were observed during the clinical studies (see section 5.1, Table 12).

Management of ocular adverse reactions

Dose modifications are based on corneal examination findings and/or changes in best corrected visual acuity (BCVA) (see sections 4.4 and 4.8). The treating physician should review the patient's ophthalmic examination findings before dosing and determine the dose of Blenrep based on the highest category from the corneal examination and/or BCVA finding in the most severely affected eye as both eyes may not be affected to the same degree.

During the ophthalmic examination, the eye care professional should assess the following:

- The corneal examination finding(s) and the decline in BCVA.
- If there is a decline in BCVA, the relationship to Blenrep should be determined.
- The category grading for these examination findings and BCVA changes should be communicated to the treating physician.

The corneal examination findings may or may not be accompanied by changes in BCVA. Note: One eye may be more severely affected than the other. It is important for physicians to consider not only corneal examination findings but also visual acuity changes and reported symptoms as they evaluate dose delays and reductions.

Do not re-escalate Blenrep dose after a dose reduction is made for ocular adverse reactions.

Table 3: Recommended dose modifications for ocular adverse reactions

Severity[a]	**Recommended dose modifications**
Grade 1 *Corneal examination finding(s)* Mild superficial punctate keratopathy with worsening from baseline, with or without symptoms. *Change in BCVA* Decline from baseline of 1 line on Snellen Equivalent Visual Acuity.	Continue treatment at current dose.
Grade 2 *Corneal examination finding(s)* Moderate superficial punctate keratopathy, patchy microcyst-like deposits, peripheral sub-epithelial haze, or a new peripheral stromal opacity. *Change in BCVA* Decline from baseline of 2 lines (and Snellen Equivalent Visual Acuity not worse than 20/200). Or Grade 3 *Corneal examination finding(s)* Severe superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, central sub-epithelial haze, or a new central stromal opacity. *Change in BCVA* Decline from baseline of 3 or more lines (and Snellen Equivalent Visual Acuity not worse than 20/200).	Withhold treatment until improvement in both corneal examination findings and BCVA to Grade 1 or better. Resume treatment at reduced dose level 1 as per Tables 1 and 2.[b]
Grade 4 *Corneal examination finding(s)* Corneal epithelial defect.[c] Or *Change in BCVA* Decline to Snellen Equivalent Visual Acuity of worse than 20/200.	Withhold until improvement in both corneal examination findings and BCVA to Grade 1 or better. Resume treatment at reduced dose level 1 for BVd and level 2 for BPd, if applicable. For worsening symptoms that are unresponsive to dose reductions or withholding of treatment, consid*er permanent discontinuation*.

BCVA = best corrected visual acuity; BPd = Blenrep with pomalidomide and dexamethasone; BVd = Blenrep with bortezomib and dexamethasone.

[a] Ocular adverse reaction severity is defined by the most severely affected eye as both eyes may not be affected to the same degree.
[b] If toxicity is identified prior to dosing Cycle 2 for Blenrep with pomalidomide and dexamethasone, dose at 1.9 mg/kg every 4 weeks.
[c] A corneal defect may lead to corneal ulcers. These should be managed promptly and as clinically indicated by an eye care professional.

Table 4: Recommended dose modifications for other adverse reactions[a]

Adverse Reaction	**Severity**	**Recommended dose modifications**
Thrombocytopenia	Grade 3	No bleeding: • For patients on 2.5 mg/kg, reduce Blenrep to 1.9 mg/kg. For patients on 1.9 mg/kg or lower, continue at same dose.[b] With bleeding: • Withhold Blenrep until improvement to Grade 2 or better. For patients previously on 2.5 mg/kg, resume Blenrep at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, resume at same dose. Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	Withhold the dose. Consider restarting if recovered to Grade 3 or better, and only if there is no active bleeding at time of treatment restart. For patients previously on 2.5 mg/kg, resume Blenrep at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, resume at same dose. If thrombocytopenia is considered disease-related, is not accompanied by bleeding, and recovers with transfusion to >25 $x10^9$/L, continuing treatment at the same dose may be considered.
Infusion-related reactions	Grade 2	Interrupt infusion and provide supportive treatment. Once symptoms resolve to Grade 1 or better, resume at a decreased infusion rate by at least 50% and may consider premedication.
	Grade 3	Interrupt infusion and provide supportive treatment. Once symptoms resolve to Grade 1 or better, resume with premedication and at lower

		infusion rate extended to 2 to 4 hours. Any future infusion requires premedication.
	Grade 4	Permanently discontinue Blenrep. If anaphylactic or life-threatening infusion reaction, permanently discontinue the infusion and institute appropriate emergency care.
Other adverse reactions	Grade 3	Withhold Blenrep until improvement to Grade 1 or better. For patients previously on 2.5 mg/kg, resume Blenrep at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, resume at same dose.
	Grade 4	Consider permanent discontinuation of Blenrep. If continuing treatment, withhold Blenrep until improvement to Grade 1 or better. For patients previously on 2.5 mg/kg, resume Blenrep at 1.9 mg/kg. For patients on 1.9 mg/kg or lower, resume at same dose.

[a] Other adverse reactions were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

[b] For Blenrep with bortezomib and dexamethasone, may consider reverting to previous dose, if appropriate once thrombocytopenia recovers to Grade 2 or better.

Special populations

Elderly

No dose adjustment is recommended for patients who are aged 65 years or over (see section 5.2).

Renal impairment

No dose adjustment is recommended in patients with mild (60 eGFR<90 mL/min), moderate (30 eGFR<60 mL/min), severe renal impairment (eGFR<30 mL/min not requiring dialysis), or end stage renal disease (eGFR<15 mL/min requiring dialysis) (see section 5.2).

Hepatic impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin greater than upper limit of normal [ULN] to ≤ 1.5 × ULN and any aspartate transaminase [AST] or total bilirubin ≤ ULN with AST > ULN). There are limited data in patients with moderate hepatic impairment, and therefore dosing of Blenrep in these patients should be carefully considered (see section 5.2). There are no data in patients with severe hepatic impairment.

Body weight

Blenrep is dosed based on actual body weight and has been studied in patients with body weight 37-170 kg (see section 5.2).

Paediatric population

The safety and efficacy of Blenrep in children and adolescents aged under 18 years of age have not been established. No data are available.

Method of administration

Blenrep is for intravenous use.

Blenrep must be reconstituted and diluted by a healthcare professional prior to administration as an intravenous infusion over 30 minutes.

Blenrep must not be administered as an intravenous push or bolus injection.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ocular adverse reactions

Ocular adverse reactions (e.g., blurred vision, dry eye, eye irritation, and photophobia) have been reported with the use of Blenrep (see section 4.8). The most commonly reported corneal examination findings include superficial punctuate keratopathy, microcyst-like epithelial changes, and haze, with or without changes in visual acuity. Clinically relevant changes in visual acuity may be associated with difficulty in driving or operating machinery (see section 4.7).

Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, should be performed before each of the first 4 doses of Blenrep and during treatment as clinically indicated.

Patients should be advised to administer preservative-free artificial tears at least 4 times a day during treatment (see section 4.2). Patients should avoid using contact lenses until the end of treatment. Bandage contact lenses may be used under the direction of an ophthalmologist.

Patients experiencing corneal examination findings (keratopathies such as superficial punctate keratopathy or microcyst-like deposits) with or without changes in visual

acuity may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings (see section 4.2).

Cases of corneal ulcer (ulcerative and infective keratitis) have been reported (see section 4.8). These should be managed promptly and as clinically indicated by an eye care professional. Treatment with Blenrep should be interrupted until the corneal ulcer has healed (see section 4.2).

Thrombocytopenia

Thrombocytopenic events (thrombocytopenia and platelet count decreased) have been reported with the use of Blenrep (see section 4.8). Thrombocytopenia may lead to serious bleeding events, including gastrointestinal and intracranial bleeding.

Complete blood counts are to be obtained at baseline and monitored during treatment, as clinically indicated. Patients experiencing Grade 3 or 4 thrombocytopenia or those on concomitant anticoagulant treatments may require more frequent monitoring and may be managed with a dose delay or dose reduction (see section 4.2). Supportive therapy (e.g., platelet transfusions) may be provided according to standard medical practice.

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been reported with the use of Blenrep. Most IRRs were Grade 1 or 2 and resolved within the same day (see section 4.8). Patients experiencing IRR may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings (see section 4.2).

Pneumonitis

Cases of pneumonitis, including fatal events, have been observed with Blenrep, although a causal association has not been established. Evaluation of patients with new or worsening unexplained pulmonary symptoms (e.g., cough, dyspnoea) must be performed to exclude possible pneumonitis. In case of suspected Grade 3 or higher pneumonitis, it is recommended that Blenrep is withheld and appropriate treatment initiated (see section 4.2). Blenrep should only be resumed after an evaluation of the benefit and risk.

Hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation can occur in patients treated with medicinal products directed against B cells, including Blenrep. Patients with evidence of positive HBV serology must be monitored for clinical and laboratory signs of HBV reactivation. If reactivation of HBV occurs while on Blenrep, patients must be treated according to clinical guidelines.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed. Based on available *in vitro* and clinical data, there is a low risk of pharmacokinetic or pharmacodynamic drug interactions for belantamab mafodotin. Combination therapies with bortezomib, lenalidomide, pomalidomide, and/or dexamethasone do not affect the pharmacokinetic properties of belantamab mafodotin (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

Women
The pregnancy status of child-bearing women must be verified prior to initiating therapy with Blenrep. Women of child-bearing potential must use effective contraception during treatment with Blenrep and for at least 4 months after the last dose.

Men
Men with female partners of child-bearing potential must use effective contraception during treatment with Blenrep and for at least 6 months after the last dose.

Pregnancy

There are no data from the use of belantamab mafodotin in pregnant women. Based on the mechanism of action of the cytotoxic component monomethyl auristatin F (MMAF), belantamab mafodotin can cause embryo-foetal harm when administered to a pregnant woman (see section 5.3). Human immunoglobulins (IgG) are known to cross the placental barrier, and therefore, being an IgG, belantamab mafodotin has the potential to be transmitted from the mother to the developing foetus.

Blenrep is not recommended during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated she must be clearly advised on the potential risk to the foetus.

Breast-feeding

It is unknown whether belantamab mafodotin is excreted into human milk. Immunoglobulin G (IgG) is present in human milk in small amounts. Since belantamab mafodotin is a humanised IgG monoclonal antibody, and based on the mechanism of action, it may potentially cause serious adverse reactions in breastfed children.

Breast-feeding should be discontinued prior to initiating treatment with Blenrep and for at least 3 months after the last dose of Blenrep.

Fertility

Based on findings in animals and the mechanism of action, belantamab mafodotin may impair fertility in females and males of reproductive potential (see section 5.3).

Therefore, physicians should counsel women of childbearing potential and men being treated with Blenrep regarding fertility preservation.

4.7 Effects on ability to drive and use machines

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

Patients must be advised to use caution when driving or operating machines while on Blenrep as it may affect patients' vision and influence their ability to drive or use machines due to impact on visual acuity and other ocular adverse reactions (see sections 4.4 and 4.8).

4.8 Undesirable effects

In combination with bortezomib and dexamethasone

The safety of Blenrep has been evaluated in 242 patients who received Blenrep in combination with bortezomib and dexamethasone (BVd) in DREAMM-7. The dosing regimen was 2.5 mg/kg once every 3 weeks with individual dose modification for adverse events as needed (see sections 4.2 and 5.1). Adverse reactions leading to permanent discontinuation of any component of therapy occurred in 31% of patients and in 9% of patients were due to ocular events including ocular adverse reactions, visual acuity changes, or corneal examination findings. Adverse reactions leading to dose delays of any component of therapy occurred in 94% of patients and in 78% of patients were due to ocular events. Adverse reactions leading to dose reductions of any component of therapy occurred in 75% of patients and in 44% of patients were due to ocular events.

The most frequent adverse reactions (≥20%) in BVd included reduced visual acuity (89%), thrombocytopenia (87%), corneal examination findings (86%), blurred vision (66%), dry eye (51%), photophobia (47%), foreign body sensation in eyes (44%), eye irritation (43%), eye pain (32%), diarrhoea (32%), and upper respiratory tract infection (20%).

Serious adverse reactions of BVd occurred in 50% of patients. Serious adverse reactions in ≥2% of patients included pneumonia (11%), pyrexia (5%), thrombocytopenia (5%), and anemia (2%). Fatal adverse reactions occurred in 10% of patients and the most common was pneumonia (3%).

In combination with pomalidomide and dexamethasone

The safety of Blenrep has been evaluated in 150 patients who received Blenrep in combination with pomalidomide and dexamethasone (BPd) in DREAMM-8. The dosing regimen was 2.5 mg/kg once followed by 1.9 mg/kg every 4 weeks with

individual dose modification for adverse events as needed (see sections 4.2 and 5.1). Adverse reactions leading to permanent discontinuation of any component of therapy occurred in 15% of patients and in 9% of patients were due to ocular events including ocular adverse reactions, visual acuity changes, or corneal examination findings. Adverse reactions leading to dose delays of any component of therapy occurred in 91% of patients and 83% of patients were due to ocular events. Adverse reactions leading to dose reductions of any component of therapy due to adverse reactions occurred in 61% of patients and in 59% of patients were due to ocular events.

The most frequent adverse reactions (≥20%) in BPd included reduced visual acuity (91%), corneal examination findings (87%), blurred vision (79%), neutropenia (63%), foreign body sensation in eyes (61%), dry eye (61%), thrombocytopenia (55%), eye irritation (50%), photophobia (44%), eye pain (33%), fatigue (27%), upper respiratory tract infection (27%), pneumonia (24%), anaemia (23%), and diarrhoea (23%).

Serious adverse reactions of BPd occurred in 63% of patients. Serious adverse reactions in ≥2% of patients included pneumonia (18%) and neutropenia (6%). Fatal adverse reactions occurred in 11% of patients and the most common was pneumonia (1%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials of Blenrep in combination with either bortezomib and dexamethasone or pomalidomide and dexamethasone, and post-market settings, are listed in Tables 5 and 6 by system organ class and by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1 000 to <1/100
Rare: ≥1/10 000 to <1/1 000

Table 5: Summary of adverse reactions with Blenrep in combination with bortezomib and dexamethasone

System organ class (SOC)	Adverse Reactions[a]	Frequency	Incidence	
			All Grades (%)	Grade 3+4 (%)
Eye Disorders	Visual acuity reduced[b]	Very common	89	57
	Corneal examination findings[b]		86	72
	Vision blurred		66	22

	Dry eye		51	7
	Photophobia		47	2
	Foreign body sensation in eyes		44	3
	Eye irritation		43	5
	Eye pain		32	<1
	Visual impairment		11	5
	Lacrimation increased	Common	9	<1
	Diplopia		5	0
	Eye pruritus		2	0
	Ocular discomfort		1	0
	Corneal ulcer[c]	Uncommon	<1	<1
Blood and Lymphatic System Disorders	Thrombocytopenia[d]	Very common	87	73
	Anaemia		19	8
	Neutropenia[d]		17	14
	Lymphopenia[d]		12	8
	Leukopenia[d]		10	5
Gastrointestinal Disorders	Diarrhea	Very common	32	4
	Nausea		16	<1
	Vomiting	Common	6	<1
Hepatobiliary Disorders	Porto-sinusoidal vascular disorder[e]	Uncommon	<1	<1
Infections and Infestations	Upper respiratory tract infection	Very common	20	0
	Pneumonia		18	9
	Hepatitis B reactivation	Uncommon	<1	<1

General Disorders and Administration Site Conditions	Pyrexia	Very common	19	<1
	Fatigue		19	4
Investigations	Increased alanine aminotransferase	Very common	19	6
	Increased aspartate aminotransferase		15	1
	Increased gamma glutamyltransferase		15	9
	Increased creatinine phosphokinase	Common	5	2
Renal and Urinary Disorders	Albuminuria[d]	Common	5	<1
Injury, poisoning, and procedural complications	Infusion-related reactions[f]	Common	2	0

[a] Adverse reactions, except ophthalmic examination findings, were graded according to CTCAE v5.0.
[b] Based on ophthalmic examination findings, which includes keratopathy.
[c] Includes infective keratitis and ulcerative keratitis
[d] Grouped term includes other related terms.
[e] Signs or symptoms may include abnormal liver function tests, portal hypertension, varices and ascites.
[f] Includes events determined to be related to infusion. Infusion reactions may include, but are not limited to pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, and tachycardia.

Table 6. Summary of adverse reactions with Blenrep in combination with pomalidomide and dexamethasone

System organ class (SOC)	**Adverse Reactions[a]**	**Frequency**	**Incidence**	
			All Grades	**Grade 3+4**

			(%)	(%)
Eye Disorders	Visual acuity reduced[b]	Very common	91	60
	Corneal examination findings[b]		87	62
	Vision blurred		79	17
	Dry eye		61	8
	Foreign body sensation in eyes		61	6
	Eye irritation		50	4
	Photophobia		44	3
	Eye pain		33	2
	Visual impairment		15	10
	Lacrimation increased	Common	6	<1
	Diplopia		5	<1
	Eye pruritus		3	<1
	Corneal ulcer[c]		2	<1
	Ocular discomfort		1	0
Blood and Lymphatic System Disorders	Neutropenia[d]	Very Common	63	57
	Thrombocytopenia[d]		55	38
	Anemia		23	10
	Leukopenia[d]	Common	9	5
	Lymphopenia[d]		8	5
Infections and Infestations	Upper respiratory tract infection	Very common	27	1
	Pneumonia		24	16
	Hepatitis B reactivation[e]	Uncommon	-	-
General Disorders and Administration Site Conditions	Fatigue	Very common	27	6
	Pyrexia		19	<1
Gastrointestinal Disorders	Diarrhoea	Very common	23	1
	Nausea		12	<1
	Vomiting	Common	5	0
Hepatobiliary Disorders	Porto-sinusoidal vascular disorder[f]	Uncommon	<1	<1
Investigations	Increased alanine aminotransferase	Very common	15	1
	Increased aspartate aminotransferase		10	3
	Increased gamma glutamyltransferase	Common	7	1

Injury, Poisoning, and Procedural Complications	Infusion-related reactions[g]	Common	7	1
Renal and Urinary Disorders	Albuminuria	Common	3	0

BCVA = best-corrected visual acuity.

[a] Adverse reactions, except ophthalmic examination findings, were graded according to CTCAE v5.0.

[b] Based on ophthalmic examination findings, which includes keratopathy.

[c] Includes infective keratitis and ulcerative keratitis

[d] Grouped term includes other related terms.

[e] Not observed in DREAMM-8 as of DCO 29 January 2024; frequency assigned as "uncommon" based on overall clinical assessment.

[f] Signs or symptoms may include abnormal liver function tests, portal hypertension, varices and ascites.

[g] Includes events determined to be related to infusion. Infusion reactions may include, but are not limited to pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, and tachycardia.

Description of selected adverse reactions

Ocular adverse reactions

DREAMM-7: Combination with bortezomib and dexamethasone:

In DREAMM-7 study, (combination with bortezomib and dexamethasone), the most common adverse reactions (>25%) included reduced visual acuity (89%, 57% Grade 3 and 4) and corneal examination findings (86%, 72% Grade 3 and 4) based on the ophthalmic examination findings, blurred vision (66%, 22% Grade 3 and 4), dry eye (51%, 7% Grade 3 and 4), photophobia (47%, 2% Grade 3 and 4), foreign body sensation in eyes (44%, 3% Grade 3 and 4), eye irritation (43%, 5% Grade 3 and 4), and eye pain (32%, <1% Grade 3 and 4).

Corneal examination findings (keratopathies such as superficial punctate keratopathy and microcyst-like deposits) were reported based on the ophthalmic examination findings as Grade 1 in 4% of patients, Grade 2 in 10% of patients, Grade 3 in 54% of patients, and Grade 4 in 19% of patients. Cases of corneal ulcer (ulcerative and infective keratitis) were reported with an incidence of <1% (n = 2).

In DREAMM-7, 86% (209/242) of patients reported at least 1 corneal examination finding or BCVA-related event (Grade ≥2) in the BVd arm. Of patients who experienced an event, 91% (190/209) continued treatment on or after the onset of the first event and received a median of 8 additional doses (range: 1 to 52).

Table 7 includes a summary of ocular adverse reactions, bilateral reduction in BCVA in patients with normal baseline (Snellen equivalent visual acuity 20/25 or better in at least one eye), and corneal examination findings in DREAMM-7.

Table 7: Ocular first events, median duration, and resolution in DREAMM-7

	Ocular adverse reactions[a]	Bilateral Reduction in BCVA[b]		Corneal examination findings (≥Grade 2 events)[c]
		20/50 or worse for patients	20/200 or worse for patients	
Number of patients with event (%)	191 (79)	82 (34)	5 (2)	198 (82)
Median time to first onset (days)	41	73.5	105	44
Improvement of first event[d], n (%)	NA	80 (98)	5 (100)	NA
Resolution of first event[e], n (%)	84 (44)	77 (94)	4 (80)	172 (87)
Median time to resolution of first event (days)	52	64	86.5	95.5
Ongoing first event[e], n (%)	107 (56)	5 (6)	1 (20)	26 (13)
Treatment ongoing, n (%)	39 (20)	–	–	3 (2)
Discontinued treatment and follow-up ongoing, n (%)	42 (22)	1 (1)	–	4 (2)
Discontinued treatment and follow-up ended, n (%)	26 (14)	4 (5)	1 (20)	19 (10)

BCVA = Best-correct visual acuity; NA = Not applicable.

[a] Resolution of ocular adverse reactions was defined as time to being free from any ocular adverse reactions.

[b] Resolution of visual acuity was defined as time to 20/25 or better in at least one eye.

[c] Resolution of corneal examination findings was defined as time to Grade 1 or better based on the ophthalmic examination findings.

[d] Improvement was defined as no longer 20/50, or 20/200, or worse in at least one eye.

[e] At the time of the data cut-off (2 OCT 2023).

DREAMM-8: Combination with pomalidomide and dexamethasone:

In DREAMM-8 study, (combination with pomalidomide and dexamethasone), the most common adverse reactions (>25%) included reduced visual acuity (91%, 60% Grade 3 and 4) and corneal examination findings based on the ophthalmic examination findings (87%, 62% Grade 3 and 4), blurred vision (79%, 17% Grade 3 and 4), dry eye (61%, 8% Grade 3 and 4), foreign body sensation in eyes (61%, 6% Grade 3 and 4), eye irritation (50%, 4% Grade 3 and 4), photophobia (44%, 3% Grade 3 and 4), and eye pain (33%, 2% Grade 3 and 4).

Corneal examination findings (keratopathies such as superficial punctate keratopathy and microcyst-like deposits) were reported based on the ophthalmic examination findings as Grade 1 in 7% of patients, Grade 2 in 18% of patients, Grade 3 in 56% of patients, and Grade 4 in 6% of patients. Cases of corneal ulcer (ulcerative keratitis) were reported with an incidence of 2% (n = 3).

In DREAMM-8, 87% (131/150) of patients reported at least 1 corneal examination finding or BCVA-related event (Grade ≥2) in the BPd arm. Of patients who experienced an event, 92% (120/131) continued treatment on or after the onset of the first event and received a median of 5 additional doses (range: 1 to 21).

Table 8 includes a summary of ocular adverse reactions, bilateral reduction in BCVA in patients with normal (Snellen equivalent visual acuity 20/25 or better in at least one eye) baseline, and corneal examination findings in DREAMM-8.

Table 8: Ocular first events, median duration, and resolution in DREAMM-8

	Ocular adverse reactions [a]	**Bilateral reduction in BCVA** [b]		**Corneal examination findings (≥Grade 2 events)** [c]
		20/50 or worse for patients	**20/200 or worse for patients**	
Number of patients with event (%)	133 (89)	51 (34)	2 (1)	120 (80)
Median time to first onset (days)	29	112	NA[d]	46.5
Improvement of first event[e], n (%)	NA	47 (92)	2 (100)	NA
Resolution of first event[f], n (%)	105 (79)	43 (84)	1 (50)	108 (90)
Median time to resolution of first event (days)	120.5	57	NA[d]	92
Ongoing first event[f], n (%)	28 (21)	8 (16)	1 (50)	12 (10)
Treatment ongoing, n (%)	8 (6)	3 (6)	–	1 (<1)
Discontinued treatment and follow-up ongoing, n (%)	7 (5)	1 (2)	–	4 (3)
Discontinued treatment and follow-up ended, n (%)	13 (10)	4 (8)	1 (50)	7 (6)

BCVA = Best-correct visual acuity; NA = Not applicable.

[a] Resolution of ocular adverse reactions was defined as time to being free from any ocular adverse reactions.

[b] Resolution of visual acuity was defined as time to 20/25 or better in at least one eye.

[c] Resolution of corneal examination findings was defined as time to grade 1 or better based on the ophthalmic examination findings.

[d] In patients with 20/200 or worse, two patients were reported. The first onset was 29 and 673 days. Both events improved to better than bilateral 20/200 by the data cut-off, of which 1 event resolved after 57 days.

[e] Improvement was defined as no longer 20/50, or 20/200, or worse in at least one eye.

[f] At the time of the data cut-off (29 JAN 2024).

Infusion-related reactions

In DREAMM-7 (combination with bortezomib and dexamethasone), the incidence of IRR was 2% (n = 5). All IRRs were reported as maximum Grade 1 (<1%) and Grade 2 (1%).

In DREAMM-8 (combination with pomalidomide and dexamethasone), the incidence of IRR was 7% (n = 11). Most IRRs were reported as maximum Grade 1 (1%) and Grade 2 (5%), while 1% experienced Grade 3 IRRs. One patient discontinued treatment due to IRR.

Thrombocytopenia

In DREAMM-7 (combination with bortezomib and dexamethasone), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 87% of patients (n = 211). Grade 2 thrombocytopenic events occurred in 10% of patients, Grade 3 in 26%, and Grade 4 in 47%. Clinically significant bleeding (≥Grade 2) occurred in 7% of patients with concomitant low platelet levels (Grades 3 to 4).

In DREAMM-8 (combination with pomalidomide and dexamethasone), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 55% of patients (n = 82). Grade 2 thrombocytopenic events occurred in 11% of patients, Grade 3 in 26%, and Grade 4 in 12%. Clinically significant bleeding (≥Grade 2) occurred in 3% of patients with concomitant low platelet levels (Grades 3 to 4).

Infections

In DREAMM-7 (combination with bortezomib and dexamethasone), pneumonia was reported in 18% of patients (n = 44) with 12% reported as ≥Grade 3. Seven patients had a pneumonia event with a fatal outcome.

In DREAMM-8 (combination with pomalidomide and dexamethasone), pneumonia was reported in 24% of patients (n = 36) with 17% reported as ≥Grade 3. Two patients had a pneumonia event with a fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

There is no known specific antidote for belantamab mafodotin overdose. If overdose is suspected, patients must be monitored for any signs or symptoms of adverse effects and appropriate supportive treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, and antibody drug conjugates, ATC code: L01FX15.

Mechanism of action

Belantamab mafodotin is a humanised IgG1 kappa monoclonal antibody conjugated with a cytotoxic agent, mcMMAF. Belantamab mafodotin binds to cell surface BCMA and is rapidly internalised. Once inside the tumour cell, the cytotoxic agent (cys-mcMMAF) is released disrupting the microtubule network, leading to cell cycle arrest and apoptosis. The antibody also enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis induced by belantamab mafodotin is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells.

Pharmacodynamic effects

Exposure-Response Relationship in Combination Therapies
For BVd and BPd combination therapies, higher belantamab mafodotin Cycle 1 exposure was associated with higher probability of response (e.g., very good partial response [VGPR+]) and higher incidence of some adverse reactions (e.g., ≥Grade 2 corneal examination findings). For most of the range of belantamab mafodotin Cycle 1 exposure, the probability of VGPR or better was higher than the probability of ocular adverse reactions and BCVA-related endpoints.

Cardiac electrophysiology
Belantamab mafodotin or cys-mcMMAF had no meaningful QTc prolongation (>10 ms) at doses of up to 3.4 mg/kg once every 3 weeks.

Immunogenicity

The incidence of anti-belantamab mafodotin antibodies (ADAs) was consistently low in patients treated with belantamab mafodotin in combination therapies with no observed clinical impact on pharmacokinetics, safety, and efficacy.

In the pivotal combination therapy studies (DREAMM-7 and DREAMM-8) and the Phase 1/2, open-label dose exploration study (DREAMM-6), 3% of patients (15/515) tested positive for treatment emergent ADAs. Two patients tested positive for neutralising anti-belantamab mafodotin antibodies (NAbs).

Clinical efficacy and safety

DREAMM-7: Blenrep in combination with bortezomib and dexamethasone

The efficacy and safety of Blenrep in combination with bortezomib and dexamethasone (BVd) were investigated in a multicentre, randomised (1:1), open-label, Phase 3 study conducted in patients with relapsed and/or refractory multiple myeloma (MM) who had received at least one prior line of therapy.

In the BVd arm (N = 243), patients received Blenrep 2.5 mg/kg by intravenous infusion (IV) every 3 weeks on day 1 of each 21-day Cycle; bortezomib 1.3 mg/m^2 (subcutaneously) on days 1, 4, 8, and 11 of Cycles 1 to 8 (21-day Cycles); and dexamethasone 20 mg (IV 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 21-day Cycles for Cycles 1 to 8: on days 1, 8 and 15 for Cycles 1 to 3 and on day 1 for Cycles 4 to 8. Daratumumab was administered on day 1 every 4 weeks from Cycle 9 onwards. Dexamethasone and bortezomib schedules were the same in both arms. The dose level of dexamethasone in each arm was reduced by half in patients aged 75 years and older. Treatment continued in both arms until disease progression, death, unacceptable toxicity, withdrawal of consent, or study end. 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 previously refractory to daratumumab or twice weekly bortezomib 1.3 mg/m^2 were excluded while patients refractory to weekly bortezomib were included.

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. Baseline demographics and characteristics were similar across both arms. Baseline characteristics for the BVd arm (N = 243) were: median age: 65 years (35% aged 65-74 years and 15% aged 75 years or older); 53% male, 47% female; 85% White, 12% Asian, 3% Black; R-ISS stage at screening I (42%), II (53%), III (4%); 28% high cytogenetics risk, median number of 1 prior lines (minimum 1, maximum 7); 5% with extramedullary disease (EMD) present; and of those who received treatment (n = 242), Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 (50%), 1 (46%), or 2 (4%). 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), 1% of patients received prior daratumumab therapy, and 67% of patients previously received autologous stem cell transplantation (ASCT). There were 9% of patients refractory to proteasome inhibitor therapy and 39% of patients refractory to immunomodulator therapy.

Patients treated with Blenrep in combination with bortezomib and dexamethasone had a statistically significant improvement in PFS, overall survival (OS) and minimal residual disease (MRD) negativity rate in the overall population compared with daratumumab, bortezomib, and dexamethasone. Efficacy results at the time of the first interim analysis (data cut-off 2 October 2023, except OS where data is presented from the second interim analysis data cut-off 7 October 2024) are presented in Table 9 and Figures 1 and 2.

Table 9: Efficacy results in DREAMM-7

	Blenrep plus bortezomib and dexamethasone (BVd)[a] N = 243	**Daratumumab plus bortezomib and dexamethasone (DVd)[a] N = 251**
Progression-free survival (PFS)[b]		
Number (%) of patients with event	91 (37)	158 (63)
Median in months (95% CI)[c]	36.6 (28.4, NR)	13.4 (11.1, 17.5)
Hazard ratio (95% CI)[d]	0.41 (0.31, 0.53)	
p-value[e]	<0.00001	
Probability of PFS at 18 months, % (95% CI)[f]	69 (62, 75)	43 (36, 49)
Overall survival (OS)		
Number (%) of patients with event	68 (28)	103 (41)
Median in months (95% CI)[c]	NR (NR, NR)	NR (41, NR)
Hazard ratio (95% CI)[d]	0.58 (0.43, 0.79)	
p-value[e]	0.00023	
Probability of OS at 24 months, % (95% CI)[f]	79 (73, 84)	67 (61, 73)
Probability of OS at 36 months (95% CI)[f]	74% (68, 79)	60% (54, 66)
Duration of response (DoR)[b, g]		
Number of responders, n	201	179
Number (%) of responders: follow-up ongoing[h]	106 (53)	52 (29)
Median in months (95% CI)[d]	35.6 (30.5, NR)	17.8 (13.8, 23.6)
Minimal residual disease (MRD) negativity rate[b, h, i]		
Percent of patients, (95% CI)	24.7 (19.4, 30.6)	9.6 (6.2, 13.9)
p-value[j]	<0.00001	
Overall response rate (ORR)[b, g, k], % (95% CI)	82.7 (77.4, 87.3)	71.3 (65.3, 76.8)
Stringent complete response (sCR), n (%)	34 (14)	13 (5.2)
Complete response rate (CRR), n (%)	50 (20.6)	30 (12)
Very good partial response (VGPR), n (%)	76 (31.3)	73 (29.1)
Partial response (PR), n (%)	41 (16.9)	63 (25.1)
Median time to response (TTR) in months (minimum, maximum)[b]	1.41 (0.7, 8.4)	0.85 (0.7, 11.1)
Median time to best response in months (min, max)[b]	4.5 (0.7, 32.5)	2.23 (0.7, 25.7)

	Blenrep plus bortezomib and dexamethasone (BVd)[a] N = 243	Daratumumab plus bortezomib and dexamethasone (DVd)[a] N = 251
PFS 2		
Number (%) of patients with event	70 (29)	106 (42)
Median in months (95% CI)[c]	NR	34.6 (27.6, NR)
Hazard ratio (95% CI)[d]	0.56 (0.41, 0.76)	

CI = Confidence interval; NR = Not reached.

[a] Efficacy data are based on the intent-to-treat (ITT) population, except DOR which is based on responders only. Data presented is from the first interim analysis data cut-off (2 OCT 2023) except OS, where data is from the second interim analysis data cut-off (7 OCT 2024).

[b] Response was based on IRC per IMWG criteria.

[c] By Brookmeyer and Crowley method.

[d] Based on stratified Cox regression model.

[e] One-sided p-value based on stratified log-rank test.

[f] By Kaplan-Meier method.

[g] For patients with a partial response or better.

[h] For patients with a complete response or better.

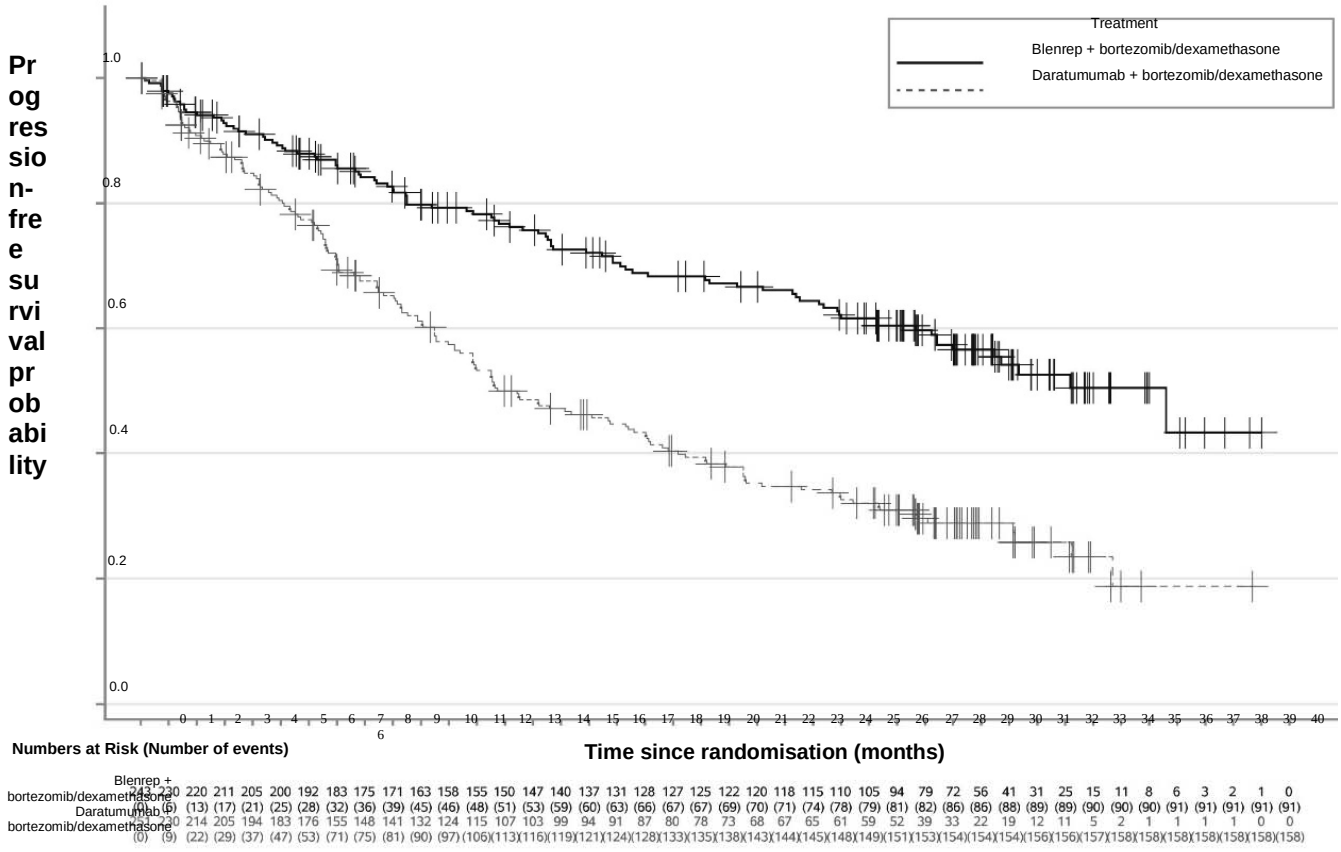
[i] Assessed by NGS at 10^{-5} threshold.

[j] Two-sided p-value based on stratified Cochran-Mantel-Haenszel test.

[k] ORR: sCR+CR+VGPR+PR.

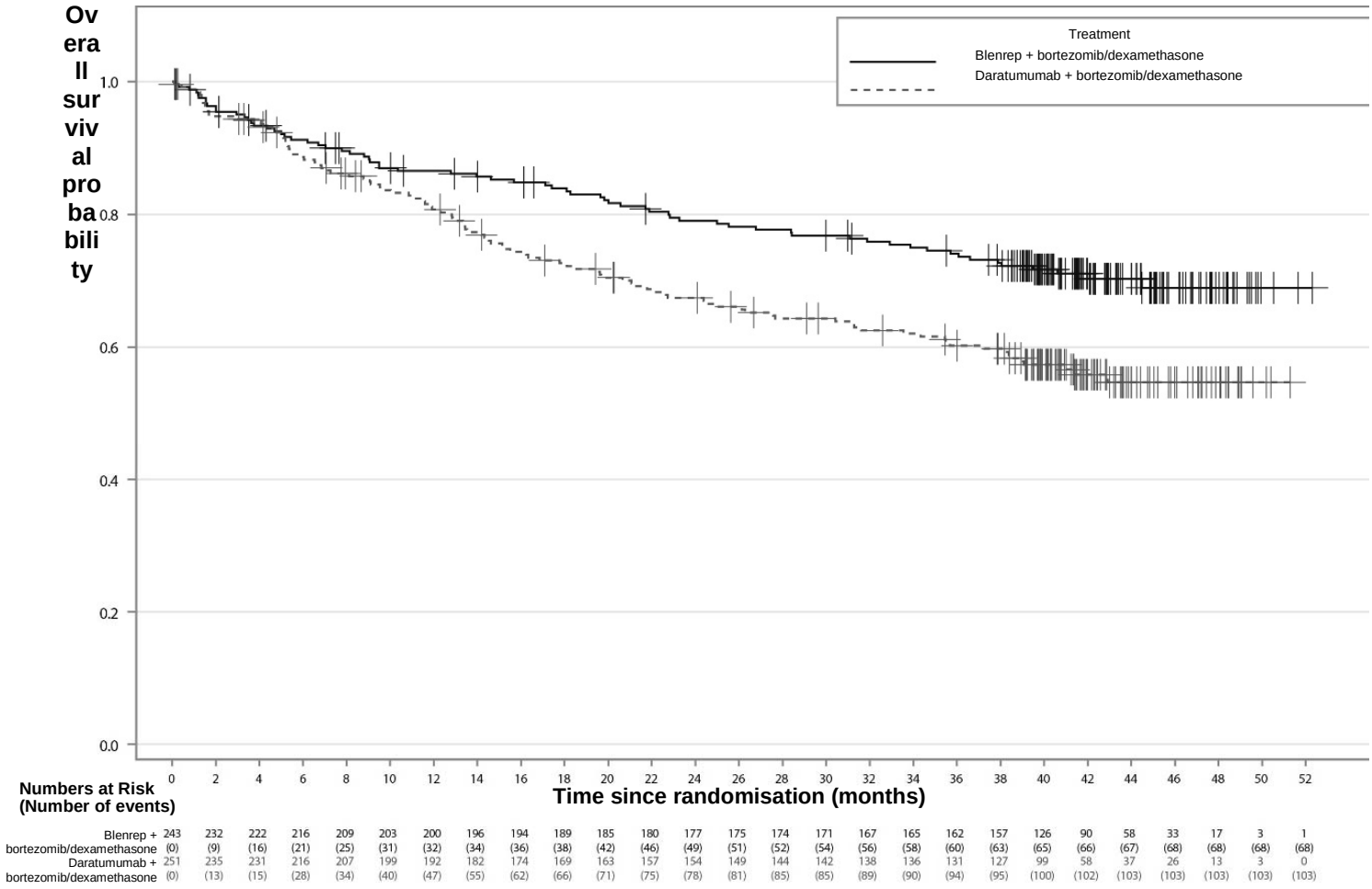
The PFS of BVd was consistent across all pre-specified subgroups including patients with high-risk cytogenetics, and patients exposed or refractory to lenalidomide.

Figure 1: Kaplan-Meier curve of progression-free survival per IRC in



DREAMM-7

Figure 2: Kaplan-Meier curve of overall survival in DREAMM-7



The median duration of follow-up was 29.2 months (Interquartile Range (IQR) 21.7 to 32.5) with a median duration of exposure of 15.9 months (range 0.69 to 40.2 months) in the BVd arm and 27.6 months (IQR 12.3 to 30.4) with a median duration of exposure of 12.9 months (range 0.23 to 40.5 months) in the DVd arm.

Throughout the study, the recommended dose modifications for Blenrep, which included dose delays and reductions, managed adverse reactions and enabled patients to continue treatment. Patient received a median dose of 2.1 mg/kg Blenrep (mean dose: 2.2 mg/kg) with a median of 9 doses (IQR 4, 16), and median dosing interval of 5.7 weeks (IQR 3, 10). For patients who continued treatment after the onset of the

first ≥Grade 2 corneal examination finding, they received a median of 8 additional doses (range: 1 to 52), and 93% (177/190) achieved a response to therapy of partial response or better.

Exposure to Blenrep observed during DREAMM-7 is presented in Table 10.

Table 10: Dose exposure of Blenrep in DREAMM-7

		Time intervals			
		0 to ≤6 months	**>6 to ≤12 months**	**>12 months**	**Overall**
Total number of doses		1133	577	1122	2832
Number of doses administered by dose level (%)	2.5 mg/kg	768 (68)	198 (34)	201 (18)	1167 (41)
	1.9 mg/kg	365 (32)	379 (66)	921 (82)	1665 (59)
Time between doses per patient (weeks)[a]	n	231	130	124	231
	Mean	4.8	6.8	10.9	7.2
	Median (IQR)	3.6 (3, 6)	4.7 (3, 8)	9.5 (5, 15)	5.7 (3, 10)

IQR = Interquartile range.

[a] Intervals for 0 to ≤ 6 months, > 6 to ≤ 12 months, and > 12 months, were calculated either by using days or days converted into months.

DREAMM-8: Blenrep in combination with pomalidomide and dexamethasone

The efficacy and safety of Blenrep in combination with pomalidomide and dexamethasone (BPd) were investigated in a multicentre, randomised (1:1), open-label, Phase 3 study conducted in patients with relapsed and/or refractory MM following treatment with at least one prior line of therapy, including lenalidomide.

In the BPd arm (N = 155), patients received Blenrep 2.5 mg/kg IV once on day 1 in Cycle 1 (28-day Cycle) followed by Blenrep 1.9 mg/kg IV 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/m^2 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). Dexamethasone 20 mg PO was administered on the day of and the day after bortezomib. The dose level of dexamethasone in each arm was reduced by half in patients aged 75 years and older. Treatment in both arms continued until disease progression, unacceptable toxicity, withdrawal of consent, initiation of another anticancer therapy, or end of study/death. 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 multiple myeloma (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 intolerant of, or refractory to bortezomib; or previously treated, or were intolerant to pomalidomide were excluded. Additionally, patients must have been deemed ineligible for prior ASCT, or must have received ASCT at least 100 days prior to first dose of Blenrep, to be considered eligible.

The primary efficacy outcome measures were 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. Baseline demographics and characteristics were similar across both arms. Baseline characteristics for the BPd arm (N = 155) were: median age: 67 years (46% aged 65-74 years and 12% aged 75 years or older); 64% male, 36% female; 86% White, 13% Asian; ISS stage at screening I (60%), II (25%), III (14%); 34% high cytogenetic risk, median number of 1 prior line of therapy (minimum 1, maximum 6); 13% with EMD present; and of those who received treatment (n = 150), ECOG PS 0 (53%), 1 (45%), or 2 (3%). 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. There were 81% of patients refractory to lenalidomide therapy, 26% of patients refractory to proteasome inhibitor therapy, and 23% of patients refractory to anti-CD38 therapy.

Patients treated with Blenrep in combination with pomalidomide and dexamethasone had a statistically significant improvement in PFS in the overall population compared with pomalidomide, bortezomib and dexamethasone. Efficacy results at the time of the first interim analysis (data cut-off 29 January 2024) are presented in Table 11 and Figures 3 and 4.

Table 11: Efficacy results in DREAMM-8

	Blenrep plus pomalidomide and dexamethasone (BPd)[a] N = 155	**Pomalidomide plus bortezomib and dexamethasone (PVd)[a] N = 147**
Primary endpoint		
Progression-free survival (PFS)[b]		
Number (%) of patients with event	62 (40)	80 (54)
Median in months (95% CI)[c, d, e]	NR (20.6, NR)	12.7 (9.1, 18.5)
Hazard ratio (95% CI)[f]	0.52 (0.37, 0.73)	
p-value[g]	<0.001	
Probability of PFS at 12 months, % (95% CI)[h]	71 (63, 78)	51 (42, 60)

	Blenrep plus pomalidomide and dexamethasone (BPd)[a] N = 155	Pomalidomide plus bortezomib and dexamethasone (PVd)[a] N = 147
Secondary endpoints		
Overall survival (OS)		
Number (%) of patients with event	49 (32)	56 (38)
Median in months (95% CI)[c]	NR (33, NR)	NR (25.2, NR)
Hazard ratio (95% CI)[f]	0.77 (0.53, 1.14)	
Probability of OS at 12 months, % (95% CI)[h]	83 (76, 88)	76 (68, 82)
Duration of response (DOR)[b, k]		
Number of responders	120	106
Number (%) of responders: follow-up ongoing[e]	66 (55)	33 (31)
Median in months (95% CI)[c]	NR (24.9, NR)	17.5 (12.1, 26.4)
Minimal residual disease (MRD) negativity rate[b, i, j]		
Percent of patients (95% CI)	23.9 (17.4, 31.4)	4.8 (1.9, 9.6)
Overall response rate (ORR)[b, k, l], % (95% CI)	77 (70, 83.7)	72 (64.1, 79.2)
Stringent complete response (sCR), n (%)	14 (9)	4 (3)
Complete response rate (CRR), n (%)	48 (31)	20 (14)
Very good partial response (VGPR), n (%)	37 (24)	32 (22)
Partial response (PR), n (%)	21 (14)	50 (34)
Median time to response (TTR) in months (minimum, maximum)[b]	1.07 (0.9, 9.3)	1.05 (0.7, 11.2)
Median time to best response in months (min, max)[b]	5.59 (0.9, 26.1)	2.5 (0.7, 25.7)
PFS 2		
Number (%) of patients with event	56 (36)	73 (50)
Median in months (95% CI)[c]	NR (33, NR)	22.4 (13.8, NR)
Hazard ratio (95% CI)[f]	0.61 (0.43, 0.86)	

CI = Confidence interval; NR = Not reached.

[a] Efficacy data are based on the intent-to-treat (ITT) population, except DOR which is based on responders only.

[b] Response was based on IRC per IMWG criteria.

[c] By Brookmeyer and Crowley method.

[d] Median follow-up of 21.8 months.

[e] At the time of the data cut-off (29 JAN 2024).

[f] Based on stratified Cox regression model.

[g] One-sided p-value based on stratified log-rank test.

[h] By Kaplan-Meier method.

[i] For patients with a complete response or better.

[j] Assessed by NGS at 10-5 threshold.

[k] For patients with a partial response or better.

[l] ORR: sCR+CR+VGPR+PR.

The PFS of BPd was consistent across all pre-specified subgroups including patients with high-risk cytogenetics, those refractory to lenalidomide, or refractory to anti-CD38 agents.

Figure 3: Kaplan-Meier curve of progression-free survival per IRC in DREAMM-8

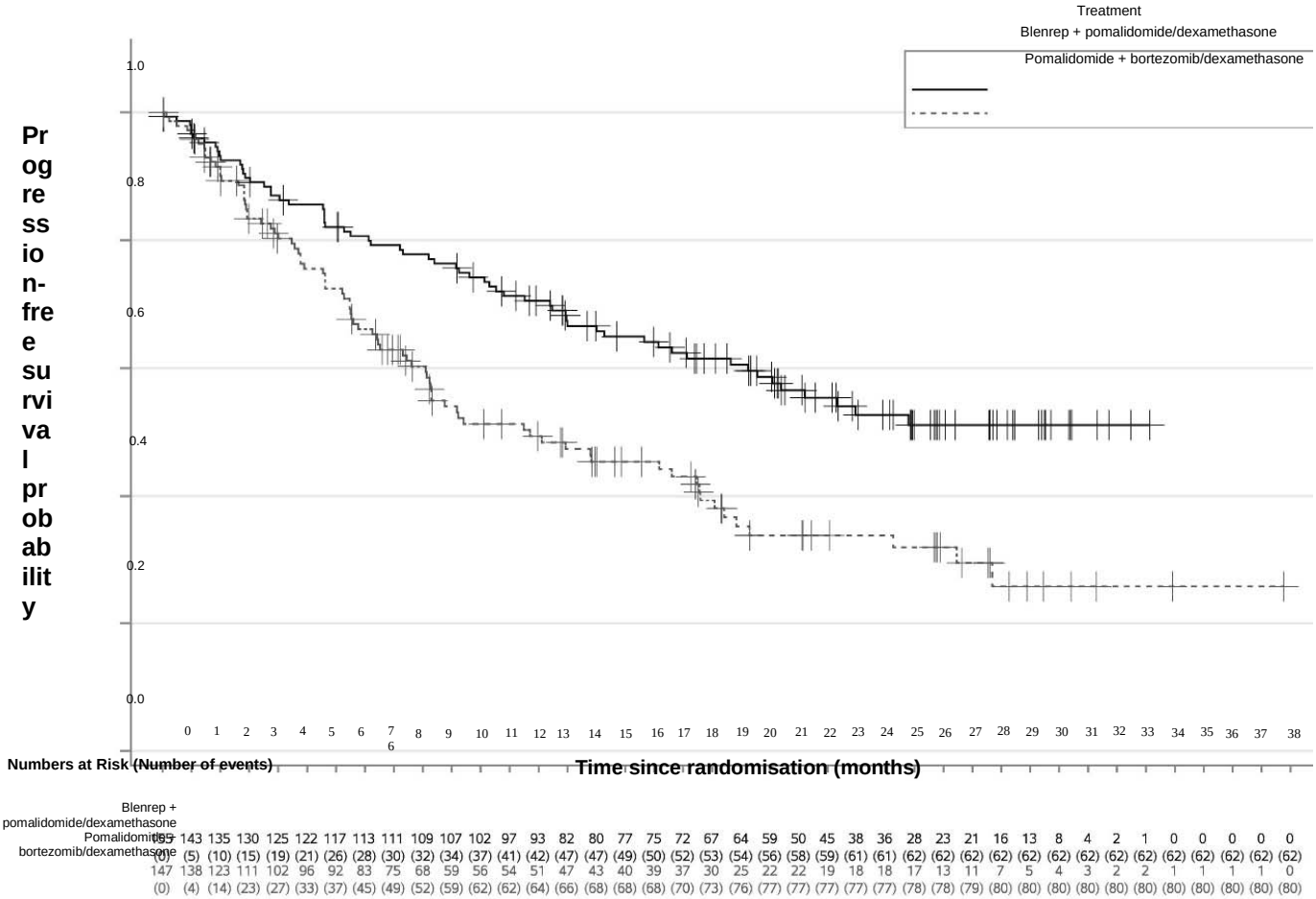
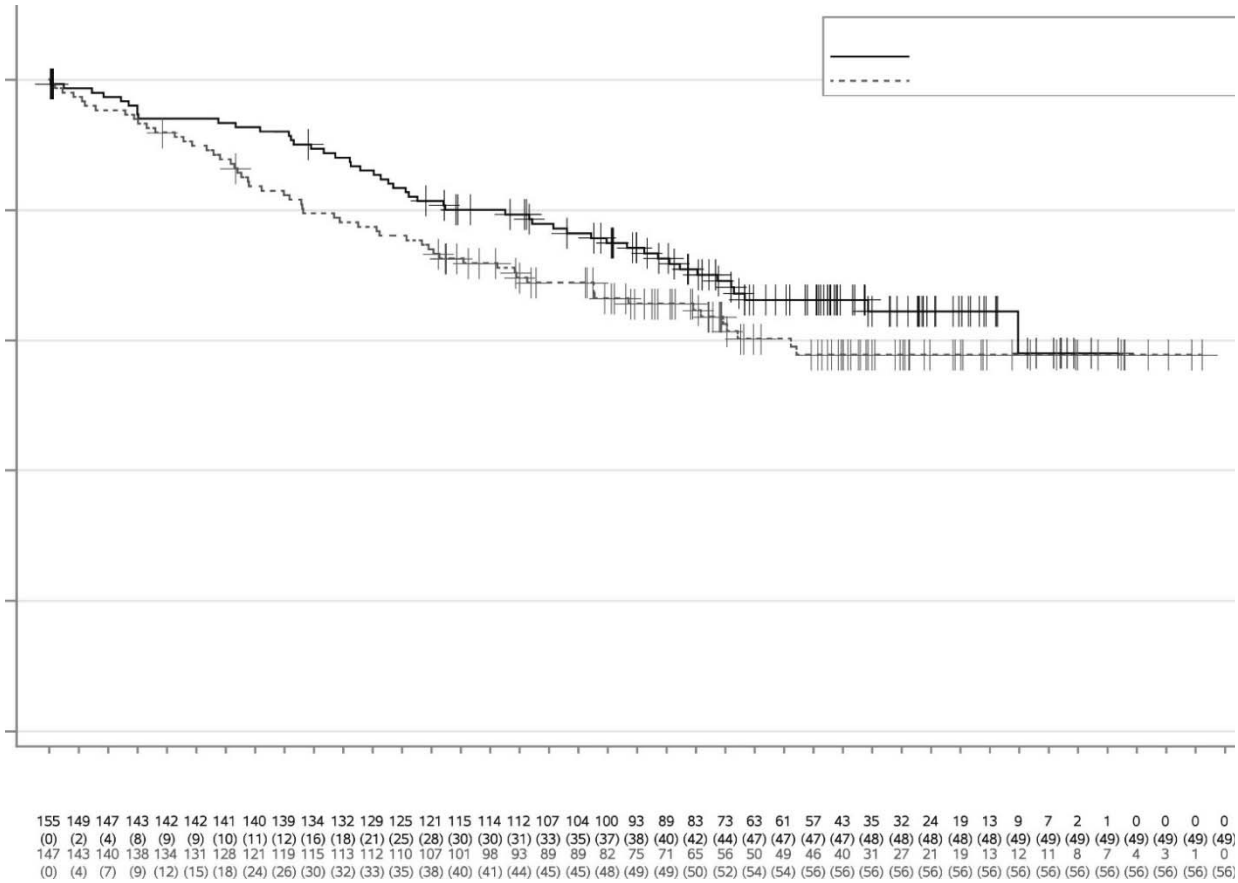


Figure 4: Kaplan-Meier curve of overall survival in DREAMM-8



The median duration of follow-up was 22.4 months (IQR 13.8 to 27.8) with a median duration of exposure of 16.5 months (range 0.92 to 35.1 months) in the BPd arm and 20.5 months (IQR 11.2 to 27.3) with a median duration of exposure of 8.5 months (range 0.26 to 39.9 months) in the PVd arm.

Throughout the study, the recommended dose modifications for Blenrep, which included dose delays and reductions, managed adverse reactions and enabled patients to continue treatment. Patients received a median dose of 2 mg/kg (mean dose:2 mg/kg) with a median of 6 doses of Blenrep (IQR 4, 10), and median dosing interval of 8.7 weeks (IQR 5, 13). For patients who continued treatment after the onset of the first ≥Grade 2 corneal examination finding, they received a median of 5 additional doses (range: 1 to 21), and 88% (106/120) achieved a response to therapy of partial response or better.

Exposure to Blenrep observed during DREAMM-8 is presented in Table 12.

Table 12: Dose exposure of Blenrep in DREAMM-8

		Time intervals			
		0 to ≤6 months	**>6 to ≤12 months**	**>12 months**	**Overall**
Total number of doses		570	242	286	1098
Number of doses administered by dose level, (%)	2.5 mg/kg	151 (26)	–	–	151 (14)
	1.9 mg/kg	415 (73)	235 (97)	267 (93)	917 (84)
	1.4 mg/kg	4 (<1)	7 (3)	19 (7)	30 (3)
Time between doses per patient (weeks)[a]	n	129	79	77	142
	Mean	5.3	11.9	14.2	9.5
	Median (IQR)	4.1 (4,5)	11.8 (5,16)	14.1 (10,18)	8.7 (5,13)

IQR = Interquartile range.

a. Intervals for 0 to ≤ 6 months, > 6 to ≤ 12 months, and > 12 months, were calculated either by using days or days converted into months.

Paediatric population

The licensing authority has waived the obligation to submit the results of studies with Blenrep in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Maximum concentration for belantamab mafodotin ADC occurred at or shortly after the end of infusion while cys-mcMMAF concentrations peaked ~24 hours after dosing.

Table 13 describes the pharmacokinetics of belantamab mafodotin for 2.5 mg/kg doses on Cycle 1 Day 1 at the end of the first 3-week interval.

Table 13: Belantamab mafodotin pharmacokinetics at the end of the first 3-week interval[a]

	AUC[b]	**C_{avg21}**	**C_{max}**	**C_{tau}**
ADC (%)	3950 µg•h/mL (30.6)	7.83 µg/mL (30.6)	43.7 µg/mL (22.1)	2.03 µg/mL (62.5)
cys-mcMMAF (%)	94.2 ng•h/mL (42.3)	0.243 ng/mL (42.4)	0.976 ng/mL (45.3)	–

ADC = antibody drug conjugate; AUC = Area under the curve; C_{avg21} = belantamab mafodotin average concentration over 21 days; C_{max} = maximum plasma concentration; C_{tau} = concentration at the end of a dosing interval.

a Data presented as geometric mean (%CV), based on population PK models.

b AUC for ADC is $AUC_{(0\text{-}21days)}$ and $AUC_{(0\text{-}7days)}$ for cys-mcMMAF.

Accumulation of belantamab mafodotin (ADC) was minimal to moderate as observed in clinical studies with a every 3 weeks dosing regimen.

Distribution

In vitro, cys-mcMMAF exhibited low protein binding, (70% unbound at a concentration of 5 ng/mL) in human plasma in a concentration-dependent manner.

Based on the population PK analysis, the geometric mean (geometric CV%) for steady-state volume of distribution of belantamab mafodotin was 10.8 L (22%).

Biotransformation

The monoclonal antibody portion of belantamab mafodotin is expected to undergo proteolysis to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Cys-mcMMAF had limited metabolic clearance in human hepatic S9 fraction incubation studies.

Drug interactions

In vitro studies demonstrated that cys-mcMMAF is not an inhibitor, an inducer, or a sensitive substrate of cytochrome P450 enzymes, but is a substrate of organic anion transporting polypeptide (OATP)1B1 and OATP1B3, multidrug resistance-associated protein (MRP)1, MRP2, MRP3, bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp).

Effect of other drugs on belantamab mafodotin
A population pharmacokinetic (PK) analysis was used to assess combination therapy on belantamab mafodotin ADC and cys-mcMMAF PK. Combination therapies with bortezomib, lenalidomide, pomalidomide and/or dexamethasone, did not affect the PK of ADC and cys-mcMMAF.

Effect of belantamab mafodotin on other drugs
For combination therapies with lenalidomide, bortezomib, and pomalidomide, PK profiles were evaluated in clinical trials and compared with historical data. The observed PK for lenalidomide, bortezomib, and pomalidomide suggested lack of impact of belantamab mafodotin on the PK of the included combination therapies.

Elimination

Based on the population PK analysis, the geometric mean (geometric CV%) belantamab mafodotin (ADC) initial systemic clearance (CL) was 0.901 L/day (40%), and the elimination half-life was 13 days (26%). Following treatment, steady-state CL was 0.605 L/day (43%) or approximately 33% lower than initial systemic CL with an elimination half-life of 17 days (31%).

The fraction of intact cys-mcMMAF excreted in urine was not substantial (approximately 18% of the dose) after Cycle 1 dose, with no evidence of other MMAF-related metabolites.

Linearity/non-linearity

Belantamab mafodotin exhibits dose-proportional pharmacokinetics over the recommended dose range with a reduction in clearance over time.

Special populations

Elderly patients (≥65 years old)
Based on a population of patients aged 32 to 89 years, age was not a significant covariate in population pharmacokinetics analyses.

Renal impairment
In patients with severe renal impairment (eGFR: 15 – 29 mL/min), belantamab mafodotin C_{max} decreased by 23% and $AUC_{(0\text{-}tau)}$ decreased by 16% compared with patients with normal renal function or mild renal impairment (eGFR ≥60 ml/min). For cys-mcMMAF, C_{max} and $AUC_{(0\text{-}168h)}$ decreased by 56% and 44%, respectively compared to patients with normal renal function or mild renal impairment. Renal function (eGFR: 12 to 150 mL/min) was not a significant covariate in population pharmacokinetic analyses that included patients with normal renal function, mild (60≤eGFR<90 mL/min), moderate (30≤eGFR<60 mL/min), or severe renal impairment (eGFR<30 mL/min not requiring dialysis).

No impact on belantamab mafodotin PK was observed for patients with end stage renal disease (eGFR<15 mL/min requiring dialysis).

Belantamab mafodotin is not expected to be removed via dialysis due to its molecular size. While free cys-mcMMAF may be removed via dialysis, cys-mcMMAF systemic exposure is very low and has not been shown to be associated with efficacy or safety based on exposure-response analysis.

Hepatic impairment
No formal studies have been conducted in patients with hepatic impairment. Hepatic function, as per National Cancer Institute Organ Dysfunction Working Group classification, was not a significant covariate in population pharmacokinetic analyses that included patients with normal hepatic function, mild (total bilirubin >ULN to ≤1.5 × ULN and any AST or total bilirubin ≤ ULN with AST >ULN) or moderate hepatic impairment (total bilirubin >1.5 x ULN to ≤3 × ULN and any AST).

Body weight
Body weight (37 to 170 kg) was a significant covariate in population pharmacokinetic analyses, but this effect was not clinically relevant with the weight-proportional dosing regimen.

5.3 Preclinical safety data

Animal toxicology and/or pharmacology
In non-clinical studies, the principal adverse findings (directly related to belantamab mafodotin) in the rat and monkey, at exposures ≥1.2 times of the recommended clinical dose of 2.5 mg/kg, were elevated liver enzymes sometimes associated with hepatocellular necrosis at ≥10 and ≥3 mg/kg, respectively, and increases in alveolar macrophages associated with eosinophilic material in the lungs at ≥3 mg/kg (rat only). Most findings in animals were related to the cytotoxic drug conjugate, the histopathological changes observed in the testes and lungs, were not reversible in rats.

Single cell necrosis in the corneal epithelium and/or increased mitoses of corneal epithelial cells was observed in rat and rabbit. Inflammation of the corneal stroma correlating with superficial haze and vascularisation was observed in rabbits. Belantamab mafodotin was taken up into cells throughout the body by a mechanism unrelated to BCMA receptor expression on the cell membrane.

Carcinogenesis/mutagenesis
Belantamab mafodotin was genotoxic in an *in vitro* micronucleus screening assay in human lymphocytes, consistent with the pharmacological effect of cys-mcMMAF-mediated disruption of microtubules causing aneuploidy.

No carcinogenicity or definitive genotoxicity studies have been conducted with belantamab mafodotin.

Reproductive toxicology
No animal studies have been performed to evaluate the potential effects of belantamab mafodotin on reproduction or development. The mechanism of action is to kill rapidly dividing cells which would affect a developing embryo which has rapidly dividing cells. There is also a potential risk of heritable changes via aneuploidy in female germ cells.

Effects on male and female reproductive organs have been observed in animals at doses of ≥10 mg/kg, which is approximately 4 times the exposure of the clinical dose. Luteinised nonovulatory follicles were seen in the ovaries of rats after 3 weekly doses. Findings in male reproductive organs that were adverse and progressed following repeat dosing in rat, included marked degeneration/atrophy of seminiferous tubules that generally did not reverse following dosing cessation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium citrate dihydrate
Citric acid monohydrate
Trehalose dihydrate
Disodium edetate dihydrate
Polysorbate 80 (E433)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

48 months.

Reconstituted solution

The reconstituted solution can be stored for up to 4 hours at room temperature (20ºC to 25ºC) or stored in a refrigerator (2°C to 8°C) for up to 4 hours. Do not freeze.

Diluted solution

From a microbiological point of view, the product should be used immediately.

If not used immediately, the diluted solution can be stored in a refrigerator (2ºC to 8ºC) prior to administration for up to 24 hours. Do not freeze. If refrigerated, allow the diluted solution to equilibrate to room temperature prior to administration.

The diluted infusion solution may be kept at room temperature (20ºC to 25ºC) for a maximum of 6 hours (including infusion time).

6.4 Special precautions for storage

Store in a refrigerator (2ºC to 8ºC).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 glass vial sealed with bromobutyl rubber stopper and aluminium overseal with a plastic removable cap containing 100 mg powder.

Pack size: 1 vial

6.6 Special precautions for disposal

Preparation of solution for infusion

Blenrep is a cytotoxic anticancer medicinal product. Proper handling procedures must be followed. Use aseptic technique for the reconstitution and dilution of the dosing solution.

Calculate the dose (mg), total volume (mL) of solution required and the number of vials needed based on the patient's actual body weight (kg).

Reconstitution

1. Remove the vial(s) of Blenrep from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature.
2. Reconstitute each 100 mg vial with 2 mL of water for injection to obtain a concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. DO NOT SHAKE.

3. Visually inspect the reconstituted solution for particulate matter and discoloration. The reconstituted solution should be a clear to opalescent, colourless to yellow to brown liquid. Discard the reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

Dilution

1. Withdraw the necessary volume for the calculated dose from each vial.
2. Add the necessary amount of Blenrep to the infusion bag containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Mix the diluted solution by gentle inversion. The final concentration of the diluted solution should be between 0.2 mg/mL to 2 mg/mL. DO NOT SHAKE.
3. Discard any unused reconstituted solution of Blenrep left in the vial.

If the diluted solution is not used immediately, it may be stored in a refrigerator (2ºC to 8ºC) for up to 24 hours prior to administration. If refrigerated, allow the diluted solution to equilibrate to room temperature prior to administration. The diluted solution may be kept at room temperature (20ºC to 25ºC) for a maximum of 6 hours (including infusion time).

Administration

1. Administer the diluted solution by intravenous infusion over a minimum of 30 minutes using an infusion set made of polyvinyl chloride or polyolefin.
2. Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulfone (PES) based filter is recommended.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline UK Limited
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