Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Belantamab mafodotin

RMP version to be assessed as part of this application	
RMP Version number	2
Data lock point for this RMP	21 June 2019
Date of final sign off:	Please refer to QPPV signature below

Rationale for submitting an updated RMP:

To update the Specific Obligation due dates for Studies 205678 (DREAMM-2) and 207495 (DREAMM-3).

Summary of significant changes in this RMP:

PART	MODULE	Changes made in EU-RMP version 2
All Parts		The 205678 (DREAMM-2) final study report submission date was updated to Feb 2023. The 207495 (DREAMM-3) study report submission date was updated to Q1 2023. Updated telephone number for QPPV

Other RMP versions under evaluation

Not applicable

RMP Version number	Submitted on	Procedure number
Not applicable		

Details of the currently approved RMP Not applicable		
Version number	Approved with procedure	Date of approval (opinion date)
1.0	EMEA/H/C/004935/0000	23 July 2020

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Belantamab mafodotin
Pharmacotherapeutic group(s) (ATC Code)	L01XC39
Marketing Authorisation Holder/ Applicant	GlaxoSmithKline (Ireland) Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	BLENREP
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Belantamab mafodotin is an antibody-drug conjugate (ADC) that contains belantamab, an afucosylated, humanized monoclonal IgG1k antibody specific for B-cell maturation agent (BCMA), produced using recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary) that is conjugated with maleimidocaproyl monomethyl auristatin F (MMAF).
	Summary of mode of action (MoA): Belantamab mafodotin employs distinct MoAs including antibody-drug conjugate (ADC), antibody-dependent cellular cytotoxicity and phagocytosis (ADCC/ADCP), and immunogenic cell death (ICD) markers. This could enable belantamab mafodotin to deliver anti-tumour activity towards both dividing and non-dividing tumour cells and associate the tumour cell kill with an adaptive

	immune response, potentially providing enhanced efficacy over existing approved therapies.
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD)
Indication(s) in the EEA	Current: *BLENREP* is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.
Dosage in the EEA	Current: The recommended dose of belantamab mafodotin is 2.5 mg/kg administered intravenously once every 21 days. It is recommended that treatment should be continued until disease progression or unacceptable toxicity.
Pharmaceutical form(s) and strengths	Current: Powder for concentrate for solution for infusion. Each vial contains 100 mg of lyophilised powder in a single-dose vial for reconstitution.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations

ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
ALT	Alanine aminotransferase
ASIR	Age-standardized incident rate
ASMR	Age-standardized mortality rate
AST	Aspartate aminotransferase
AUC	Area under curve
BCMA	Anti-B-cell maturation agent
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CSI	Core Safety Information
CK	Creatine kinase
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DE	Dose Escalation
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EV	EudraVigilance
GDS	Global Data Sheet
GGT	Gamma-glutamyltransferase
GRMP	Global Risk Management Plan
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDAC	Histone deacetylase
ICH	International Council for Harmonisation
IgG1	Immunoglobulin G1
IRC	Independent Review Committee
IRR	Infusion-related reaction
ISS	Integrated Summary of Safety
IV	Intravenous
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
mc	Maleimidocaproyl
MM	Multiple Myeloma
MEC	Microcyst-like epithelial changes
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mode of action
MRD	Minimal Residual Disease
MRP	Multidrug resistance-associated proteins
OATP	Organic anion-transporting polypeptides
OL	Open label
ORR	Overall response rate

PBRER	Periodic Benefit Risk Evaluation Report
P-gp	P-glycoprotein
PI	Proteasome inhibitor
PK	Pharmacokinetics
Pom/Dex	Pomalidomide/Dexamethasone
PR	Partial response
PSUR	Periodic Safety Update Report
PT	Preferred Term
RHD	Recommended Human Dose
R-ISS	Revised international staging system
RRMM	Relapsed refractory multiple myeloma
SAE	Serious Adverse Event
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SOC	System Organ Class
TFUQ	Targeted Follow-up Questionnaire
UK	United Kingdom
US	United States
VGPR	Very Good Partial Response

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
BLENREP	None

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Indication

BLENREP is indicated as monotherapy for treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose diease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Incidence

According to GLOBOCAN, the total number of incident cases of MM worldwide in 2018 was estimated to be 159,985. The annual global age-standardized incidence rate (ASIR) of MM in 2018 was 1.7 per 100,000 [Ferlay, 2018]. Due to the difference of diagnostic techniques and awareness of MM, the incidence varies significantly by geographic regions. For 2018, the annual ASIR of MM was estimated to be 2.9 per 100,00 in Europe and 4.1 per 100,000 in the US (Table 2) [Ferlay, 2018].

Table 2 Incidence of MM in 2018, across key geographic regions and countries

	Number of incident cases			Crude incidence rate (per 100,000)			ASIR (per 100,000)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
Global*	159,985	89,897	70,088	2.1	2.3	1.9	1.7	2.1	1.4
Europe**	48,297	26,336	21,961	6.5	7.3	5.7	2.9	3.6	2.3
France	6,205	3,537	2,668	9.5	11.0	8.0	3.8	5.0	2.8
Germany	7,131	3,958	3,173	8.7	9.8	7.6	3.2	3.9	2.6
Italy	6,034	3,338	2,696	10.2	11.5	8.9	3.7	4.6	3.0
Spain	3,261	1,855	1,406	7.0	8.2	5.9	2.8	3.5	2.2
UK	6,757	3,899	2,858	10.1	11.9	8.5	4.3	5.4	3.4
US	25,962	14,656	11,306	7.9	9.1	6.9	4.1	5.0	3.3
Japan	6,313	3,353	2,960	5.0	5.4	4.5	1.5	1.8	1.2
China	20,066	11,781	8,285	1.4	1.6	1.2	0.9	1.1	0.75

ASIR = Age-standardised incidence rate, UK = United Kingdom, US = United States

*Global estimates were based on 185 countries across the world.

**Estimates for Europe were based on following countries: Belarus, Bulgaria, Czechia, Hungary, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia, Ukraine, Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, UK, Albania, Bosnia and Herzegovina, Croatia, Greece, Italy, Malta, Montenegro, Portugal, Serbia, Slovenia, Spain, the former Yugoslav Republic of Macedonia, Austria, Belgium, France, Germany, Luxembourg, Switzerland, the Netherlands, and Cyprus.

Note: Standard population for age-standardisation was the World Standard Population.

Source: Ferlay, 2018

The incidence of MM in 2018 in 28 European countries (EU-28) is listed in Table 3.

Table 3 Incidence of MM in 2018, in EU-28

	Number of Incident Cases			Crude Incident Rate (per 100,000)			ASIR (per 100,000)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
Austria	562	302	260	6.4	7.0	5.8	2.7	3.2	2.2
Belgium	1,029	661	368	8.9	11.6	6.3	4.1	5.6	2.7
Bulgaria	160	70	90	2.3	2.0	2.5	1.1	1.1	1.1
Croatia	229	131	98	5.5	6.5	4.5	2.4	3.1	1.8
Cyprus	57	32	25	4.8	5.4	4.2	2.7	3.2	2.3
Czech Republic	566	312	254	5.3	6.0	4.7	2.4	3.0	1.9
Denmark	374	209	165	6.5	7.3	5.7	2.8	3.3	2.3
Estonia	80	36	44	6.1	5.9	6.3	2.7	3.2	2.3
Finland	471	250	221	8.5	9.1	7.9	3.2	3.8	2.7
France	6,205	3,537	2,668	9.5	11.0	8.0	3.8	5.0	2.8
Germany	7,131	3,958	3,173	8.7	9.8	7.6	3.2	3.9	2.6
Greece	809	424	385	7.3	7.7	6.8	3.0	3.5	2.6
Hungary	449	230	219	4.6	5.0	4.3	2.2	2.7	1.8
Ireland	325	194	131	6.8	8.1	5.4	3.7	4.7	2.8
Italy	6,034	3,338	2,696	10.2	11.5	8.9	3.7	4.6	3.0
Latvia	100	46	54	5.2	5.2	5.2	2.3	2.9	2.0
Lithuania	178	91	87	6.2	6.9	5.6	2.9	3.8	2.3
Luxembourg	38	19	19	6.4	6.4	6.5	3.1	3.5	2.8
Malta	30	16	14	6.9	7.4	6.5	2.9	3.4	2.5
Poland	2,051	1,038	1,013	5.4	5.6	5.1	2.5	3.1	2.1
Portugal	1,034	495	539	10.0	10.2	9.9	4.0	4.2	3.9
Romania	652	336	316	3.3	3.5	3.1	1.7	2.0	1.5
Slovakia	371	175	196	6.8	6.6	7.0	3.5	3.9	3.2
Slovenia	145	79	66	7.0	7.6	6.3	2.9	3.5	2.5
Spain	3,261	1,855	1,406	7.0	8.2	5.9	2.8	3.5	2.2
Sweden	818	475	343	8.2	9.5	6.9	3.5	4.3	2.8
The Netherlands	1,185	709	476	6.9	8.3	5.5	3.0	3.8	2.3
United Kingdom	6,757	3,899	2,858	10.1	11.9	8.5	4.3	5.4	3.4

ASIR = Age-standardised incidence rate
Note: Standard population for age-standardisation was the World Standard Population.
Source: Ferlay, 2018

Prevalence

The global one-, three-, and five-year partial prevalence estimates of MM in 2018 were reported as 1.5, 3.6, and 4.9 per 100,000, respectively [Ferlay, 2018]. Similar to MM incidence, the MM prevalence is observed to be higher in the developed nations than in developing countries. In Europe, the estimated one-, three- and five-year partial prevalence of MM in 2018 were reported as 5, 12 and 16.2 per 100,000, respectively (Table 4) [Ferlay, 2018].

Table 4 One-, three-, and five-year partial prevalence of MM in 2018, across key geographic regions and countries

	One-year Prevalence		Three-year Prevalence		Five-year Prevalence	
	Number of Prevalent Cases	Prevalence per 100,000	Number of Prevalent Cases	Prevalence per 100,000	Number of Prevalent Cases	Prevalence per 100,000
Global*	115,169	1.5	277,250	3.6	376,005	4.9
Europe**	37,192	5.0	89,103	12.0	120,391	16.2
France	4,741	7.3	11,306	17.3	15,206	23.3
Germany	5,699	6.9	13,602	16.5	18,338	22.3
Italy	4,626	7.8	11,062	18.7	14,917	25.2
Spain	2,466	5.3	5,888	12.7	7,932	17.1
UK	5,286	7.9	12,630	19.0	17,007	25.5
US	21,131	6.5	50,837	15.6	68,821	21.1
China	13,516	1.0	32,743	2.3	44,643	3.1
Japan	4,751	3.7	11,272	8.9	15,100	11.9

UK = United Kingdom, US = United States

*Global estimates were based on 185 countries across the world.

**Estimates for Europe were based on following countries: Belarus, Bulgaria, Czechia, Hungary, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia, Ukraine, Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, UK, Albania, Bosnia and Herzegovina, Croatia, Greece, Italy, Malta, Montenegro, Portugal, Serbia, Slovenia, Spain, the former Yugoslav Republic of Macedonia, Austria, Belgium, France, Germany, Luxembourg, Switzerland, the Netherlands, and Cyprus.

Note: Standard population for age-standardisation was the World Standard Population.

Source: Ferlay, 2018

Partial prevalence of MM in 2018 in EU-28 is listed in Table 5. Partial prevalence refers to the number of MM patients being alive at a specific date.

Table 5 One-, three- and five-year prevalence of MM in 2018, EU-28

	One-year Prevalence (per 100,000)			Three-year Prevalence (per 100,000)			Five-year Prevalence (per 100,000)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
Austria	5.1	5.5	4.6	12.0	13.0	10.9	16.2	17.5	14.9
Belgium	7.0	9.1	5.0	16.9	21.8	12.1	22.8	29.3	16.4
Bulgaria	1.7	1.5	1.9	4.0	3.6	4.5	5.5	4.9	6.1
Croatia	4.0	4.7	3.4	9.7	11.4	8.2	13.1	15.3	11.1
Cyprus	3.7	4.0	3.4	8.6	9.4	7.7	11.9	13.1	10.8
Czech Republic	4.2	4.7	3.7	10.1	11.2	8.9	13.6	15.2	12.1
Denmark	5.3	5.9	4.7	12.7	14.2	11.2	17.1	18.9	15.3
Estonia	4.7	4.6	4.8	11.2	10.8	11.7	15.3	14.7	15.9
Finland	6.5	7.1	6.1	15.7	16.8	14.7	21.1	22.5	19.8
France	7.3	8.5	6.1	17.3	20.2	14.5	23.3	27.2	19.6
Germany	6.9	7.8	6.1	16.5	18.5	14.6	22.3	24.8	19.8
Greece	5.5	5.8	5.2	13.1	13.8	12.4	17.7	18.6	16.8
Hungary	3.5	3.8	3.2	8.5	9.1	7.9	11.5	12.2	10.8
Ireland	5.5	6.6	4.5	13.2	15.7	10.7	17.7	21.0	14.3
Italy	7.8	8.8	6.8	18.7	21.0	16.4	25.2	28.2	22.2
Latvia	3.9	3.7	4.0	9.3	9.2	9.3	12.5	12.3	12.7
Lithuania	4.7	5.3	4.3	11.4	12.6	10.4	15.4	16.9	14.2

Luxembourg	5.3	5.1	5.4	12.0	11.8	12.3	15.6	15.5	15.7
Malta	5.3	6.0	4.7	12.5	12.9	12.1	17.1	18.4	15.8
Poland	4.1	4.3	3.9	9.8	10.3	9.4	13.3	13.9	12.7
Portugal	7.4	7.3	7.5	17.8	17.5	18.1	24.1	23.5	24.6
Romania	2.4	2.6	2.3	5.9	6.2	5.6	8.0	8.4	7.6
Slovakia	5.2	5.1	5.3	12.5	12.0	12.9	16.9	16.2	17.5
Slovenia	5.5	6.0	5.0	13.1	14.3	11.9	17.9	19.3	16.5
Spain	5.3	6.1	4.5	12.7	14.5	10.9	17.1	19.5	14.7
Sweden	6.6	7.6	5.5	15.7	18.0	13.3	21.1	24.2	18.1
The Netherlands	5.7	6.7	4.6	13.6	16.1	11.0	18.3	21.7	15.0
United Kingdom	7.9	9.2	6.7	19.0	21.9	16.1	25.5	29.4	21.7

Note: Standard population for age-standardisation was the World Standard Population.
Source: Ferlay, 2018

SI.1.1 Demographics of the population in the proposed indication and risk factors for the disease:

MM incidence and prevalence by gender in EU-28 countries is shown in Table 5. MM incidence increased with age, as 81.6% of the MM cases diagnosed in 2018 were estimated to be 60 years of age or older. Age-standardized incidence rate of MM among males is 50% higher than females in Europe for 2018. 30.2% of all incident cases in 2018 worldwide were from Europe [Ferlay, 2018]. The five major EU countries (France, Germany, Italy, Spain, UK) contributed 60.8% of the MM incident cases in Europe for 2018 [Ferlay, 2018].

SI.1.2 The main existing treatment options

Recent development of effective novel agents offers several improved treatment options for RRMM patients. Treatment selection depends on several disease- and patient-related factors, as well as prior treatment type [Laubach, 2016]. Current therapy recommendations at first relapse in patients who had not previously received a novel agent include treatment with a proteasome inhibitor (PI)-based regimen, or immunomodulatory agent-based regimen, or a combination of both. If patients were previously treated with either a PI- or immunomodulatory agent-based regimen, the alternative regimen is recommended at first relapse. In general, doublet or triplet regimens are preferred over single agents given improved response rates and disease control without additional toxicity [Nijhof, 2018]. Targeted therapies are not yet standard of care in RRMM patients, but potential options are emerging.

Commonly utilized backbone regimens in Europe to which novel agents are being added include lenalidomide and dexamethasone or bortezomib and dexamethasone [Moreau, 2017]. Monoclonal antibodies, e.g. elotuzumab and daratumumab, are used in combination with both backbone regimens. Elotuzumab, combined with lenalidomide and dexamethasone, demonstrated median PFS of 19.4 months compared to 14.9 months for lenalidomide and dexamethasone alone [Lonial, 2015]. Triplet regimens including daratumumab, with lenalidomide and dexamethasone and with bortezomib and dexamethasone, have demonstrated superiority to both doublet regimens [Dimopoulos, 2016; Mateos, 2018; Palumbo, 2016]. Daratumumab monotherapy was approved by the EMA in 2016 for RRMM patients with at least three prior lines of therapy, including a PI and an immunomodulatory agent, or who are double refractory to a PI and immunomodulatory agent.

The addition of PI, carfilzomib, to lenalidomide and dexamethasone demonstrated improved efficacy over the doublet regimen (ORR 87% vs. 67%; median PFS 26.3 vs. 17.6 months) [Stewart, 2015]. Carfilzomib and dexamethasone have also shown clinical benefit over bortezomib and dexamethasone (ORR 77% vs. 63%; median PFS 18.7 vs. 9.4 months) [Dimopoulos, 2016]. In 2015, carfilzomib was approved by the EMA as a monotherapy for RRMM patients previously treated with lenalidomide and bortezomib, as well as in combination with lenalidomide and dexamethasone and dexamethasone alone in MM patients with at least one prior therapy in 2016. The first oral PI, ixazomib, used in combination with lenalidomide and dexamethasone, has shown superiority over the doublet regimen in RRMM patients (ORR 78% vs. 72%; median PFS 20.6 vs. 14.7 months) [Moreau, 2016]. It was approved by the EMA in 2016 for patients with at least one prior line of therapy.

Combination therapy of bortezomib, dexamethasone, and the histone deacetylase (HDAC) inhibitor panobinostat was approved by the EMA in 2015 for RRMM patients who received two prior regimens, including bortezomib and an immunomodulatory agent. The triplet combination has demonstrated promising clinical results, compared to bortezomib and dexamethasone, and a tolerable safety profile [San-Miguel, 2014].

Pomalidomide, an immunomodulatory agent, was approved by the EMA in 2013 in combination with dexamethasone in RRMM patients who had received at least two prior lines of treatment, including lenalidomide and bortezomib. A phase III clinical trial comparing pomalidomide and low-dose dexamethasone with high-dose dexamethasone in RRMM patients demonstrated significantly improved median PFS (4.0 vs. 1.9 months) and OS (12.7 vs. 8.1 months) (Miguel et al., 2013). Adding cyclophosphamide to pomalidomide and dexamethasone contributed to increased response rates and PFS; a phase II clinical trial comparing the pomalidomide, cyclophosphamide and dexamethasone combination with pomalidomide and dexamethasone in RRMM patients reported ORR of 64.7% vs. 38.9% and median PFS of 9.5 vs. 4.4 months [Baz, 2016].

The following relapsed MM treatment algorithm (Figure 1) is based on recommendations from the European Society for Medical Oncology (ESMO) guidelines 2017 [Moreau, 2017]:

Figure 1 Treatment Algorithm for Relapsed Multiple Myeloma

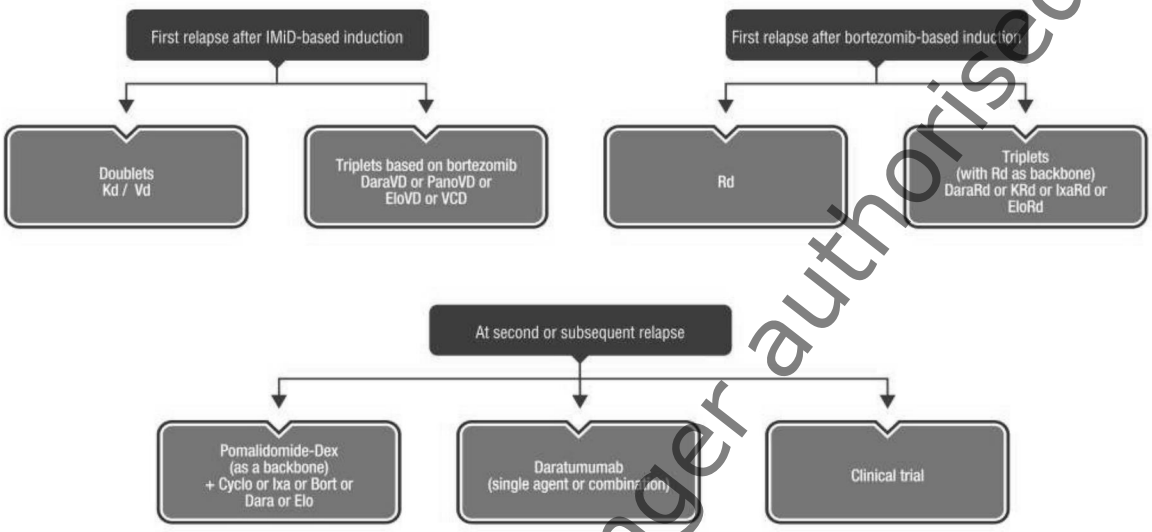


Figure 2. Treatment of relapse.
Bort, bortezomib; Cyclo, cyclophosphamide; Dara, daratumumab; DaraRd, daratumumab, lenalidomide, low dose dexamethasone; DaraVD, daratumumab, bortezomib, dexamethasone; Dex, dexamethasone; Elo, elotuzumab; EloRd, elotuzumab, lenalidomide, low dose dexamethasone; EloVD, elotuzumab, bortezomib, dexamethasone; IMiD, immunomodulatory drug; Ixa, izaxomib; IxaRd, izaxomib, lenalidomide, low dose dexamethasone; Kd, carfilzomib, low dose dexamethasone; KRd, carfilzomib, lenalidomide, low dose dexamethasone; PanoVD, panobinostat, bortezomib, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; Vd, bortezomib, low dose dexamethasone.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

MM is almost always preceded by monoclonal gammopathy of undetermined significance (MGUS), which is an asymptomatic condition characterised by the presence of a monoclonal immunoglobulin (M-protein) in the absence of any clinical signs or symptoms of MM or other lymphoproliferative disorders [Landgren, 2009]. MGUS can progress to smouldering MM, which is another asymptomatic precursor to MM in which the risk of progression to malignant disease in the first five years after diagnosis is much higher, and then to MM requiring treatment [Kyle 2007, Rajkumar, 2014]. The revised international staging system (R-ISS) of MM depends on the measurement of serum albumin, levels of serum β2-microglobulin, chromosomal abnormalities, and serum lactate dehydrogenase (LDH). According to R-ISS, stages are defined as follows: serum albumin ≥ 3.5 g/dl, serum β2-microglobulin < 3.5 mg/l, standard-risk chromosomal abnormalities, and normal LDH (stage I); serum β2-microglobulin ≥ 5.5 mg/l and either high-risk chromosomal abnormalities or high LDH (stage III); and, neither R-ISS stage I or stage III (stage II). R-ISS stage corresponds with overall survival in MM patients [Palumbo, 2015].

According to GLOBOCAN, the age-standardized mortality rate (ASMR) of MM was 1.1 per 100,000. Mortality of MM was estimated to be 1.6 per 100,000 in Europe and 1.8 per 100,000 in the US. Mortality rate of MM in 2018 in EU-28 is listed in Table 6.

Table 6 Mortality rate of MM in 2018, in EU-28

	Estimated number of deaths			Crude mortality rate (per 100,000)			ASMR (per 100,000)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
Austria	438	232	206	5.0	5.4	4.6	1.7	2.1	1.4
Belgium	572	314	258	5.0	5.5	4.4	1.7	2.2	1.3
Bulgaria	117	59	58	1.7	1.7	1.6	0.7	0.8	0.6
Croatia	207	108	99	5.0	5.4	4.6	1.8	2.3	1.4
Cyprus	58	34	24	4.9	5.7	4.0	2.5	3.1	2.1
Czech Republic	397	186	211	3.7	3.6	3.9	1.4	1.6	1.3
Denmark	302	178	124	5.2	6.2	4.3	1.8	2.4	1.3
Estonia	64	24	40	4.9	3.9	5.8	1.9	2.0	1.9
Finland	284	145	139	5.1	5.3	4.9	1.7	2.0	1.4
France	3,398	1,810	1,588	5.2	5.6	4.8	1.6	2.1	1.2
Germany	4,622	2,519	2,103	5.6	6.2	5.0	1.7	2.1	1.3
Greece	502	252	250	4.5	4.6	4.4	1.5	1.7	1.3
Hungary	280	138	142	2.9	3.0	2.8	1.2	1.5	1.0
Ireland	204	119	85	4.2	5.0	3.5	2.0	2.6	1.5
Italy	3,703	1,996	1,707	6.2	6.9	5.6	1.8	2.2	1.5
Latvia	79	35	44	4.1	3.9	4.2	1.7	2.1	1.5
Lithuania	102	45	57	3.5	3.4	3.7	1.3	1.6	1.2
Luxembourg	22	11	11	3.7	3.7	3.7	1.7	1.9	1.5
Malta	15	8	7	3.5	3.7	3.3	1.2	1.4	1.0
Poland	1,563	814	749	4.1	4.4	3.8	1.8	2.3	1.4
Portugal	708	342	366	6.9	7.0	6.8	2.3	2.5	2.3
Romania	439	236	203	2.2	2.5	2.0	1.1	1.3	0.9
Slovakia	273	122	151	5.0	4.6	5.4	2.3	2.6	2.1
Slovenia	116	58	58	5.6	5.6	5.5	1.9	2.3	1.7
Spain	2,114	1,128	986	4.6	5.0	4.2	1.4	1.8	1.2
Sweden	554	289	265	5.5	5.8	5.3	1.9	2.2	1.7
The Netherlands	1,013	584	429	5.9	6.9	5.0	2.2	2.8	1.6
United Kingdom	3,400	1,881	1,519	5.1	5.7	4.5	1.7	2.1	1.4

SI.1.4 Important co-morbidities

In a prospective cohort study, which followed 1,159 RRMM patients in North America (US/Canada) and Europe (France/Germany/Italy/UK) for a median period of 12 months [Vij, 2018], 80% of the enrolled patients in Europe had at least one comorbidity. Vascular and metabolic disorders were the most common comorbidities reported in 49% and 34% RRMM patients, respectively. Vascular (63% vs 42%), metabolic (46% vs. 27%), musculoskeletal (42% vs. 22%), nervous system (33% vs. 21%), and GI (35% vs. 16%) comorbidities were significantly more common in RRMM patients in North America compared to those in European countries [Vij, 2018]. The prevalence of hypertension and diabetes among RRMM patients were reported by other observational studies as 42.8% and 22.8%,

respectively [Song, 2016, Hari, 2018]

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Belantamab mafodotin has been evaluated in a range of non-clinical toxicology studies including 3-week (with a 12-week recovery period) and 3-month (with a 12-week recovery period) repeat dose studies conducted in rat and cynomolgus monkeys. The main preclinical findings are listed below.

Key safety findings from non-clinical studies and relevance to human usage:

Corneal Events

Corneal events in clinical investigations are a class effect reported with ADCs including belantamab mafodotin which have the MMAF payload. These events were not represented well in nonclinical species with belantamab mafodotin [Eaton, 2015]. Corneal events are the most frequently reported adverse events (AEs) associated with belantamab mafodotin in the clinic and include keratopathy, blurred vision, dry eyes and photophobia. In the nonclinical studies with belantamab mafodotin, bilateral single cell necrosis in the corneal epithelium and/or increased mitoses of corneal epithelial cells were observed in rat and rabbit only. Typically, no findings were noted following extensive ophthalmoscopy examination although unilateral superficial corneal haze was noted in one rabbit. The reason for the greater sensitivity of human eye to adverse events with MMAF is currently unknown. Bioimaging indicates that labelled belantamab mafodotin can be taken up into cells by macropinocytosis and is unrelated to BCMA expression. Following uptake, cells catabolize belantamab mafodotin releasing cys-mcMMAF, resulting in cytotoxicity via apoptosis consistent with its mechanism of action.

Embryo-foetal toxicity

Embryo-foetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity due to reports of BCMA expression in human placental cells [Langat, 2008]. Belantamab mafodotin was genotoxic in an in vitro micronucleus screening assay in human lymphocytes. The mechanism of action is to kill rapidly dividing cells which would affect a developing embryo which has rapidly dividing tissue.

Chemicals such as cys-mcMMAF that bind to tubulin cause microtubule depolymerisation resulting in spindle disorganization followed by altered chromosome alignment and segregation and the generation of aneuploidy in female germ cells, ultimately leading to aneuploidy in the offspring [Marchetti, 2016]; thus, there is a potential risk of heritable changes via germ cells following treatment with belantamab mafodotin.

There are no data from the use of belantamab mafodotin in pregnant women. Belantamab mafodotin should be used during pregnancy only if the expected benefits to the mother outweigh the potential risks to the fetus. Pregnant women, or patients becoming pregnant while receiving belantamab mafodotin, or treated male patients as partners of pregnant women, should be informed of the potential hazard to the fetus. Contraception requirements are provided in the product labelling.

Impaired Male Fertility

Findings in male reproductive organs, which were adverse and progressed following repeat-dosing in rat, occurred at 10 mg/kg and above [approximately 4 times the recommended human dose (RHD) of 2.5 mg/kg, based on ADC AUC] and included marked degeneration/atrophy of seminiferous tubules that was generally not reversible. Seminiferous tubule degeneration was also noted in monkeys (at doses approximately 4 times the exposure at RHD) and was fully reversible following the 12-week off dose period.

Effects on Female Fertility

Luteinized nonovulatory follicles were observed in the ovaries of rats after 3-weekly doses of 10 mg/kg and above (approximately 4 times the exposure of RHD of 2.5 mg/kg, based on AUC) which were not present after 12 weeks off-dose and were not reproduced in the 13-week rat study (possibly due to extended dosing interval of 3 weeks allowing recovery between doses).

Potential for cardiotoxicity related to an inflammatory response

There has been no clear evidence for systemic inflammatory responses in the clinic for doses of belantamab mafodotin administered at doses up to 4.6 mg/kg. Nor is there evidence from clinical studies to date that belantamab mafodotin adversely affects the QT/QTc interval or is associated with any clinically relevant cardiovascular effects.

In nonclinical studies, predominantly in monkey, increased activation of macrophages was noted in a number of organs at ≥3 mg/kg/week (at comparable plasma exposures in humans given 2.5 mg/kg), which were associated with elevated serum C-reactive protein, decreased serum albumin and increased white cell count, reflective of a systemic inflammatory response; these laboratory findings were also associated with haematology changes, including decreased red cell mass and platelet counts, with sporadic evidence of regenerative responses. Minimal inflammatory changes (inflammatory cell infiltrate and/or haemorrhage) were also noted in hearts (atrial epicardium, ventricle endocardium) of single monkeys, which were non-adverse and reversible.

ECGs were monitored in monkeys for up to 24 hours following repeat dosing for up to 13 weeks and did not produce any evidence of test-article induced electrocardiographic waveform abnormalities, arrhythmias or QTc changes. Serum cardiac troponin I was also measured in the rat and monkey 3-week studies and no treatment-related effects were observed.

Increases in heart rate (16%) observed in male monkeys after 5 weekly doses of belantamab mafodotin at 10 mg/kg, were considered related to their deteriorating clinical condition, likely as a result of immune complex disease due to ADAs.

No signals of cardiac toxicity, including adverse effects on the QT/QTc interval or association with any clinically relevant cardiovascular effects, have been reported to date in clinical trials with belantamab mafodotin.

Hepatotoxicity

In nonclinical studies, the liver was found to be a target organ for toxicity, with increased liver weights and/or raised hepatobiliary enzymes and transaminases observed in both rat and monkey. These changes in the liver were without clinical consequence in the shorter duration studies and in the rat 13-week study. In the monkey 13-week study, progression of liver toxicity to include minimal multifocal hepatocellular necrosis was observed at all doses administered (≥3 mg/kg/week, at comparable plasma exposures in humans given 2.5 mg/kg) and considered to be adverse. Mild elevations of liver enzymes have been reported in studies BMA117159 and 205678.

Nephrotoxicity

A low incidence of renal-related adverse events has been observed in patients receiving belantamab mafodotin and in many cases coincided with disease progression. Of note, renal impairment may occur in the setting of multiple myeloma disease progression.

Non-clinical safety studies have demonstrated dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey) directly related to belantamab mafodotin, accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study.

Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with ADA, led to the early euthanasia of one monkey following 5 weekly doses of 10 mg/kg. Glomerulonephritis associated with immune complex formation is not expected to be reversible.

Pulmonary toxicity (Pneumonitis)

In rats, nonclinical safety experiments have demonstrated the presence of adverse progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in single and repeat dose studies at all doses tested which were dose- and duration-related in incidence and severity. Although there was a decrease or absence in the incidence of eosinophilic material in alveoli after a 12 week off-dose period, the increased alveolar macrophages and inflammatory cell infiltrates were similar in incidence and severity, and the incidence of alveolar inflammation with thickened alveolar septa and type 2 pneumocyte hypertrophy/hyperplasia was increased at ≥10 mg/kg/dose. No lung findings were seen in the monkey.

Immunosuppression

Decreases in immunoglobulins were seen in monkeys at all doses. Decreases in lymphoid cellularity/necrosis (dose-responsive in severity) was noted in the spleen and/or lymph nodes at ≥3 mg/kg/week, which was associated with decreases in thymic cellularity in rats.

MM subjects frequently are immunodeficient due to the underlying condition. Assessment of changes in immunoglobulin levels is challenging in patients with MM. Participants with active infections are excluded from belantamab clinical studies. Serious and non-serious infections have been reported in the clinical studies, including reports of lung infection and pneumonia as well as two deaths considered potentially related to study treatment: one case of sepsis (2.5-mg/kg dose) and one case of hemophagocytic lymphohistiocytosis (in association with viral/bacterial infection, 3.4-mg/kg dose). There have also been reports of neutropenia and decreased neutrophil counts in about 20% of subjects in the clinical studies, but these did not result in discontinuation of treatment in monotherapy studies Two fatal SAEs of severe neutropenia (one febrile) with concurrent infections were reported with the combination of belantamab mafodotin and lenalidomide which resulted in the implementation of additional guidance for the management of neutropenia/infections and more stringent haematological monitoring and stopping criteria.

Potential for Other Laboratory Abnormalities

An increased magnitude of aspartate aminotransferase (AST) relative to alanine aminotransferase (ALT) consistent with increased skeletal troponin I was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase and aldolase was observed in the rat 3-week study, suggesting aetiology alternative to liver.

Cases of elevated AST, lactic dehydrogenase (LDH) and creatine kinase (CK), and gamma-glutamyltransferase (GGT) alone or concomitant with no clear clinical correlate have been observed in clinical studies.

Immunogenicity

Although belantamab mafodotin was associated with immunogenicity in most monkeys and in a few rats following repeat dosing, these were generally without effects on exposure or pharmacodynamic activity.

In monkeys there was evidence of immune complex disease following repeated dosing leading to morbidity at 10 mg/kg/week, likely associated with ADA, via microscopic pathology and immunohistochemistry. Animal studies are generally not predictive of immunogenicity and sequelae related to immunogenicity in humans [Kronenberg, 2017].

To date, treatment-emergent anti-belantamab mafodotin antibody responses have been low incidence (<1%) and with no obvious impact on safety, efficacy, pharmacokinetics, and/or pharmacodynamics.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

As of 15 September 2019, a total of 321 participants with RRMM have been exposed to at least one dose of belantamab mafodotin either as a single agent (n=291) or as part of combination regimens (n=30) during the clinical development program. Of all participants exposed, 118 participants have been treated with the starting dose of 2.5 mg/kg that is recommended for single-agent use of belantamab mafodotin (Table 7).

Table 7 Summary of Exposure Across the Clinical Development Program

	Number of Participants Exposed to Belantamab Mafodotin [a]				
	<2.5 mg/kg	2.5 mg/kg	3.4 mg/kg	4.6 mg/kg	Total
Pivotal Study					
205678 DREAMM-2	-	95	123	-	218
Supportive Study					
BMA117159 DREAMM-1	21	8	38	6	73
Ongoing Studies					
205207 DREAMM-4 [b]	-	3	3	0	6
207497 DREAMM-6 [c]	2	12	10	-	24
Total	23	118	174	6	321

a. Participants with RRMM exposed to at least one dose of belantamab mafodotin as of 21 June 2019 for DREAMM-2, 31 August 2018 for DREAMM-1 and 15 September 2019 for ongoing studies. Participants are grouped according to the starting dose to which they received. Includes frozen liquid and lyophilised presentations.
b. In DREAMM-4, belantamab mafodotin is administered in combination with pembrolizumab.
c. In DREAMM-6, belantamab mafodotin is administered in combination with either lenalidomide and dexamethasone or bortezomib and dexamethasone.

Exposure for Monotherapy: DREAMM-2 (205678) and DREAMM-1 (BMA117159)

In DREAMM-2, participants are to receive belantamab mafodotin until disease progression, unacceptable toxicity, or death. In DREAMM-1, participants were to receive belantamab mafodotin for a maximum of 16 cycles.

In the 2.5 mg/kg pooled data, participants were exposed to belantamab mafodotin for a total of 28.9 participant-years [ISS Source Table 1.5100]. Participants received a median of 3.0 treatment cycles and spent a median of 9.1 weeks on study treatment. The median dose intensity was 2.48 mg/kg per 3-week cycle (Table 8).

In the All Treated pooled data, participants were exposed to belantamab mafodotin for a total of 103.4 participant-years [ISS Source Table 1.5100]. Participants received a median of 3.0 treatment cycles and spent a median of 14.9 weeks on study treatment. The median dose intensity was 2.78 mg.kg per 3-week cycle.

In the analysis of the pooled data, while similar efficacy was demonstrated between the 2.5 mg/kg and 3.4 mg/kg doses, overall the safety profile of single-agent belantamab mafodotin was more favourable at the 2.5 mg/kg dose [Integrated Summary of Safety].

Table 8 Summary of Exposure (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Number of cycles			
n	103	137	161
Mean±SD	3.7±2.44	5.2±4.23	4.9±4.01
Median (range)	3.0 (1 to 15)	3.0 (1 to 16)	3.0 (1 to 16)
Dose intensity (mg/kg/3 weeks)			
n	103	137	161
Mean±SD	2.10±0.580	2.52±0.890	2.55±0.859
Median (range)	2.48 (0.7 to 3.1)	2.78 (0.6 to 3.7)	2.78 (0.6 to 3.7)
Time on study treatment (weeks) [a]			
n	103	137	161
Mean±SD	14.6±11.25	22.3±20.31	21.0±19.23
Median (range)	9.1 (2 to 54)	15.9 (2 to 98)	14.9 (2 to 98)

ISS Source Table 1.5000

a. The time on study drug does not exclude dose delay.

Note: 19 to 22% of participants across the pooled datasets remain ongoing in the two studies as of the cut-off dates for DREAMM-1 (31 August 2018) and DREAMM-2 (21 June 2019).

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

To date, there have been no clinical trials conducted specifically in special patient populations (i.e. pregnant or lactating women, patient with certain renal, hepatic or cardiac disorders) as part of the development program for belantamab mafodotin.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Drug interactions: In clinical trials, advise was given to use caution with strong inhibitors of P-gp and to avoid use of strong inhibitors of Organic-Anion-Transporting Polypeptide (OATP) unless medically necessary.	No formal drug interaction studies have been performed with Belantamab mafodotin. Cys-mcMMAF, the cytotoxic component of belantamab mafodotin, has been shown to be a substrate of OATP 1B1 and 1B3 and a possible substrate of P-gp *in vitro*.	No	Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterised in humans; however, cys-mcMMAF was shown to be a substrate of OATP transporters and a possible substrate of P-gp *in vitro*. Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP1B1/1B3 should be avoided unless considered medically necessary.
Renal impairment: Patients with active renal conditions or severe renal impairment were not allowed in clinical trials; however, in the DREAMM-2 (205678) study, patients with an eGFR of ≥30 ml/min/1.73 m^2 were allowed to enrol.	Patients with multiple myeloma have an increased risk of renal impairment, therefore caution was exercised in initial DREAMM-1 (BMA117159) study.	Yes	Primary glomerular injury and tubular degeneration were observed in rats at doses ≥30 mg/kg, and in monkeys at doses 10 mg/kg. The morphologic changes were accompanied by large molecular proteinuria (albuminuria) and enzymuria. The renal changes were dose-dependent and reversible. Overall, there has been a low incidence of renal events in the

			monotherapy programme to date. A renal impairment study (209626 / DREAMM-12) is being performed to evaluate the potential impact of severe renal impairment on the PK and safety of Belantamab mafodotin and to provide dosing guidance if needed.
Hepatic impairment: Patients with hepatic impairment and unstable liver disease were not allowed in clinical trials	For belantamab mafodotin, alterations of hepatobiliary excretory and metabolic activities due to hepatic impairment may lead to a slower elimination and thus increased exposure to cys-mcMMAF.	Yes	Mild elevations of liver enzymes have been reported in monotherapy programme. Potentially patients with hepatic impairment may be at risk. A hepatic impairment study (209627 / DREAMM-13) is being performed to determine if any dose adjustments are needed.
Current corneal epithelial disease, except for mild punctate keratopathy	Due to the risk for corneal adverse events with belantamab mafodotin treatment, there was an initial concern that pre-existing corneal epithelial disease may predispose a patient to corneal adverse events.	No	Corneal toxicities are among the most commonly reported events associated with belantamab mafodotin. Keratopathy or microcyst-like epithelial changes (MEC) in the corneal epithelium with or without changes in visual acuity, blurred vision, and dry eye is included as an important identified risk in Section SVII.3.1. The exclusion criteria for current corneal epithelial disease has been removed because the current data do not support that patients with pre-existing corneal disease are predisposed to increased corneal risk.
Patients with significant cardiovascular risk factors	There is a potential risk of cardiac findings related to a systemic inflammatory	No	Preclinical findings suggest a potential for cardiac findings related to

	response with belantamab mafodotin treatment.		a systemic inflammatory response. However, to date there is no evidence of systemic inflammatory response or cardiotoxicity in the monotherapy programme.

SIV.2 Limitations to detect adverse reactions in clinical trial development programme

The clinical development programme is not very likely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, given that only a relatively small patient population has been studied thus far (see Part II, Module SIII).

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 9 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure (Based on ISS Safety Population)
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: Patients with hepatic impairment[1]	 Mild hepatic impairment 2.5 mg/kg: n=10 subjects 3.4 mg/kg: (Frozen): n=10 subjects 3.4 mg/kg: (Lyophilized): n=4 subjects Moderate hepatic impairment 2.5 mg/kg: n=2 subjects
Patients with severe renal impairment[2]	Mild renal impairment [ISS Source Table 1.5112]: 2.5 mg/kg: n=48 subjects; 13.60 patient-years 3.4 mg/kg (Frozen): n=52 subjects; 16.77 patient-years 3.4 mg/kg (All): n=65 subjects; 19.88 patient-years Moderate renal impairment [ISS Source Table 1.5113]: 2.5 mg/kg: n=24 subjects; 6.70 patient-years 3.4 mg/kg (Frozen): n=22 subjects; 6.84 patient-years 3.4 mg/kg (All): n=28 subjects; 8.39 patient-years Severe renal impairment [ISS Source Table 1.5114]:

Patients with severe cardiovascular impairment	2.5 mg/kg: n=2 subjects, 0.23 patient-years 3.4 mg/kg (Frozen): n=5 subjects, 1.40 patient-years 3.4 mg/kg (All): n=5 subjects, 1.40 patient-years
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme Not included in the clinical development programme
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme
Other	Not included in the clinical development programme

[1] Patients with moderate to severe hepatic impairment were excluded from study participation; however, there were 2 subjects whose hepatic status worsened to moderate between the Screening visit and Cycle 1 Day visit.
[2] Patients with severe renal impairment were excluded from study participation; however, there were 7 subjects whose renal status worsened to severe between the Screening visit and Cycle 1 Day 1 visit.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

There is no data for this section as belantamab mafodotin has not been marketed in any country.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

There is no evidence for and no anticipation of patient abuse or misuse of belantamab mafodotin. Belantamab mafodotin must be administered via an intravenous infusion by a trained healthcare practitioner.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

- Infusion-related reactions (IRR)
- Thrombocytopenia (potentially resulting in bleeding complications)
- Pulmonary toxicity (Pneumonitis)
- Cardiotoxicity due to an inflammatory response
- Immunogenicity
- Other laboratory abnormalities, including elevated transaminases (of unknown clinical significance)
- Embryo-foetal toxicity
- Effects on female fertility
- Impaired male fertility
- Genotoxicity

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Pulmonary toxicity (Pneumonitis)

This potential risk is based on non-clinical findings (see PART II: Module SII).

Routine pharmacovigilance is deemed appropriate for this potential risk.

Cardiotoxicity due to an inflammatory response

This potential risk is based on non-clinical findings (see PART II: Module SII).

There has been no clear evidence for systemic inflammatory responses in the clinic for doses of belantamab mafodotin administered at doses up to 4.6 mg/kg. Nor is there evidence from clinical studies to date that belantamab mafodotin adversely affects the QT/QTc interval or is associated with any clinically relevant cardiovascular effects. There have been no signals to date of decreased left ventricular ejection fraction in the clinic to date.

Immunogenicity

This potential risk is based on the fact that belantamab mafodotin is a biotherapeutic agent. Immunogenicity was observed with belantamab mafodotin in animal studies (see PART II:

Module SII). However, it is noted that animal studies are generally not predictive of immunogenicity and sequelae related to immunogenicity in humans [Kronenberg, 2017].

To date, treatment-emergent anti-belantamab mafodotin antibody responses have been low incidence (<1%) and with no obvious impact on safety, efficacy, pharmacokinetics, and/or pharmacodynamics.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Infusion-related reactions

This identified risk is based on the observation that IRRs are expected for biologic agents, including belantamab mafodotin. IRRs have been closely monitored across the clinical trial programme for belantamab mafodotin. Within the Integrated Summary of Safety, IRRs were reported in 21/103 (20%) of the 2.5 mg/kg dose group and in 31/161 (19%) of the 3.4 mg/kg dose group. This risk will be managed through routine risk minimisation, which includes messaging in the EU Summary of Product Characteristics (SmPC) with dose interruption and modification guidelines. In current and future studies, premedication prior to first infusion of belantamab mafodotin is not mandatory but should be considered, if clinically appropriate.

Thrombocytopenia (potentially leading to bleeding complications, both minor and major)

This identified risk is based on available literature on using auristatin with ADCs [Donaghy, 2016], nonclinical studies, as well as observations within the DREAMM-1 and DREAMM-2 studies that revealed that thrombocytopenic events (Grades 1 to 4) are among the most common AEs associated with belantamab mafodotin. Patients with RRMM frequently present with thrombocytopenia, i.e., 45% of treated participants in DREAMM-1 and DREAMM-2 had thrombocytopenia at baseline (13% with Grade 2 or above) [ISS Source Table 3.7310]. This risk will be managed through routine risk minimisation, which includes messaging in the EU SmPC with dose interruption and modification guidelines.

Other laboratory abnormalities, including elevated transaminases (of unknown clinical significance)

This potential risk is based on an increased magnitude of AST relative to ALT consistent with increased skeletal troponin I which was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase and aldolase was observed in the rat 3-week study, suggesting aetiology alternative to liver.

Cases of elevated AST, lactic dehydrogenase (LDH) and CK, and GGT alone or concomitant with no clear clinical correlate have been observed in clinical studies. These findings are included as ADRs in the EU SmPC and routine pharmacovigilance and risk management is deemed appropriate given the current data.

Embryo-foetal toxicity

This identified risk is based on non-clinical findings (see PART II: Module SII). While nonclinical reproductive studies with belantamab mafodotin have not been conducted, this identified risk is based on the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells (see PART II: Module SII) [Langat, 2008].

Chemicals such as cys-mcMMAF that bind to tubulin cause microtubule depolymerisation resulting in spindle disorganization followed by altered chromosome alignment and segregation and the generation of aneuploidy in female germ cells, ultimately leading to aneuploidy in the offspring [Marchetti, 2016]; thus, there is a potential risk of heritable changes via germ cells following treatment with belantamab mafodotin.

There are no data from the use of belantamab mafodotin in pregnant women. This information has been included in the EU SmPC and routine pharmacovigilance and risk management is deemed appropriate given the current data.

Effects on female fertility

This identified risk is based on non-clinical findings (see PART II: Module SII) in animal studies in which luteinized nonovulatory follicles were observed in the ovaries of rats after 3-weekly doses of 10 mg/kg and above (approximately 4 times the exposure of RHD of 2.5 mg/kg, based on AUC) which were not seen following 12 weeks off dose. These results were not reproduced in the 13-week rat study (possibly due to extended dosing interval of 3 weeks allowing recovery between doses).

The effects of belantamab mafodotin on human female fertility have not been studied. However, results of repeat-dose toxicity studies in rats indicate the potential for belantamab mafodotin to impair female reproductive function and fertility. This information has been included in the EU SmPC and routine pharmacovigilance and risk management is deemed appropriate given the current data.

Impaired male fertility

This identified risk is based on animal studies in which belantamab mafodotin treatment has resulted in testicular toxicity and adverse effects on spermatogenesis (see PART II: Module SII). Reversibility of testicular toxicity is unknown at this time.

The effects of belantamab mafodotin on human male fertility have not been studied. However, results of repeat-dose toxicity studies in rats indicate the potential for belantamab mafodotin to impair male reproductive function and fertility. This information has been included in the EU SmPC and routine pharmacovigilance and risk management is deemed appropriate given the current data.

Genotoxicity

This identified risk is based on the chemicals such as cys-mcMMAF that bind to tubulin are known to cause microtubule depolymerisation resulting in spindle disorganization followed by altered chromosome alignment and segregation and the generation of aneuploidy in female germ cells, ultimately leading to aneuploidy in the offspring [Marchetti, 2016]; thus, there is a potential risk of heritable changes via germ cells following treatment with belantamab mafodotin (see PART II: Module SII). This information has been included in the EU SmPC

and routine pharmacovigilance and risk management is deemed appropriate given the current data.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk #1: Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye

Scientific evidence for risk to be added in the safety specification

Corneal events are a class effect reported with other MMAF-containing ADCs and have been reported with belantamab mafodotin. 'Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination)' is considered an important identified risk based on the changes in the corneal epithelium on ocular examination that have frequently been observed in the belantamab mafodotin clinical trial programme. This finding was most commonly associated with blurred vision, dry eyes, photophobia, and changes in visual acuity.

There is no evidence from AE reporting and extensive ocular examinations that eye structures other than the cornea (such as the lens, retina, etc.) are affected by treatment with belantamab mafodotin.

Risk Benefit Impact

Based on the DREAMM-1 and DREAMM-2 results, the corneal events associated with belantamab mafodotin treatment are consistent with those reported in the published literature for other MMAF-conjugated ADCs and are manageable with supportive care [Eaton, 2015], mainly by dose delays and/or dose reductions. Patients will be actively monitored for any ocular event with appropriate management and risk mitigation implemented as applicable. This is further discussed in Part V of this document. The corneal findings have been found to be mostly mild and reversible after the drug has been withdrawn.

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the identified risk of keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye. The risk of corneal events and visual changes can be managed in clinical practice through dose modifications. Additional risk minimisation efforts further described in Part V, Section V.2 of this document.

Important Potential Risk #1: Nephrotoxicity

Scientific evidence for risk to be added in the safety specification

A low incidence of renal-related adverse events has been observed in patients receiving belantamab mafodotin and in many cases coincided with disease progression. Of note renal impairment may occur in the setting of multiple myeloma disease progression.

Nephrotoxicity is considered an important potential risk based on non-clinical safety studies which demonstrated dose-dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey) directly related to belantamab mafodotin, accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study (GSK study 2018N375127).

Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with ADA, following 5 weekly doses of 10 mg/kg, led to the early euthanasia of one monkey. Glomerulonephritis associated with immune complex formation is not expected to be reversible.

Risk-Benefit impact

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the potential risk of nephrotoxicity.

Important Potential Risk #2: Increased risk of infections due to immunosuppression and/or neutropenia

Scientific evidence for risk to be added in the safety specification

MM participants frequently are immunodeficient due to the underlying condition. Assessment of changes in immunoglobulin levels is challenging in participants with MM.

Immunosuppression is considered a potential risk based on nonclinical studies in which belantamab mafodotin has been associated with decreases in immunoglobulins in monkeys at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for belantamab mafodotin).

Neutropenia is considered a potential risk due to the prevalence of haematologic findings in patients with MM.

In nonclinical studies, myelotoxicity was associated with decreases in haemoglobin, white cells, and lymphocytes at higher doses in rats.

In the 13-week monkey study, at the highest dose administered, red blood smear morphological changes suggestive of red blood cell membrane damage were related to decreases in red blood cell mass, with evidence of regeneration. These morphologic changes were considered likely related to immune complex disease.

Neutropenia, anaemia, leukopenia and lymphopenia have been reported in MM participants receiving belantamab mafodotin.

Risk-Benefit impact

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the potential risk of immunosuppression.

Missing information #1: Safety in patients with severe renal impairment

Scientific evidence for risk to be added in the safety specification

Nephrotoxicity is an important potential safety concern (see Important potential risks above).

Patients with MM have an increased risk of renal impairment.

It is unknown if there is increased risk to patients with severe renal impairment who may receive belantamab mafodotin (safety, efficacy or PK) or if patients with renal compromise are at higher risk for adverse events; however, data in patients with mild/moderate renal impairment does not indicate increased safety risk in this population.

Risk-Benefit impact

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the unknown safety of belantamab mafodotin use in patients with severe renal impairment.

A renal impairment study is planned (Study 209626 / DREAMM-12).

Missing information #2: Safety in patients with hepatic impairment

Scientific evidence for risk to be added in the safety specification

Elevated transaminases have been reported.

It is unknown if there is an increased risk to patients with hepatic impairment who may receive belantamab mafodotin (safety, efficacy or PK).

Elimination pathways for belantamab mafodotin or cys-mcMMAF in humans have not been characterized. Cys-mcMMAF was not a sensitive substrate of cytochrome P450 enzymes or most transporters *in vitro*. Cys-mcMMAF was an *in vitro* substrate of organic anion-transporting polypeptides (OATP) 1B1 and OATP1B3, multidrug resistance-associated proteins (MRP) 1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp).

Risk-Benefit impact

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the unknown safety of belantamab mafodotin use in patients with impairment.

A hepatic impairment study is planned (Study 209627 / DREAMM-13).

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk #1: Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye

Potential mechanisms:

Corneal events have been reported with other MMAF-containing antibody drug conjugates.

The exact mechanism leading to the development of corneal events with MMAF and other microtubule inhibitors has yet to be fully elucidated. The leading hypothesis is these events may be related to nonspecific uptake of the ADC [de Goeij, 2016; Zhao et al, 2018] into actively dividing epithelial cells residing in the basal layer of the cornea. Given the toxin is a microtubulin inhibitor, apoptosis occurs which clinically manifests as a superficial punctate keratopathy/keratitis with microcyst-like changes resulting in a variety of other ocular symptoms.

Evidence source(s) and strength of evidence:

Although considered non-adverse, increased mitosis of corneal epithelial cells, with bilateral single-cell necrosis, was observed in rats (≥3 mg/kg) and rabbits (≥15 mg/kg). The corneal events seen clinically with belantamab mafodotin are not well predicted in nonclinical species. The reason for the greater sensitivity of human eye to adverse events with MMAF is currently unknown. In vitro studies of primary human cells indicate that non-specific cellular uptake of belantamab mafodotin unrelated to the BCMA receptor can occur. These findings were supported by in vivo bioimaging studies with labelled belantamab mafodotin. Cellular uptake of belantamab mafodotin by human corneal epithelial and renal proximal tubule appears to be mediated by macropinocytosis.

The cytotoxic effects of belantamab mafodotin on human primary epithelial cells in vitro was consistent with the primary MoA of belantamab mafodotin (i.e. cellular uptake of belantamab mafodotin and release of the cytotoxic component, cys-mcMMAF leading to microtubule inhibition and apoptosis).

Changes to the corneal epithelium on ocular examination have frequently been observed in the belantamab mafodotin clinical trial programme and have been closely monitored. This finding was most commonly associated with blurred vision, dry eyes, photophobia, and changes in visual acuity.

Characterisation of the risk:

Eye disorders

An overview of AEs captured in the MedDRA System Organ Class (SOC) of Eye disorders and graded using CTCAE is presented in this section. In DREAMM-2, per protocol, sites were directed to report ocular examination findings as "microcyst-like epithelial keratopathy", which mapped to the MedDRA Preferred Term (PT) keratopathy and was the most frequent Eye disorders term reported. This instruction was not provided in DREAMM-1 therefore keratopathy events were not pooled for the ISS. Details of keratopathy events were evaluated in the DREAMM-2 CSR, Section 7.3.1.1.

In the 2.5 mg/kg pooled data, AEs within the SOC of Eye Disorders were reported for a total of 73 (71%) participants (Table 10). The most commonly reported AE PTs were keratopathy (68 participants, 66%), vision blurred (19 participants, 18%) and dry eye (12 participants, 12%). A Grade 3/4 AE in the Eye Disorders SOC was reported for 27 (26%) participants, the most common of which was keratopathy (26 [25%] participants).

Table 10 Eye Disorders (CTCAE) by PT Reported for ≥2% of Participants in Any Dose Group (DREAMM-1/DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Any Event	73 (71)	103 (75)	125 (78)
Keratopathy	68 (66)	77 (56)	99 (61)
Vision blurred	19 (18)	46 (34)	53 (33)
Dry eye	12 (12)	33 (24)	38 (24)
Photophobia	4 (4)	16 (12)	19 (12)
Eye pain	2 (2)	7 (5)	8 (5)
Lacrimation increased	0	7 (5)	7 (4)
Diplopia	2 (2)	4 (3)	6 (4)
Eye pruritus	1 (<1)	4 (3)	5 (3)
Blepharitis	1 (<1)	4 (3)	4 (2)
Cataract	1 (<1)	3 (2)	4 (2)
Ocular hyperaemia	1 (<1)	3 (2)	4 (2)
Visual acuity reduced	3 (3)	4 (3)	4 (2)
Keratitis	1 (<1)	3 (2)	3 (2)
Foreign body sensation in eyes	0	3 (2)	3 (2)
Meibomian gland dysfunction	0	3 (2)	3 (2)
Ocular toxicity	0	3 (2)	3 (2)
Eye irritation	3 (3)	2 (1)	2 (1)
Ocular discomfort	2 (2)	0	0

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Ocular hypertension	2 (2)	2 (1)	2 (1)
Retinal haemorrhage	2 (2)	1 (<1)	1 (<1)
Vitreous floaters	2 (2)	1 (<1)	1 (<1)
Visual impairment	2 (2)	1 (<1)	1 (<1)

ISS Source Table 3.3000

Blurred vision

Blurred vision *events* were defined by the following MedDRA Preferred Terms: Blindness, Diplopia, Glare, Halo vision, Night blindness, Vision blurred, Visual acuity reduced, Visual acuity tests abnormal, Visual field defect, and visual impairment. In the 2.5 mg/kg pooled data, 23 (22%) participants experienced a blurred vision event (Table 11). The most commonly reported PT was vision blurred, reported for 19 (18%) participants.

Table 11 Blurred Vision Events by PT (DREAMM-1/DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	<2.5 mg/kg (N=21)	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)	4.6 mg/kg (N=6)	All Treated (N=291)
Any event	**5 (24)**	**23 (22)**	**52 (38)**	**59 (37)**	**5 (83)**	**92 (32)**
Vision blurred	3 (14)	19 (18)	46 (34)	53 (33)	4 (67)	79 (27)
Diplopia	1 (5)	2 (2)	4 (3)	6 (4)	0	9 (3)
Visual acuity reduced	0	3 (3)	4 (3)	4 (2)	0	7 (2)
Visual impairment	3 (14)	2 (2)	1 (<1)	1 (<1)	1 (17)	7 (2)
Night blindness	0	0	1 (<1)	1 (<1)	0	1 (<1)
Visual acuity tests abnormal	0	0	1 (<1)	1 (<1)	0	1 (<1)

ISS Source Table 3.3240

In the 2.5 mg/kg pooled data, blurred vision events were mostly Grade 1 or 2 (Table 12). Four (4%) participants experienced blurred vision with a maximum severity of Grade 3; all of whom had recovered/resolved at the data cut-offs. No participant experienced an SAE of blurred vision. The dose was reduced or delayed due to blurred vision for 7 (7%) participants. At the data cut-offs, there were 11 (11%) participants whose blurred vision events had recovered/resolved. There were 8 (8%) participants whose blurred vision had not recovered/resolved at the data cut-offs, of whom 4 participants remain on study treatment and 4 participants had discontinued study treatment but remain in follow-up.

Table 12 Characteristics of Blurred Vision Events (CTCAE) (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Number of subjects with event, n (%)	23 (22)	52 (38)	59 (37)
Number of events	31	105	117
Event Characteristics (% based on all subjects) [a], n/N (%)			
Serious	0/103	0/137	0/161
Study treatment related	19/103 (18)	51/137 (37)	58/161 (36)
Number of Occurrences (% based on all subjects), n/N (%)			
One	18/103 (17)	30/137 (22)	34/161 (21)
Two	3/103 (3)	10/137 (7)	12/161 (7)
Three or more	2/103 (2)	12/137 (9)	13/161 (8)
Outcome (% based on all subjects) [b], n/N (%)			
Recovered/Resolved	11/103 (11)	26/137 (19)	26/161 (16)
Recovered/Resolved with Sequelae	0/103	4/137 (3)	5/161 (3)
Recovering/Resolving	4/103 (4)	6/137 (4)	8/161 (5)
Not Recovered/Not Resolved	8/103 (8)	16/137 (12)	20/161 (12)
Fatal	0/103	0/137	0/161
Maximum Grade (% based on all subjects), n/N (%)			
Grade 1	12/103 (12)	17/137 (12)	18/161 (11)
Grade 2	7/103 (7)	31/137 (23)	35/161 (22)
Grade 3	4/103 (4)	4/137 (3)	6/161 (4)
Grade 4	0/103	0/137	0/161
Grade 5	0/103	0/137	0/161
Action Taken (% based on all subjects) [a], n/N (%)			
Study treatment withdrawn	0/103	0/137	0/161
Dose reduced	2/103 (2)	18/137 (13)	20/161 (12)
Dose not changed	17/103 (17)	43/137 (31)	45/161 (28)
Dose interrupted/delayed	6/103 (6)	24/137 (18)	28/161 (17)
Dose reduced or interrupted/delayed	7/103 (7)	26/137 (19)	31/161 (19)
Infusion interrupted but completed	0/103	0/137	0/161
Infusion stopped early and not completed	0/103	0/137	0/161

ISS Source Table 3.3200

a. Subjects may be included in more than one category for 'Event Characteristics' and 'Action Taken'.
b. Worst case hierarchy: Fatal>Not Recovered/Not Resolved>Recovering/Resolving>Recovered/Resolved with sequelae>Recovered/Resolved

In the 2.5 mg/kg pooled data, the median time to onset of the first occurrence of a blurred vision event was 41.0 days and the median duration was 32.5 days (Table 13).

Table 13 Time to Onset, Outcome and Duration of Blurred Vision Events (CTCAE) (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Time to onset of first occurrence, days, n (%)			
n	23	52	59
Mean (SD) Median (range)	58.6 (53.41) 41.0 (6 to 224)	45.0 (51.31) 30.5 (1 to 342)	43.1 (48.55) 29.0 (1 to 342)
1 - 21	4 (17)	12 (23)	13 (22)
22 - 42	8 (35)	22 (42)	27 (46)
43 - 63	5 (22)	7 (13)	8 (14)
64 - 105	2 (9)	7 (13)	7 (12)
>105	4 (17)	4 (8)	4 (7)
Duration of first occurrence [a] [b], n (%)			
n	12	38	39
Mean (SD)	90.4 (150.89)	123.5 (143.07)	121.4 (141.76)
Median (range)	32.5 (6 to 543)	85.0 (1 to 675)	82.0 (1 to 675)

ISS Source Table 3.3220

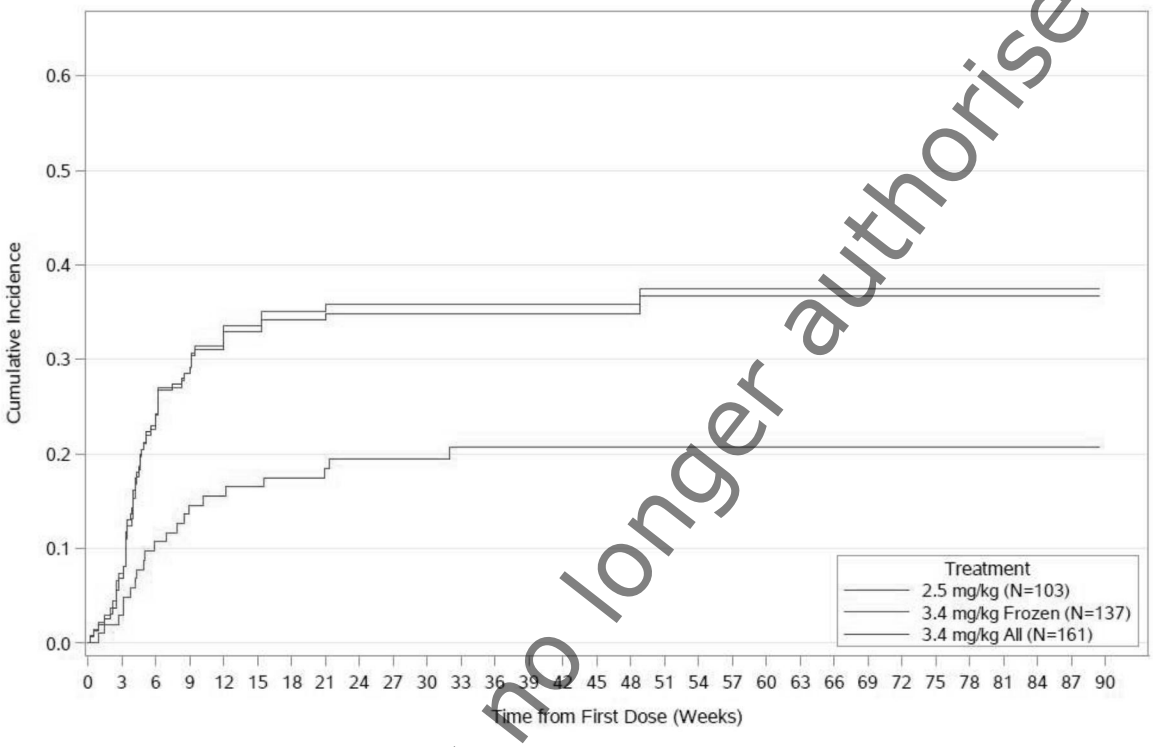
a. The duration is defined as time from onset of any blurred vision event to the first time the subject is free of any such event. It requires at least one day gap between the resolution of all events from first occurrence to the onset of second occurrence.

b. Imputed AE stop date was used in the calculation of duration if the outcome of the event was resolved/resolved with sequalae and AE stop date was partial with day missing. Imputed AE start date was used in the calculation if the start date was partial with day missing.

In the 2.5 mg/kg pooled data, the median percentage of time on treatment with a blurred vision event was 53.0% [ISS Source Table 3.3230].

The cumulative incidence of blurred vision events was approximately 21% in the 2.5 mg/kg pooled data, and 38% in the 3.4 mg/kg All pooled data at Week 30 (Figure 2).

Figure 2 Cumulative Incidence Plot of Subjects with Blurred Vision Events (First Occurrence) by CTCAE (DREAMM-1/DREAMM-2 Safety Population)



Source: ISS Figure 3.0010

Dry eyes

Dry eye *events* were defined by the following MedDRA Preferred Terms: Dry eye, Ocular discomfort, Eye pruritus, and Foreign body sensation in eyes. In the 2.5 mg/kg pooled data, 14 (14%) participants experienced a dry eye event (Table 14). The most commonly reported PT was dry eye, reported for 12 (12%) participants.

Table 14 Dry Eye Events by PT (DREAMM-1/DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	<2.5 mg/kg (N=21)	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)	4.6 mg/kg (N=6)	All Treated (N=291)
Any event	**4 (19)**	**14 (14)**	**38 (28)**	**44 (27)**	**3 (50)**	**65 (22)**
Dry eye	4 (19)	12 (12)	33 (24)	38 (24)	1 (17)	55 (19)
Eye pruritus	0	1 (<1)	4 (3)	5 (3)	1 (17)	7 (2)
Foreign body sensation in eyes	0	0	3 (2)	3 (2)	1 (17)	4 (1)
Ocular discomfort	0	2 (2)	0	0	0	2 (<1)

ISS Source Table 3.3140

In the 2.5 mg/kg pooled data, dry eye events were mostly Grade 1 or 2 (Table 15). One (<1%) participant experienced a dry eye event with a maximum severity of Grade 3 that led to a dose delay and was not recovered/not resolved at the data cut-offs; participant discontinued study treatment due to disease progression and remains in follow-up. No participant experienced an SAE of dry eye. The dose was delayed due to dry eye for 3 (3%) participants. At the data cut-offs, there were 9 (9%) participants whose dry eye event had recovered/resolved. There were 5 (%) participants whose dry eye had not recovered/resolved at the data cut-offs, of whom 4 participants remain on study treatment and 1 participant had discontinued study treatment but remains in follow-up.

Table 15 Characteristics of Dry Eye Events (CTCAE) (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Number of subjects with event, n (%)	14 (14)	38 (28)	44 (27)
Number of events	16	47	56
Event Characteristics (% based on all subjects) [a], n/N (%)			
Serious	0/103	0/137	0/161
Study treatment related	14/103 (14)	38/137 (28)	43/161 (27)
Number of Occurrences (% based on all subjects), n/N (%)			
One	13/103 (13)	30/137 (22)	34/161 (21)
Two	0/103	7/137 (5)	8/161 (5)
Three or more	1/103 (<1)	1/137 (<1)	2/161 (1)
Outcome (% based on all subjects) [b], n/N (%)			
Recovered/Resolved	9/103 (9)	6/137 (4)	8/161 (5)
Recovered/Resolved with Sequelae	0/103	4/137 (3)	4/161 (2)
Recovering/Resolving	0/103	6/137 (4)	7/161 (4)
Not Recovered/Not Resolved	5/103 (5)	22/137 (16)	25/161 (16)
Fatal	0/103	0/137	0/161
Maximum Grade (% based on all subjects), n/N (%)			
Grade 1	9/103 (9)	22/137 (16)	24/161 (15)
Grade 2	4/103 (4)	14/137 (10)	18/161 (11)
Grade 3	1/103 (<1)	2/137 (1)	2/161 (1)
Grade 4	0/103	0/137	0/161
Grade 5	0/103	0/137	0/161
Action Taken (% based on all subjects) [a], n/N (%)			
Study treatment withdrawn	0/103	0/137	0/161
Dose reduced	0/103	3/137 (2)	4/161 (2)
Dose not changed	11/103 (11)	32/137 (23)	38/161 (24)
Dose interrupted/delayed	3/103 (3)	6/137 (4)	6/161 (4)
Dose reduced or interrupted/delayed	3/103 (3)	7/137 (5)	8/161 (5)
Infusion interrupted but completed	0/103	0/137	0/161
Infusion stopped early and not completed	0/103	0/137	0/161

ISS Source Table 3.3100

a. May be included in more than one category for 'Event Characteristics' and 'Action Taken'.
b. Worst case hierarchy: Fatal>Not Recovered/Not Resolved>Recovering/Resolving>Recovered/Resolved with sequelae>Recovered/Resolved

In the 2.5 mg/kg pooled data, the median time to onset of the first occurrence of a dry eye event was 41.5 days and the median duration was 36.0 days (Table 16).

Table 16 Time to Onset, Outcome and Duration of Dry Eye Events (CTCAE) (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Time to onset of first occurrence, days, n (%)			
n	14	38	44
Mean (SD)	45.6 (34.81)	25.4 (22.70)	27.3 (23.41)
Median (range)	41.5 (12 to 151)	20.0 (1 to 141)	21.0 (1 to 141)
1 - 21	4 (29)	20 (53)	22 (50)
22 - 42	5 (36)	15 (39)	16 (36)
43 - 63	2 (14)	2 (5)	3 (7)
64 - 105	2 (14)	0	2 (5)
>105	1 (7)	1 (3)	1 (2)
Duration of first occurrence [a] [b], n (%)			
n	9	14	17
Mean (SD)	89.7 (178.65)	97.9 (109.27)	89.8 (101.46)
Median (range)	36.0 (12 to 564)	68.5 (2 to 401)	56.0 (2 to 401)

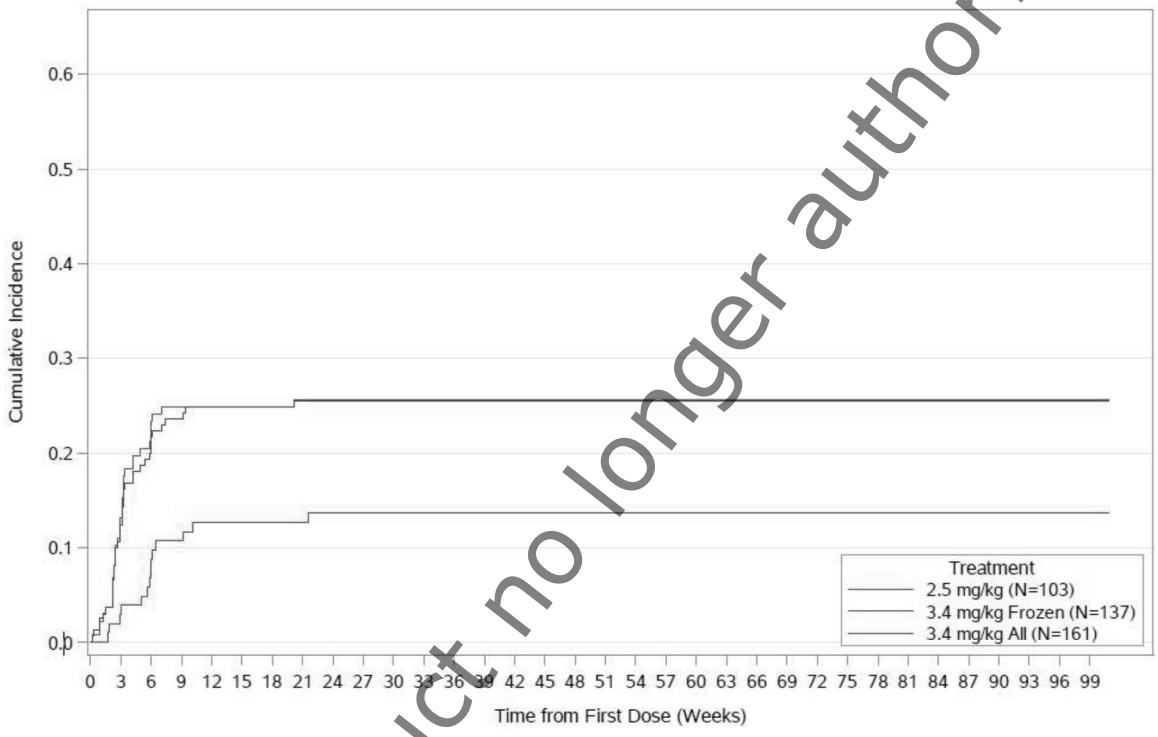
ISS Source Table 3.3120

a. The duration is defined as time from onset of any dry eye event to the first time the subject is free of any such event. It requires at least one day gap between the resolution of all events from first occurrence to the onset of second occurrence.
b. Imputed AE stop date was used in the calculation of duration if the outcome of the event was resolved/resolved with sequelae and AE stop date was partial with day missing. Imputed AE start date was used in the calculation if the start date was partial with day missing.

In the 2.5 mg/kg pooled data, the median percentage of time on treatment with a dry eye event was 19.0% [ISS Source Table 3.3130].

The cumulative incidence of dry eye events was approximately 14% in the 2.5 mg/kg pooled data, and 27% in the 3.4 mg/kg All pooled data at Week 30 Figure 3).

Figure 3 Cumulative Incidence Plot of Subjects with Dry Eye Events (First Occurrence) by CTCAE (DREAMM-1/DREAMM-2 Safety Population)



ISS Figure 3.0000

Corneal Events (GSK Scale)

Following observations in DREAMM-1 and discussions with Health Authorities, the Applicant developed a grading scale that combined ocular examination findings and Best Corrected Visual Acuity (BCVA) for use in the DREAMM-2 study (referred to as the GSK Scale in the protocol). This scale was used to describe ocular findings on exam because the CTCAE grading v4.0 did not include grading for changes in visual acuity. Since CTCAE v5.0 has been released and now includes grading for eye disorders including blurred vision, dry eye and keratitis, the Applicant is utilizing CTCAE grading for future studies.

In the 2.5 mg/kg cohort from DREAMM-2, 67 (71%) participants experienced a corneal event (Table 17). Most corneal events had a maximum severity of Grade 3 (43 [45%] participants), and 2 (%) participants had a Grade 4 event. Of those 2 participants with a Grade 4 event, 1 participant is ongoing and continues to receive study treatment and 1 participant discontinued study treatment due to disease progression and remains in follow-up. Of the 67 participants who had a corneal event, 60% did not experience a blurred vision or dry eye event [DREAMM-2 CSR, Table 3.12030]. The dose was reduced or delayed for 44 (46%) participants, and study treatment was discontinued for 1 participant.

Table 17 Characteristics of Corneal Events (DREAMM-2 Full Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg Frozen (N=95)	3.4 mg/kg Frozen (N=99)	3.4 mg/kg Lyo (N=24)
Number of subjects with event, n (%)	67 (71)	76 (77)	22 (92)
Event Characteristics, n/N (%)			
Study treatment related	66/95 (69)	74/99 (75)	22/24 (92)
Maximum Grade, n/N (%)			
Grade 1	7/95 (7)	4/99 (4)	1/24 (4)
Grade 2	15/95 (16)	23/99 (23)	4/24 (17)
Grade 3	43/95 (45)	46/99 (46)	17/24 (71)
Grade 4	2/95 (2) [0]	3/99 (3) [0]	0/24
Action Taken [0], n/N (%)			
Study treatment discontinued	1/95 (1)	5/99 (5) [0]	1/24 (4)
Dose reduced	12/95 (13)	23/99 (23)	5/24 (21)
Dose not changed	57/95 (60)	64/99 (65)	18/24 (75)
Dose delayed	44/95 (46)	51/99 (52)	16/24 (67)
Dose reduced or delayed	44/95 (46)	51/99 (52)	16/24 (67)

DREAMM-2 CSR, Table 3.0350

Subject [redacted] and Subject [redacted] (2.5 mg/kg) and Subject [redacted] and Subject [redacted] (3.4 mg/kg) had visual acuity-related events. Subject [redacted] (3.4 mg/kg) had a peripheral corneal ulcer with a 1-line change in visual acuity.

Three subjects discontinued due to corneal events: Subject [redacted], Subject [redacted], Subject [redacted]. Progressive disease was the primary reason for discontinuation for Subject [redacted] and Subject [redacted].

Subjects could have more than one action taken and be represented more than once.

In the 2.5 mg/kg cohort from DREAMM-2, the median time to onset of the first occurrence of a Grade ≥2 corneal event was 34.5 days and the median duration was 84.5 days (Table 18).

Table 18 Onset and Duration of the First Occurrence of Corneal Events of Grade 2 or Above (DREAMM-2 Full Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg Frozen (N=95)	3.4 mg/kg Frozen (N=99)	3.4 mg/kg Lyo (N=24)
Subjects experiencing events of Grade ≥2	60 (63)	72 (73)	21 (88)
Time of Onset, days, n (%)			
n	60	72	21
1-21	10 (17)	23 (32)	6 (29)
22-42	24 (40)	31 (43)	11 (52)
43-63	16 (27)	12 (17)	4 (19)
>63	10 (17)	6 (8)	0
Mean±SD	40.7±23.93	35.0±23.97	27.8±12.16
Median (range)	34.5 (19 to 143)	23.0 (9 to 150)	23.0 (18 to 62)
Duration, days, n (%)			
n	38	41	6
1-21	4 (11)	7 (17)	0
22-42	7 (18)	6 (15)	2 (33)
>42	27 (71)	28 (68)	4 (67)
Mean±SD	79.6±48.86	81.6±59.74	54.3±36.64
Median (range)	84.5 (8 to 193)	86.0 (9 to 253)	43.0 (23 to 127)

DREAMM-2 CSR, Table 3.0910

In the 2.5 mg/kg cohort from DREAMM-2, the median percentage of time on treatment with a corneal event was 53.4% [DREAMM-2 CSR, Table 3.1330].

Best Corrected Visual Acuity (BCVA)

A possible worsening in BCVA was defined as change from baseline >0.12 to <0.3 in logMAR score and a definite worsening in BCVA is defined as a change from baseline ≥0.3 in logMAR score.

In the 2.5 mg/kg pooled data, participants who experienced a definite worsening of visual acuity had a median time to onset of 63.0 days and a median duration of 23.0 days for their first event (Table 19). Most participants who experienced a definite worsening of visual acuity experienced 1 or 2 events (89%). As of the cut-off date, while 60 (62%) of patients were still on study, the worsening of visual acuity resolved in the majority of participants prior to the end of treatment exposure (64%) and 20% of participants' worsening visual acuity resolved post end of treatment exposure.

Table 19 Characteristics for Worsening in Best Corrected Visual Acuity Score (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Time to onset of first occurrence, days, n (%)			
n	44	69	86
Mean (SD)	65.4 (36.06)	72.3 (57.74)	67.6 (53.54)
Median (range)	63.0 (21 to 190)	56.0 (18 to 274)	45.0 (18 to 274)
1 - 21	1 (2)	4 (6)	5 (6)
22 - 42	8 (18)	21 (30)	28 (33)
43 - 63	14 (32)	17 (25)	23 (27)
64 - 105	17 (39)	14 (20)	16 (19)
>105	4 (9)	13 (19)	14 (16)
Outcome of first occurrence, n (%) [a]			
n	44	69	86
Resolved prior to end of treatment exposure	28 (64)	46 (67)	58 (67)
Resolved post end of treatment exposure	9 (20)	11 (16)	11 (13)
Re-started	1 (2)	1 (1)	1 (1)
Not re-started	8 (18)	10 (14)	10 (12)
Not resolved, re-started	0	4 (6)	4 (5)
Not resolved, not re-started	7 (16)	8 (12)	13 (15)
Not discontinued	0	2 (3)	4 (5)
Discontinued, follow-up ongoing	0	2 (3)	3 (3)
Discontinued, follow-up ended	7 (16)	4 (6)	6 (7)
Duration of first occurrence, days [a,b]			
n	37	57	69
Mean (SD)	31.3 (21.89)	60.7 (46.93)	56.5 (44.82)
Median (range)	23.0 (5 to 89)	45.0 (7 to 197)	43.0 (7 to 197)
Number of occurrences (based on subjects with the event), n (%)			
n	44	69	86
One	24 (55)	43 (62)	54 (63)
Two	15 (34)	13 (19)	19 (22)
Three or more	5 (11)	13 (19)	13 (15)
Outcome post treatment exposure [c]			
Number of subjects with unresolved event at the end of treatment exposure, or with event onset post treatment exposure, n (%)	23	32	36
Resolved	15 (65)	13 (41)	13 (36)
Not resolved, follow-up ongoing	0	7 (22)	9 (25)
Not resolved, follow-up ended	8 (35)	12 (38)	14 (39)
Time to resolution post treatment exposure, days			
n	15	13	13
Mean (SD)	27.2 (23.32)	95.3 (90.72)	95.3 (90.72)
Median (range)	21.0 (7 to 97)	63.0 (7 to 330)	63.0 (7 to 330)

ISS Source Table 3.3410

a. Duration is the time from onset of any visual acuity event (change from baseline logMAR score ≥0.3 in either eye) until the event is resolved (change from baseline logMAR score <0.3 in both eyes). It requires at least a 1-day gap between the resolution of all events from first occurrence to the onset of second occurrence.

b. Snellen acuity response of "no equivalent value" is treated as missing. Missing values in one eye do not prevent an event in the other from being resolved.
c. The end of treatment exposure is defined as last infusion date +20 days.

Participants with definite decreases in visual acuity (ΔlogMAR ≥0.3 as compared to baseline) include individuals with varying degrees of worst-case post-baseline Snellen equivalent values, which can range from better than 20/70 in either or both eyes to values equal to or worse than 20/200. Among this group of participants are individuals who continue on the study and the behaviour of this group will be further described in future updates.

Risk factors and risk groups:

In the DREAMM-2 study, logistic regression analysis showed a statistically significant (p=0.014) association between history of dry eye and the development of a Grade 2 or greater corneal event (DREAMM-2 CSR, Table 3.1280).

Few population-based studies have been published to describe the incidence or prevalence of eye disorders among patients with hematologic malignancies, or MM specifically. The prevalence of ocular involvement in leukemic patients has been reported to range between 9% and 90% in various studies [Kincaid, 1983; Alemayehu, 1996; Reddy, 2003; Buchan, 2003; Charif, 2002; Lang, 1998]. This extensive variation can be mainly attributed to heterogeneous incidence of ocular disorders by leukaemia type, different source population and study design. In a recently published cross-sectional study based on 93 Italian MM patients, reduced visual acuity (at least in one eye), absence of lens opacities, retina disorder and dry eye syndrome was reported with a prevalence of 48%, 13%, 54% and 53%, respectively [Pennisi, 2019]. Based on the data from Swedish patient registers between 1997 and 2012, the risk of senile cataract would increase by 1.7-fold after the MM diagnosis [Hemminki, 2016].

Eye disorders developed in 5% or more of participants in Phase 3 clinical trials of lenalidomide, elotuzumab, ixazomib and carfilzomib, based on their USPIs. 17% of the patients with at least one prior therapy, who were treated with lenalidomide + dexamethasone, developed blurred vision. 6% (Grade ≥3: 3%) and 14% (Grade ≥3: 6%) of the NDMM patients developed cataract when treated with Lenalidomide + low-dose dexamethasone for 18 cycles or until disease progression, respectively. 12% (Grade ≥3: 6%) of the previously treated MM patients treated with elotuzumab + lenalidomide + dexamethasone therapy developed cataract. Of the patients treated with ixazomib + lenalidomide + dexamethasone treatment regimen, 26% (Grade ≥3: 2%) developed any type of eye disorder, including blurred vision (6%), dry eye syndrome (5%), and conjunctivitis (6%).

Preventability

Ocular Sub-study

In an ocular sub-study in DREAMM-2, 30 participants (n=17 in 2.5 mg/kg cohort and n=13 in 3.4 mg/kg cohort) had one of their eyes randomised to receive monocular topical corticosteroids for the first four cycles of study treatment to evaluate their effect on ocular examination findings. Full details of the ocular sub-study are presented in the DREAMM-2 CSR, Section 7.3.4.

No difference was observed between eyes treated with steroid eye drops and untreated eyes in terms of the incidence of corneal events according to the GSK Scale (71% in both treated and untreated eye in the 2.5 mg/kg cohort) nor the median time to onset (23.5 days in treated eye versus 26.5 days in untreated eye in the 2.5 mg/kg cohort) [DREAMM-2 CSR, Table 3.1180]. Severity of corneal events as measured using the GSK Scale was also similar between the treated eye (29% Grade 3/4 events) and untreated eye (24% Grade 3/4 events) in the 2.5 mg/kg cohort ([DREAMM-2- CSR, Table 3.1160]. Therefore, there is no evidence that steroid eye drops are beneficial in preventing or mitigating corneal events.

In the product labelling, patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on treatment. Patients are advised to use preservative-free artificial tears eye drops at least 4 times a day, beginning on the first day of infusion and continuing until completion of treatment as this may reduce corneal symptoms. Dose modification guidelines for corneal events are also provided.

Additional risk minimisation measures will be implemented (see Part V, Section V.2). Monitoring of corneal events will continue during clinical trials and in the post-marketing setting.

Future studies will help to further characterise the corneal events associated with belantamab mafodotin, including optimal management and time to resolution of corneal signs and symptoms.

Impact on the risk-benefit balance of the product:

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the identified risk of keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye. These corneal events and visual changes can be managed in clinical practice through appropriate monitoring, as well as dose modifications, and additional risk minimisation efforts described in Part V, Section V.2 of this document.

Public health impact:

While changes to the corneal epithelium on ocular examination with or without visual changes have frequently been observed in the belantamab mafodotin clinical trial programme, the public health impact of this identified risk is expected to be low due to the limited number of patients with the specific indication and the anticipated ability to manage the risk via routine and additional risk minimisation activities, described in Part V of this EU RMP.

Important Potential Risk #1: Nephrotoxicity

Potential mechanisms:

Kidney injury is a common complication of MM and other plasma cell dyscrasias, and it is associated with increased mortality. Multiple pathogenic mechanisms can contribute to kidney

injury in patients with MM, some of which are the result of nephrotoxic free light chains and some of which are independent of paraprotein deposition.

Nonclinical studies demonstrated tubular degeneration/regeneration in the kidneys which was considered likely related to the cytotoxic drug conjugate, mcMMAF, as kidney toxicity has been reported with other auristatin ADCs [Saber, 2015].

Evidence source(s) and strength of evidence:

Non-clinical safety studies have demonstrated dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey) directly related to belantamab mafodotin, accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study.

Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with ADA, following 5 weekly doses of 10 mg/kg, led to the early euthanasia of one monkey. Glomerulonephritis associated with immune complex formation is not expected to be reversible.

Characterisation of the risk:

A low incidence of renal-related adverse events has been observed in patients receiving belantamab mafodotin and in many cases coincided with disease progression. Of note, renal impairment may occur in the setting of multiple myeloma disease progression.

In DREAMM-2, there were few participants who developed abnormalities in estimated glomerular filtration rate (eGFR) or albumin/creatinine ratio while on study [DREAMM-2 CSR, Section 7.7.1].

In the 2.5 mg/kg pooled data, there were 27 (26%) participants who had an increase from baseline in serum creatinine, mostly to Grade 1 or 2 [ISS Source Table 3.7100]. There was 1 participant who had an increase in creatinine that was considered to be of Grade 4 severity.

This was Subject [redacted] from DREAMM-2 who had an increase in creatinine (Grade 4) on study Day 61 after discontinuing study treatment on study Day 22 (stable disease) due to acute kidney injury and kidney failure considered unrelated to study treatment. This participant had Grade 1 creatinine levels at baseline and Grade 2/3 creatinine levels at all other post-baseline measurements.

Risk factors and risk groups:

Patients with multiple myeloma have an increased risk of renal impairment. A renal impairment study (Study 209626 / DREAMM-12) is planned.

Preventability:

Patients with active renal conditions or severe renal impairment were not allowed in belantamab mafodotin monotherapy clinical trials.

Nonclinical data around renal findings are included in the product labelling.

Based on review of the data from the integrated safety population, patients with mild/moderate renal impairment do not seem to have higher risk than patients with normal renal function.

Impact on the risk-benefit balance of the product:

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the potential risk of Nephrotoxicity. Nonclinical data are included in the product labelling.

Public health impact:

The public health impact of this potential risk is expected to be minimal due to the limited number of patients with the specific indication and the inclusion of relevant nonclinical renal data in the product labelling.

Important Potential Risk #2: Increased risk of infections due to immunosuppression and/or neutropenia

Potential mechanisms:

The potential mechanism for immunosuppression is a haematopoietic/immune targeting via specific (e.g. plasma B cells) or nonspecific mechanism of uptake. Transient NK cell reductions likely related to ADCC activity.

Myelotoxicity related to MMAF targeting highly dividing cells in the bone marrow and/or nonspecific uptake into dividing cells leading to cell death through binding to Fc gamma receptors, human neonatal FcRn receptor binding and/macropinocytosis.

Evidence source(s) and strength of evidence:

Decreases in immunoglobulins were seen in monkeys at all doses. Decreases in lymphoid cellularity/necrosis (dose-responsive in severity) was noted in the spleen and/or lymph nodes at ≥3 mg/kg/week, which was associated with decreases in thymic cellularity in rats.

In nonclinical studies, decreased cellularity of the bone marrow, with toxic (decreases in haemoglobin, white cells, and lymphocytes) and adaptive (rebound reticulocytosis and increases in white blood cell counts, shifts in M:E ratio, extramedullary haematopoiesis) effects on the hematopoietic system at higher doses in rats.

Neutropenia, leukopenia and lymphopenia have been reported in MM participants receiving belantamab mafodotin.

Characterisation of the risk

Immunosuppression

Immunosuppression is frequently associated with increased risks of infections. Serious and non-serious infections have been reported in the clinical studies with belantamab mafodotin, including reports of lung infections, pneumonia and sepsis.

Neutropenia

Neutropenic *events* were defined as neutropenia, neutrophil count decreased, or febrile neutropenia. In the 2.5 mg/kg pooled data, 14 (14%) participants experienced a total of 20 neutropenic events (Table 20). Neutropenic events were reported as Grade 3/4 events for 9 (9%) participants [ISS Source Table 3.4400], and study treatment-related for 9 (9%) participants. None of the neutropenic events was an SAE. There was no change to study treatment due to a neutropenic event for any participant. For the majority of participants (12/14), their neutropenic event had recovered/resolved or recovered/resolved with sequelae at the data cut-off. There were 2 (2%) participants whose neutropenic event had not recovered/resolved at the data cut-off, both of whom had discontinued study treatment but remain in follow-up.

Table 20 Characteristics of Neutropenic Events (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Number of subjects with event, n (%)	14 (14)	33 (24)	35 (22)
Number of events	20	49	53
Event Characteristics (% based on all subjects) [a], n/N (%)			
Serious	0/103	4/137 (3)	4/161 (2)
Study treatment-related	9/103 (9)	18/137 (13)	20/161 (12)
Number of Occurrences (% based on all subjects), n/N (%)			
One	10/103 (10)	22/137 (16)	23/161 (14)
Two	3/103 (3)	7/137 (5)	7/161 (4)
Three or more	1/103 (<1)	4/137 (3)	5/161 (3)
Outcome (% based on all subjects) [b], n/N (%)			
Recovered/Resolved	11/103 (11)	27/137 (20)	29/161 (18)
Recovered/Resolved with Sequelae	1/103 (<1)	2/137 (1)	2/161 (1)
Recovering/Resolving	0/103	0/137	0/161
Not Recovered/Not Resolved	2/103 (2)	4/137 (3)	4/161 (2)
Fatal	0/103	0/137	0/161
Maximum Grade (% based on all subjects), n/N (%)			
Grade 1	2/103 (2)	5/137 (4)	5/161 (3)
Grade 2	3/103 (3)	8/137 (6)	8/161 (5)
Grade 3	5/103 (5)	16/137 (12)	17/161 (11)
Grade 4	4/103 (4)	4/137 (3)	5/161 (3)
Grade 5	0/103	0/137	0/161
Action Taken (% based on all subjects) [a], n/N (%)			

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Study treatment withdrawn	0/103	0/137	0/161
Dose reduced	0/103	1/137 (<1)	2/161 (1)
Dose not changed	14/103 (14)	31/137 (23)	32/161 (20)
Dose interrupted/delayed	0/103	2/137 (1)	4/161 (2)
Dose reduced or interrupted/delayed	0/103	3/137 (2)	5/161 (3)
Infusion interrupted but completed	0/103	0/137	0/161
Infusion stopped early and not completed	0/103	0/137	0/161

ISS Source Table 3.4500

a. May be included in more than one category for 'Event Characteristics' and 'Action Taken'.

b. Worst case hierarchy: Fatal>Not Recovered/Not Resolved>Recovering/Resolving>Recovered/Resolved with sequelae>Recovered/Resolved

In the 2.5 mg/kg pooled data, the median time to onset of the first occurrence of a neutropenic event was 22.0 days and the median duration was 25.0 days (Table 21).

Table 21 Time to Onset and Duration of First Occurrence of Neutropenic Events (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Number of subjects experiencing neutropenia, n (%)	14 (14)	33 (24)	35 (22)
Time of onset, days, n (%)			
n	14	33	35
1-21 22-42 43-63 >63	6 (43) 4 (29) 0 4 (29)	12 (36) 3 (9) 4 (12) 14 (42)	12 (34) 5 (14) 4 (11) 14 (40)
Mean SD Median (range)	38.1 38.25 22.0 (1 to 123)	58.5 67.98 43.0 (1 to 342)	57.0 66.29 43.0 (1 to 342)
Duration, days [ab], n (%)			
n	13	32	34
1-21 22-42 >42	6 (46) 1 (8) 6 (46)	20 (63) 7 (22) 5 (16)	22 (65) 7 (21) 5 (15)
Mean SD Median (range)	47.3 48.03 25.0 (1 to 148)	19.3 17.32 15.5 (2 to 65)	19.1 16.84 15.5 (2 to 65)

ISS Source Table 3.4900

a. The duration is defined as time from onset of any neutropenia event to the first time the subject is free of any neutropenia event. It requires at least one day gap between the resolution of all events from first course to the onset of second course.

b. Imputed AE stop date was used in the calculation of duration if the outcome of the event was resolved/resolved with sequelae and AE stop date was partial with day missing. Imputed AE start date was used in calculation if it is partial with day missing.

In the 2.5 mg/kg pooled data, no participant had a Grade 3/4 event of neutrophil count decreased that was associated with a concomitant report of a Grade ≥2 event of infection or sepsis [ISS Source Table 3.4700 and ISS Source Table 3.4800].

Risk factors and risk groups:

Immunosuppression

MM subjects frequently are immunodeficient due to the underlying condition, and concomitant hypogammaglobulinemia. Patients with underlying immunosuppression may be at risk for infection. Assessment of changes in immunoglobulin levels is challenging in patients with MM.

Neutropenia

The frequency of neutropenia in RRMM patients with a median of 5 prior lines of therapy was reported as 17% (12% Grade 3/4 events) [Hajek, 2017], and the incidence observed with belantamab mafodotin appears to be lower with no concomitant Grade ≥2 infections.

MM patients have been estimated to have up to 7-fold risk of developing serious infections relative to the general population, based on case-control study results [Blimark, 2015]. A cohort study based on 199 Australian MM patients diagnosed between 2008 and 2012 showed that the incidence rate of bloodstream infections (BSI) was 16.9 cases per 100 patient-years [Teh, 2017]. Another observational study including 100 RRMM patients treated with Bortezomib from 2011 to 2015 in Taiwan reported 18% of patients developed pneumonia during follow-up [Huang, 2018].

In summary, neutropenia is common in patients with RRMM, and if prolonged, poses an increased risk of infection, especially for some drug classes such as immunomodulatory agents.

Preventability:

Monitoring for clinical signs of infection based on product labelling and routine standard of care in the RRMM setting, including antibacterial/antiviral prophylaxis and the immediate treatment of infections according to MM treatment guidelines.

Haematologic panel assessments and supportive therapy (e.g. transfusions, growth factors) should be provided according to standard medical practice. The product labelling contains information on the incidence of haematologic effects including neutropenia, lymphopenia and leukopenia.

Impact on the risk-benefit balance of the product:

The benefit of belantamab mafodotin as a single agent treatment for adult patients with RRMM in the heavily pre-treated immunomodulatory agent/PI refractory setting outweighs the potential risk of Increased risk of infections due to immunosuppression and/or neutropenia.

Public health impact:

The public health impact of this potential risk is expected to be minimal due to the limited number of patients with the specific indication. Additionally, standard medical practice and supportive therapy are expected to further reduce individual patient and public health impact.

SVII.3.2 Presentation of the missing information

Missing Information #1: Safety in patients with severe renal impairment

Primary glomerular injury and tubular degeneration were observed in rats at doses >30 mg/kg, and in monkeys at doses 10 mg/kg. The morphologic changes were accompanied by large molecular proteinuria (albuminuria) and enzymuria. The renal changes were dose-dependent and reversible. Overall, there has been a low incidence of renal events in the monotherapy programme to date. Patients with mild/moderate renal impairment do not seem to have higher risk than patients with normal renal function.

A renal impairment study (209626 / DREAMM-12) will be performed to evaluate the potential impact of severe renal impairment on the pharmacokinetics and safety of belantamab mafodotin and to provide dosing guidance if needed.

Missing Information #2: Safety in patients with hepatic impairment

Patients with hepatic impairment and unstable liver disease were excluded from belantamab mafodotin monotherapy clinical trials. Patients with mild hepatic impairment according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) classification were included.

Mild elevations of liver enzymes have been reported in the monotherapy programme.

A hepatic impairment study (209627 / DREAMM-13) will be performed to evaluate the potential impact of increased levels of hepatic impairment on the pharmacokinetics and safety of belantamab mafodotin and to provide dosing guidance if needed.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 22 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye
Important potential risks	• Nephrotoxicity • Increased risk of infections due to immunosuppression and/or neutropenia
Missing information	• Safety in patients with severe renal impairment • Safety in patients with hepatic impairment

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required:

Specific adverse reaction follow-up questionnaires for Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye:

A targeted follow-up questionnaire (TFQ) will be used to collect consistent information on designated corneal events (visual disturbances) reported from the post-marketing setting globally.

The TFQ is available in ANNEX 4 of the RMP.

III.2 Additional pharmacovigilance activities

Study short name and title:

Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody (205678 / DREAMM-2)

Rationale and study objectives:

Primary: To evaluate the clinical efficacy of 2 doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma

Secondary:

- To further evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM
- To evaluate the safety of belantamab mafodotin in participants with RRMM
- To evaluate the pharmacokinetic profile of belantamab mafodotin
- To assess anti-drug antibodies (ADAs) against belantamab mafodotin
- Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin
- To evaluate disease and treatment related symptoms and impact on function and health-related quality-of life

Study design:

This is a Phase II, open-label, two-arm, randomized, multicentre study to evaluate the efficacy and safety of belantamab mafodotin monotherapy at the dose levels of 2.5 mg/kg and 3.4 mg/kg administered intravenously (IV), Q3W, in participants with RRMM. Participants will be treated until disease progression or unacceptable toxicity. The study consists of a screening/baseline period, a treatment period, and a posttreatment follow-up period.

Study population:

Participants with relapsed/refractory multiple myeloma

Milestones:

Final study report: Sep 2022

Final study report submission: Feb 2023

Study short name and title:

Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (207495 / DREAMM-3)

Rationale and study objectives:

Primary: To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma (RRMM)

Key Secondary: To compare the overall survival with belantamab mafodotin vs pom/dex in participants with RRMM

Secondary:

- To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM
- To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM
- To evaluate the pharmacokinetic profile of belantamab mafodotin
- To assess anti-drug antibodies (ADAs) against belantamab mafodotin
- To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects
- To evaluate and compare changes in symptoms and health-related quality of life (HRQOL)of belantamab mafodotin to pom/dex

- To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better for belantamab mafodotin vs pom/dex

Study design:

This study is a Phase III, open-label, randomized, multicentre study evaluating the efficacy and safety of single agent belantamab mafodotin compared to pom/dex in participants with RRMM.

Study population:

Participants with relapsed/refractory multiple myeloma

Milestones:

Projected Primary endpoint analysis: October 2022

Study report submission: Q1 2023

Overall survival and Final analysis: July 2024

Study short name and title:

A Phase I Study of Belantamab Mafodotin in Multiple Myeloma Participants with Normal and Impaired Renal Function. (209626 / DREAMM-12)

Rationale and study objectives:

Primary: To describe the effects of renal impairment on the pharmacokinetics of belantamab mafodotin in participants with RRMM and with severe renal impairment, ESRD (not on dialysis) or ESRD (on dialysis) compared to participants with normal renal function

Secondary: To evaluate safety and tolerability using parameters, including adverse events, vital signs, ECGs, and clinical laboratory assessments in participants with RRMM who have normal or impaired renal functions

Study design:

This is a Phase I study to assess the PK, safety, and tolerability of belantamab mafodotin monotherapy in participants with RRMM who have had at least 3 lines of prior treatment and have either normal or impaired renal functions. Renal impairment will be classified based on the eGFR using the MDRD formula and according to FDA-defined categories of severe, ESRD (not on dialysis), or ESRD (on dialysis).

Study population:

Participants with RRMM who have normal and varying degrees of impaired renal function

Milestones:

Final study report: 3Q2024

Study short name and title:

A Phase I Study of Belantamab Mafodotin in Multiple Myeloma Participants with Normal and Impaired Hepatic Function (209627 / DREAMM-13)

Rationale and study objectives:

Primary: To evaluate the effects of hepatic impairment on the PK of belantamab mafodotin in RRMM participant with impaired hepatic function as compared to RRMM participants with normal hepatic function

Secondary: To evaluate the safety, and tolerability parameters, including AEs, vital signs, ECGs, and clinical laboratory assessments in participants with RRMM who have normal or impaired hepatic functions

Study design:

This is a Phase I study to evaluate the PK and safety of belantamab mafodotin monotherapy in RRMM participants with impaired hepatic function and in matched RRMM participants with normal hepatic function. Hepatic impairment will be classified as moderate, and severe dysfunction according to NCI-ODWG's Scale for Hepatic Impairment in Oncology

Study population:

Participants with RRMM who have normal and varying degrees of impaired hepatic function

Milestones:

Final study report: 4Q2026

III.3 Summary Table of additional Pharmacovigilance activities

Table 23 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody - Ongoing	Primary: To evaluate the clinical efficacy of 2 doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma Secondary: To further evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM To evaluate the safety of belantamab mafodotin in participants with RRMM To evaluate the pharmacokinetic profile of belantamab mafodotin To assess anti-drug antibodies (ADAs) against belantamab mafodotin Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin To evaluate disease and treatment related symptoms and impact on function and health-related quality-of life	Standard clinical and laboratory tests Collection of AEs and SAEs AEs of special interest Ocular findings on ophthalmic exam Further characterization of important identified and potential risks: • Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye • Nephrotoxicity • Increased risk of infections due to immunosuppression and/or neutropenia	Final study report Final study report submission	Sep 2022 Feb 2023
207495 (DREAMM-3): Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma – Ongoing	Primary: To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma Key Secondary: To compare the overall survival with belantamab mafodotin vs pom/dex in participants with RRMM	Incidence of AEs and changes in laboratory parameters Ocular findings on ophthalmic exam	Projected Primary endpoint analysis	Oct 2022

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	Secondary: To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the pharmacokinetic profile of belantamab mafodotin To assess anti-drug antibodies (ADAs) against belantamab mafodotin To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects To evaluate and compare changes in symptoms and health-related quality of life (HRQOL)of belantamab mafodotin to pom/dex To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better for belantamab mafodotin vs pom/dex	Symptomatic adverse effects as measured by the PRO-CTCAE and OSDI Changes in safety assessments, including vital signs and ECGs Further characterization of important identified and potential risks: • Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye • Nephrotoxicity • Increased risk of infections due to immunosuppression and/or neutropenia	Study report submission Overall survival and Final analysis	Q1 2023 Jul 2024
Category 3- Required additional pharmacovigilance activities				
209626 (DREAMM-12): A Phase 1 open label study of GSK2857916 in relapsed/refractory multiple myeloma patients with renal impairment	Primary: To describe the effects of renal impairment on the pharmacokinetics of belantamab mafodotin in participants with RRMM and with severe renal impairment, ESRD (not on dialysis) or ESRD (on dialysis) compared to participants with normal renal function	Safety of belantamab mafodotin in patients with severe renal impairment Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic	Final study report	1Q2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	Secondary: To evaluate safety and tolerability using parameters, including adverse events, vital signs, ECGs, and clinical laboratory assessments in participants with RRMM who have normal or impaired renal functions	parameters; dialysate PK parameters, as data permit Change from baseline in vital signs (blood pressure and heart rate), monitoring and incidence of adverse events, toxicity grading of clinical laboratory tests, ECG findings, and physical examinations		
209627 (DREAMM-13): A Phase 1 open label study of GSK2857916 in patients with relapsed/refractory multiple myeloma and hepatic impairment	Primary: To evaluate the effects of hepatic impairment on the PK of belantamab mafodotin in RRMM participant with impaired hepatic function as compared to RRMM participants with normal hepatic function Secondary: To evaluate the safety, and tolerability parameters, including AEs, vital signs, ECGs, and clinical laboratory assessments in participants with RRMM who have normal or impaired hepatic functions	Safety of belantamab mafodotin in patients with hepatic impairment Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic parameters Change from baseline in vital signs (blood pressure and heart rate), monitoring and incidence of AEs, toxicity grading of clinical laboratory tests, ECG findings and physical examinations	Final study report	2Q2028

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 24 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody Ongoing	Primary: To evaluate the clinical efficacy of 2 doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma Secondary: To further evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM To evaluate the safety of belantamab mafodotin in participants with RRMM To evaluate the pharmacokinetic profile of belantamab mafodotin To assess anti-drug antibodies (ADAs) against belantamab mafodotin Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin To evaluate disease and treatment related symptoms and impact on function and health-related quality-of life	Overall response rate Clinical benefit rate Duration of response Time to response Progression-free survival Time to progression Overall survival	Final study report Final study report submission	Sep 2022 Feb 2023
207495 (DREAMM-3): Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma	Primary: To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma Key Secondary: To compare the overall survival with belantamab mafodotin vs pom/dex in participants with RRMM	Progression-free survival Overall survival Overall response rate	Projected Primary endpoint analysis Study report submission	Oct 2022 Q1 2023

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Ongoing	Secondary: To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the pharmacokinetic profile of belantamab mafodotin To assess anti-drug antibodies (ADAs) against belantamab mafodotin To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects To evaluate and compare changes in symptoms and health-related quality of life (HRQOL)of belantamab mafodotin to pom/dex To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better for belantamab mafodotin vs pom/dex	Clinical benefit rate Duration of response Time to response Time to progression	Overall survival and Final analysis	Jul 2024

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 25 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Identified Risks	
Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye	Routine risk communication: SmPC Sections 4.2: Posology and method of administration 4.4: Special warnings and precautions for use 4.8: Undesirable effects PL Sections 2. What you need to know before you take Belantamab mafodotin 4. Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Potential Risks	
Nephrotoxicity	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk: Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Increased risk of infections due to immunosuppression and/or neutropenia	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk:

	Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Missing Information	
Safety in patients with severe renal impairment	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk: Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Safety in patients with hepatic impairment	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk: Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products

V.2. Additional Risk Minimisation Measures

Educational Materials for Healthcare Professionals and Patients

Objectives:

To mitigate the possible risks of keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye in patients taking belantamab mafodotin.

Rationale for the additional risk minimisation activity:

To help oncologists, eye care professionals and patients understand the corneal risks associated with belantamab mafodotin, so that corneal examination findings, and/or visual changes can be promptly identified and managed according to the product labelling.

Patients will receive educational materials to help them understand the corneal risks and potential visual impairment associated with taking belantamab mafodotin. This includes guidance on screening exams as well as treatment with preservative-free artificial tears, and how to speak with their doctors about their symptoms.

Oncologists will receive educational materials to help them understand the corneal risks associated with prescribing belantamab mafodotin and how this risk is best managed and

mitigated. They will be encouraged to work closely with the eye care professional since their treatment plan may be impacted by the eye care professional's exam findings.

Eye care professionals will receive educational materials to help them understand the corneal risks associated with belantamab mafodotin with the aim to optimise symptom recognition and reporting. They will be encouraged to work closely with the treating oncologist as their findings may impact the oncologist's treatment plan.

Target audience and planned distribution path:

Oncologists and eye care professionals will receive educational materials to help them understand the corneal risks associated with belantamab mafodotin.

Patients taking belantamab mafodotin will receive educational materials from their treating oncologist focusing on the possible risks of keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye and the main required actions to be taken in order to prevent and minimize these risks.

Following approval of the EU RMP, the Applicant will oversee and follow local processes in each member state to ensure implementation of the education materials, which includes submission to the national competent authority and will include the proposed tools to be used and a local communication and distribution plan to the predetermined target audience.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance: ongoing monitoring of corneal finding and/or visual change adverse event reports from all sources (spontaneous, clinical trials, post-marketing surveillance) with special attention to compliance with labelling recommendations.

Surveys (Patients, Oncologists, Eye care professionals): Four primary market research studies were undertaken to increase the level of confidence that all stakeholders would understand the potential risks and appropriate steps to manage the risks (among other study objectives)

In all four studies, respondents were presented with language that described the risks of AEs and advised of proper prevention and management (including escalation). They were given the opportunity to ask questions and give guidance on language that would make risks and/or management and steps for escalation clearer, as well as to share their ideas on what processes or practices might make proper management of those risks easier, and therefore more likely for the stakeholders to comply with. As these were all qualitative research studies, there was no quantitative criteria for success defined. Finalization of patient education materials will include literacy review to ensure 5th grade maximum reading level.

V.3 Summary of risk minimisation measures

Table 26 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Identified Risks		
Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye	**Routine risk minimisation measures**: SmPC Sections: 4.2, 4.4, 4.8 PL Sections: 2, 4 Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4. Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: The MAH shall ensure that in each Member State where belantamab mafodotin is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense and receive belantamab mafodotin have access to/are provided with the following educational materials to be disseminated through professional bodies consisting of the following: <u>Healthcare professionals (haematologists/oncologists/eye care professionals) educational materials:</u> • The Summary of Product Characteristics • Corneal adverse reaction guides o Detailed information on the corneal effects of belantamab mafodotin and includes management and monitoring guidance for treating HCPs o Training material includes detail on the anatomy and physiology of the eye and description of eye exams	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow-up questionnaire **Additional pharmacovigilance activities**: 205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody - Ongoing 207495 (DREAMM-3): Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) - Ongoing

	• Eye care screening sheet to ensure coordinated communication between the haematologist/oncologist and eye care professional Patient education materials: • The Package Leaflet • Corneal adverse reaction guides o Detailed information on the corneal effects of belantamab mafodotin o Includes detail on the anatomy and physiology of the eye and description of eye exams • Patient and pharmacy eye drop wallet cards.	
Potential Risks		
Nephrotoxicity	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: 205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody - Ongoing 207495 (DREAMM-3): Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) - Ongoing
Increased risk of infections due to immunosuppression and/or neutropenia	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: 205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody - Ongoing

		207495 (DREAMM-3): Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) - Ongoing
Missing Information		
Safety in patients with severe renal impairment	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: 209626 (DREAMM-12): A Phase 1 open label study of GSK2857916 in relapsed/refractory multiple myeloma patients with renal impairment
Safety in patients with hepatic impairment	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: 209627 (DREAMM-13): A Phase 1 open label study of GSK2857916 in patients with relapsed/refractory multiple myeloma and hepatic impairment

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for BLENREP

This is a summary of the risk management plan (RMP) for belantamab mafodotin. The RMP details important risks of BLENREP, how these risks can be minimised, and how more information will be obtained about BLENREP risks and uncertainties (missing information).

The BLENREP summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how BLENREP should be used.

This summary of the RMP for BLENREP should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates to the RMP for BLENREP.

I. The medicine and what it is used for

BLENREP is authorised as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least 4 prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 antibody, and who have demonstrated disease progression on the last therapy. It contains BLENREP as the active substance and it is given intravenously.

Further information about the evaluation of BLENREP's benefits can be found in the BLENREP EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of BLENREP, together with measures to minimise such risks and the proposed studies for learning more about BLENREP's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of BLENREP, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of BLENREP is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of BLENREP are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BLENREP. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye
Important potential risks	Nephrotoxicity Increased risk of infections due to immunosuppression and/or neutropenia
Missing information	Safety in patients with severe renal impairment Safety in patients with hepatic impairment

II.B Summary of important risks

Important identified risk 1: Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye	
Evidence for linking the risk to the medicine	Corneal events are a class effect reported with other MMAF-containing ADCs and have been reported with BLENREP. 'Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye' is considered an important identified risk based on the changes in the corneal epithelium on ocular examination that have frequently been observed in the BLENREP clinical trial programme. This finding was most commonly associated with blurred vision, dry eyes, photophobia, and changes in visual acuity.
Risk factors and risk groups	In the DREAMM-2 study, logistic regression analysis showed a statistically significant (p=0.014) association between history of dry eye and the development of a Grade 2 or greater corneal event (DREAMM-2 CSR, Table 3.1280).
Risk minimisation measures	**Routine risk minimisation measures**: SmPC Sections: 4.2, 4.4, 4.8 PL Sections: 2, 4 Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4. Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: Educational materials for prescribing haematologists/ oncologists, eye care professionals, and patients
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: 205678 (DREAMM-2): Open-label, randomized study of two doses of BLENREP in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody 207495 (DREAMM-3): Phase III Study of Single Agent BLENREP versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)

Important potential risk 1: Nephrotoxicity	
Evidence for linking the risk to the medicine	Non-clinical safety studies have demonstrated dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey) directly related to BLENREP, accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study. Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with ADA, following 5 weekly doses of 10 mg/kg, led to the early euthanasia of one monkey. Glomerulonephritis associated with immune complex formation is not expected to be reversible.
Risk factors and risk groups	Patients with multiple myeloma have an increased risk of renal impairment.
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: 205678 (DREAMM-2): Open-label, randomized study of two doses of BLENREP in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody 207495 (DREAMM-3): Phase III Study of Single Agent BLENREP versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)

Important potential risk 2: Increased risk of infections due to immunosuppression and/or neutropenia	
Evidence for linking the risk to the medicine	Decreases in immunoglobulins were seen in monkeys at all doses. Decreases in lymphoid cellularity/necrosis (dose-responsive in severity) was noted in the spleen and/or lymph nodes at ≥3 mg/kg/week, which was associated with decreases in thymic cellularity in rats.
Risk factors and risk groups	MM subjects frequently are immunodeficient due to the underlying condition, and concomitant hypogammaglobulinemia. Patients with underlying immunosuppression may be at risk for infection. Assessment of changes in immunoglobulin levels is challenging in patients with MM.
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **205678 (DREAMM-2):** Open-label, randomized study of two doses of BLENREP in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody **207495 (DREAMM-3):** Phase III Study of Single Agent BLENREP versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)

Missing information 1: Safety in patients with severe renal impairment	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **209626 (DREAMM-12)**: A Phase 1 open label study of GSK2857916 in relapsed/refractory multiple myeloma patients with renal impairment

Missing information 2: Safety in patients with hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** **209627 (DREAMM-13)**: A Phase 1 open label study of GSK2857916 in patients with relapsed/refractory multiple myeloma and hepatic impairment

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

DREAMM-2

Study short name and title:

Open-label, randomized study of two doses of BLENREP in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody (DREAMM-2)

Purpose of the Study:

To evaluate the clinical efficacy of 2 doses of BLENREP in participants with relapsed/refractory multiple myeloma

DREAMM-3

Study short name and title:

Phase III Study of Single Agent BLENREP versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM-3)

Purpose of the Study:

To compare the efficacy with BLENREP vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma (RRMM)

II.C.2 Other studies in post-authorisation development plan

There are no studies required for BLENREP.

PART VII: ANNEXES

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ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

GSK

Targeted Follow Up Questionnaire
Belantamab mafodotin & Visual Disturbances

Year of birth:	**Gender:** ☐ **Male** ☐ **Female**	**GSK Case No:**

Description of the Event:			
Event onset date: ___/____/___	Dose of belantamab mafodotin at onset of event:	_____	mg/kg
Belantamab mafodotin start date: ___/____/____	Number of courses of belantamab mafodotin at onset of event:		
As a result of the event, was the dose of belantamab mafodotin:		**Yes**	**No**
	Reduced?	☐	☐
	Interrupted?	☐	☐

Please describe the nature of visual problem, check all that apply:	**Both**	**Right**	**Left**
Reduction in visual acuity	☐	☐	☐
Decreased night vision	☐	☐	☐
Photophobia	☐	☐	☐
Double vision	☐	☐	☐
Dry eye	☐	☐	☐
Foreign body sensation	☐	☐	☐
If there are other symptoms, please describe:			

Best Corrected Visual Acuity (BCVA):		
	Right	**Left**
What was the patients best corrected visual acuity at baseline?		
What was the BCVA at the time of the event?		
What was the BCVA at time of resolution?		
Which measuring chart was used (Snellen, etc):		

Diagnostic Tests:		
	Yes	**No**
Was an ophthalmology test performed?	☐	☐
If yes, please provide the date the test was performed, a summary of the results or attach a copy of the report:		
Were any other relevant investigations performed?	☐	☐
If yes, please provide details below or on a separate sheet of paper:		

History:		
	Yes	**No**
Does the patient have dry eyes?	☐	☐
Does the patient have cataracts?	☐	☐
Has the patient had cataract surgery?	☐	☐
Does the patient have glaucoma?	☐	☐
Does the patient have any other pre-existing ocular diagnosis? If yes, specify:	☐	☐
Does the patient wear spectacles / glasses?	☐	☐
Is there a family history of vision / eye problems?	☐	☐
Has the patient taken any medications known to cause vision/eye problems?	☐	☐
If yes, please indicate which medications (include dose, start and stop dates):		

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

The educational programme is aimed at helping haematologists/oncologists, eye care professionals and patients understand the corneal risks associated with belantamab mafodotin, so that corneal examination findings, and/or visual changes can be promptly identified and managed according to the product labelling.

Prior to the launch of belantamab mafodotin in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme with the National Competent Authority.

The MAH shall ensure that in each Member State where belantamab mafodotin is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense and receive belantamab mafodotin have access to/are provided with the following educational materials to be disseminated through professional bodies consisting of the following:

Healthcare professionals (HCP) (haematologists/oncologists/eye care professionals) educational materials:

- The Summary of Product Characteristics (SmPC)
- Corneal adverse reaction guides
    - Detailed information on the corneal effects of belantamab mafodotin and includes management and monitoring guidance for treating HCPs.
    - Training material includes details on the anatomy and physiology of the eye and description of eye exams.
- Eye care screening sheet to ensure coordinated communication between the haematologist/oncologist and eye care professional.

Patient education materials:

- The Package Leaflet (PL)
- Corneal adverse reaction guides
    - Detailed information on the corneal effects of belantamab mafodotin
    - Includes details on the anatomy and physiology of the eye and description of eye exams.
- Patient and pharmacy eye drop wallet cards.

The healthcare professional's corneal adverse reaction guides

The HCPs corneal adverse reaction guides will contain the following key information:

Relevant information of the safety concern: keratopathy or microcyst-like epithelial changes (MEC) in the corneal epithelium

- Advise patients that corneal adverse reactions may occur during treatment.

- Patients with a history of dry eyes are more prone to develop changes in the corneal epithelium.

Details on how to minimise the safety concern addressed by the additional risk minimisation measures through appropriate monitoring:

- Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, should be performed at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on treatment.
- Patients experiencing keratopathy with or without changes in visual acuity may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings.
- Emphasise the need to consult the SmPC.

Key messages to convey during patient counselling:

- Patients should be advised to administer preservative-free artificial tears at least 4 times a day during treatment.
- Patients should avoid using contact lenses until the end of treatment.
- Patients should consult their haematologist/oncologist if corneal adverse reactions occur.
- Patients who report corneal symptoms should be referred to an eye care professional.
- Patients should be advised to use caution when driving or operating machinery.

Healthcare professionals' training material

Anatomy and physiology of the eye:

- Images of the eye are provided and reviewed.
- Keratopathy is characterised based on exam findings and patient reported outcomes.

Description of eye exams:

- Use of slit lamp exams provide detailed information on the anatomical structures in the eye. They can help detect a range of conditions, including keratopathy or microcyst-like epithelial changes in the corneal epithelium (as seen on eye examination).
- Description of visual acuity provides a measure of the visual system's ability to discern fine distinctions in the visual environment.
- Best corrected visual acuity (BCVA) refers to the visual acuity achieved with correction (such as glasses), as measured on the standard Snellen Visual Acuity Chart, monocularly and binocularly.
- Summary of visual acuity scores (20/20 vs <20/20) and how a score less than 20/20 can be corrected and managed by the patients.

Eye care screening sheet:

- Includes important information related to corneal adverse reactions associated with belantamab mafodotin, adverse event management, and instructions to facilitate communication between prescribers and eye care professionals for patients.

Patient corneal adverse reaction guides:

- Corneal adverse reactions may occur during treatment. Patients with a history of dry eyes are more prone to develop changes in the corneal epithelium.
- Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, should be performed at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on treatment.
- Patients experiencing keratopathy with or without changes in visual acuity may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings.
- Tell your haematologist/oncologist about any history of vision or eye problems.
- Consult the PL.

A description of the sign and symptoms of the risk of keratopathy:

- If you experience changes with your vision whilst on belantamab mafodotin, contact your haematologist/oncologist. Symptoms include the following:
  - redness, dryness, itching, burning sensation, or sandy or gritty sensation in their eyes;
  - sensitivity to light;
  - blurred vision;
  - pain in their eyes;
  - excessive watering of their eyes.

  If you experience changes in your vision or eyes after initiating treatment (changes have improved, persisted, or worsened since your last appointment), contact your haematologist/oncologist.
- Your HCP will ask you to use eye drops called preservative-free artificial tears during treatment. Administer them as instructed.

The patient and pharmacy eye drop wallet cards will contain the following key information:

Patient eye drop wallet card:

- Patient wallet card indicates the patient is on treatment with belantamab mafodotin and contains contact information for the haematologist/oncologist and the eye care professional.
- Present to HCP during regular follow up visits.

Pharmacy eye drop wallet card:

- Patients to present the pharmacy wallet card to the pharmacist to find eye drops called preservative-free artificial tears for use, as directed.