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	1.0	
Data lock point for this RMP	29 January 2024	
Date of final sign off	05 June 2025	
Rationale for submitting an updated RMP Not Applicable		
Summary of significant changes in this RMP Not Applicable		
PART	**MODULE**	**Changes made in the present EU-RMP**
Not applicable	Not applicable	Not applicable
Other RMP versions under evaluation Not applicable		
RMP Version number	**Submitted on**	**Procedure number**
Not applicable	Not applicable	Not applicable
Details of the currently approved RMP Not applicable		
Version number	**Approved with procedure**	**Date of approval (opinion date)**
Not applicable	Not applicable	Not applicable

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

ADC	Antibody-drug conjugate
ADCC/ADCP	Antibody dependent cellular cytotoxicity and phagocytosis
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aRMM	Additional Risk Minimization Measure
ASCT	Autologous stem cell transplant
ASIR	Age-standardized incident rate
ASMR	Age-standardized mortality rate
AST	Aspartate aminotransferase
BCMA	B-cell maturation agent
BCVA	Best corrected visual acuity
BPd	Belantamab Mafodotin, Pomalidomide, and Dexamethasone
BVd	Belantamab Mafodotin, Bortezomib, and Dexamethasone
CAR-T	Chimeric antigen receptor T-cell
CHMP	Committee for Medicinal Products for Human Use
CPRD	Clinical practice research datalink
CSI	Core safety information
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate use program
cys mcMMAF	cysteine maleimidocaproyl monomethyl auristatin F
DDI	Drug drug interaction
DVd	Daratumumab, Bortezomib and Dexamethasone
EA	Exposure Adjusted rate
EAP	Expanded access program
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECP	Eye Care Professional (ophthalmologist or optometrist)
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EPAR	European public assessment report
ESRD	End stage renal disease
GDS	Global data sheet
GGT	Gamma-glutamyltransferase
GLOBOCAN	Global Cancer Observatory
HIV	Human immunodeficiency virus
IR	Incidence rate
IRR	Infusion-related reaction
ITT	Intention-to-treat
KVA	Keratopathy Visual Acuity
LDH	Lactate dehydrogenase
MRP	Multidrug resistance-associated proteins
OATP	Organic-Anion-Transporting Polypeptide
PD	Progressive disease

P-gp	P-glycoprotein
PIL	Patient information leaflet
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVd	Pomalidomide, Bortezomib, and Dexamethasone
LFTs	Liver function tests
mAb	Monoclonal antibody
mcMMAF	maleimidocaproyl monomethyl auristatin F
MEC	Microcyst-like epithelial changes
MEK	Microcyst-like epithelial keratopathy
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MoA	Modes of action
NCI-ODWG	National Cancer Institute-Organ Dysfunction Working Group
NDMM	Newly diagnosed multiple myeloma
OATP	Organic-Anion-Transporting Polypeptide
OU	Both eyes
PD	Progression of disease
PI	Proteasome inhibitor
PIL	Patient information leaflet
PK	Pharmacokinetics
PT	Preferred term
PV	Pharmacovigilance
Q3W	Every 3 weeks
QoL	Quality of Life
RMM	Risk Minimization Measure
RMP	Risk Management Plan
RRMM	Relapsed refractory multiple myeloma
SAE	Serious adverse event
SEER	Surveillance, Epidemiology and End Results
SMM	Smoldering multiple myeloma
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
SOC	System organ class
SRT	Safety review team
TFQ	Targeted follow-up questionnaire
ULN	Upper limit of normal
URTI	Upper respiratory tract infection

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Blenrep

Trademarks not owned by the GlaxoSmithKline group of companies

TABLE OF CONTENTS

PAGE

LIST OF ANNEXES

Part I: Product(s) Overview

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Belantamab mafodotin
Pharmacotherapeutic group(s) (ATC Code)	L01FX15
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Trading Services Limited
Medicinal products to which this RMP refers	Belantamab mafodotin
Invented name(s) in the European Economic Area (EEA)	BLENREP
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Belantamab mafodotin is an anti B-cell maturation antigen (BCMA) immunoconjugate with an afucosylated, humanised immunoglobulin G1 (IgG1) anti-BCMA monoclonal antibody (mAb) conjugated by a protease-resistant maleimidocaproyl (mc) linker to a microtubule disrupting agent, monomethyl auristatin F (MMAF).
	Summary of mode of action: Belantamab mafodotin is a humanised IgG1 kappa monoclonal antibody conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF). Belantamab mafodotin binds to cell surface BCMA and is rapidly internalised. Once inside the tumour cell, the cytotoxic agent (cys-mcMMAF) is released disrupting the microtubule network, leading to cell cycle arrest and apoptosis. The antibody also enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis induced by belantamab mafodotin is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells.

<table>
<tr><td></td><td>Important information about its composition:

Belantamab mafodotin is an antibody-drug conjugate that contains belantamab, an afucosylated humanised monoclonal IgG1k antibody specific for B cell maturation antigen (BCMA), produced using recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary) that is conjugated with maleimidocaproyl monomethyl auristatin F (mcMMAF).</td></tr>
<tr><td>Reference to the Product Information</td><td>Please refer to the product information (section 1.3.1 of the eCTD).</td></tr>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current:

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

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

• in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide.</td></tr>
<tr><td>Proposed: Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

Recommended dosage in combination with other therapies
<table>
<tr><th>Combination regimen</th><th>Recommended starting dosage</th></tr>
<tr><td>With bortezomib and dexamethasone (BVd)[a]</td><td>2.5 mg/kg administered once every 3 weeks</td></tr>
<tr><td>With pomalidomide and dexamethasone (BPd)</td><td>Cycle 1: 2.5 mg/kg administered once

Cycle 2 onwards: 1.9 mg/kg administered once every 4 weeks</td></tr>
</table>
[a] Bortezomib and dexamethasone are administered for the first 8 Cycles.</td></tr>
</table>

	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Belantamab mafodotin powder for concentrate for solution for infusion. Each vial contains 70 mg or 100 mg of belantamab mafodotin as a lyophilised white to yellow powder. After reconstitution, the solution contains 50 mg per mL belantamab mafodotin.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

SI.1 MULTIPLE MYELOMA

INCIDENCE

According to the Global Cancer Observatory (GLOBOCAN), the estimated number of new cases of MM worldwide across all ages in 2022 was 187,952. The incidence rate of MM in 2022, age-standardized to the worldwide population, was estimated to be 1.8 per 100,000 person-years; stratified by sex the incidence rate was 2.1/100,000 person-years for males and 1.5/100,000 person-years for females (Table 2) [Ferlay J et al, 2024; Sung H et al, 2021]. In Europe, the incidence rate was estimated to be 2.8/100,000 person-years; 3.4/100,000 person-years for males and 2.3/100,000 person-years for females. The incidence of MM increased with age: in Europe the incidence rate was 0.87/100,000 person-years for patients <60 years, 16.2/100,000 person-years for patients aged ≥60 to <75 years, and 29.0/100,000 person-years for patients aged ≥75 years.

Table 2 World age-standardized MM incidence rates per 100,000 in 2022, by sex and geographic regions

	IR, Both sexes	IR, Males	IR, Females
World	1.8 (Crude: 2.4)	2.1	1.5
Asia	1.2	1.4	1.0
Western Asia	2.0	2.3	1.8
Eastern Asia	1.3	1.5	1.1
South-Central Asia	1.1	1.3	0.88
South-Eastern Asia	0.95	1.2	0.76
Europe	2.8	3.4	2.3
Northern Europe	3.9	4.9	3.1
Western Europe	3.2	3.9	2.5
Southern Europe	3.1	3.6	2.6
Eastern Europe	1.9	2.2	1.8
Northern America [1]	4.8	5.8	4.0
Latin America and Caribbean	1.8	2.2	1.5
Oceania	3.7	4.2	3.3
Australia and New Zealand	4.1	4.6	3.7
Polynesia	3.0	3.1	3.0

	IR, Both sexes	IR, Males	IR, Females
Africa	1.1	1.2	0.99
Southern Africa	2.2	2.6	1.9
Northern Africa	1.3	1.6	1.0
Middle Africa	0.98	1.1	0.90
Eastern Africa	0.95	1.0	0.90
Western Africa	0.81	0.80	0.83

[1] For the 2022 GLOBOCAN data, Mexico was included in the Latin America and Caribbean category, and the category of 'North America' was named "Northern America', including the US and Canada.

PREVALENCE

The 5-year global prevalence of MM in 2022 was estimated to be 538,948 people, equating to a prevalence rate of 6.8/100,00 people (Table 3); 7.4/100,000 males and 6.3/100,000 females (Ferlay, 2024). By geographic region, the 5-year prevalence rate (per 100,000 people) of MM in 2022 was, Asia: 4.3, Latin America and Caribbean: 6.4, Oceania: 19.1, Europe: 20.0, and North America: 31.3. Within Europe, the 5-year prevalence rate was 9.1/100,000 people for those aged <65 years increasing to 63.9/100,000 for those aged ≥65 years.

Table 3 Estimated 5-year prevalence of MM in 2022

	5-yr prevalence	5-yr prevalence / 100,000
World	538,948	6.8
≥65 years	297,472	37.5
<65 years	241,476	3.4
Asia	200,077	4.3
≥65 years	100,231	21.8
<65 years	99,846	2.4
Europe	149,397	20.0
≥65 years	94,761	63.8
<65 years	54,636	9.1
Northern America	117,011	31.3.
≥65 years	70,155	106.7
<65 years	46,856	15.2
Latin America and Caribbean	42,717	6.4
≥65 years	20,215	32.0
<65 years	22,502	3.7
Oceania	8,370	19.1

	5-yr prevalence	5-yr prevalence / 100,000
≥65 years	5,241	90.5
<65 years	3,129	8.2

Footnotes: [a] number of people alive who have had a diagnosis of multiple myeloma during the past 5 years
Source: GLOBOCAN 2022

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

MM is a clonal plasma cell disorder and accounts for 1% of all cancers and for 10% of all hematologic malignancies globally [Moreau, 2017]. MM incidence is rising, particularly in the developed world and the highest rates are seen in North America, Australia and Europe. Between 1990-2016, global incidence of MM has more than doubled for all sociodemographic index quintiles [Cowan, 2018]. This is due in part to the aging global population as well as advances in diagnostic techniques. With the introduction of new therapies and transplant techniques, survival is also increasing. A review of data from registries across the world as well as cancer-specific databases show increasing overall survival over time (Turesson, 2018); over the past decades 5-year survival has more than doubled to 54% (Padala, 2021).

Data from the US National Cancer Institute's Surveillance, Epidemiology and End Results program (SEER) (Padala, 2021) and other epidemiological studies (Curado, 2018, Huang, 2022), show the patient characteristics reported to increase the risk for MM diagnosis include older age, Black race, male sex, and family history. MM is predominantly diagnosed in older adults with the median age at diagnosis being 69 in the US. Data from a UK primary care database (Clinical Practice Research Datalink [CPRD]) reported a median age at MM diagnosis of 71 years (IQR 63-79) and 54.7% were male (Seesaghur, 2021). Globally, men are 1.5 times more likely to be diagnosed with MM than women. In the US, MM is twice as common among Black individuals with an incidence of 16.5/100,000 among Black men and 12.0/100,000 among Black women, compared to 8.2 and 5.0, respectively, for Caucasians. Similar data were reported in England using data from Public Health England (2013-2017): age-standardised incidence rates of 25.42/100,000 population among Blacks were reported compared to <10/100,000 among Whites, Asians and mixed/multiple ethnic groups (Delon, 2022). Data from case-control studies in the Multiple Myeloma Consortium suggest that individuals who have first-degree relatives of MM patients were at higher risk of diagnosis (odds ratio [OR]: 1.90, 95% confidence interval [CI] 1.26, 2.87) with an especially strong association among men (OR 4.13, 95% CI: 2.17, 7.85) and African Americans (OR: 5.52, 95% CI: 1.87, 16.27) (Schinasi, 2016). Recent data also show possible autosomal germline mutations that can predispose a patient to MM [Wei, 2017]

SI.1.2 The main existing treatment options

Currently there are several different classes of approved agents for MM, including PIs, immunomodulatory agents, monoclonal antibodies (mAbs) targeting a range of antigens, steroids, alkylators, and selective inhibitors of nuclear export, which can be combined in doublet, triplet, or even quadruplet regimens and used with or without high dose

chemotherapy rescued by ASCT [Moreau, 2021]. More recently, CAR-T and bispecific T-cell engagers have also become available for treatment beyond first line. For newly diagnosed MM, there are several treatment options available. Lenalidomide (immunomodulatory agent) in combination with dexamethasone is a common, well-established treatment option for patients with newly diagnosed multiple myeloma. Recently, daratumumab (anti-CD38 monoclonal antibody) in combination with lenalidomide and dexamethasone is emerging as a standard of care for patients with newly diagnosed MM who are transplant-ineligible [Darzalex, EPAR Product Information, 2023], thus increasing the proportion of patients who are lenalidomide (and daratumumab) exposed at first relapse. In addition, positive results from the PERSEUS Phase 3 trial (NCS03710603) underscore the viability of daratumumab in combination with bortezomib, lenalidomide and dexamethasone as a promising first-line option for transplant-eligible patients, which may even further increase the proportion of patients exposed to lenalidomide (and daratumumab) at first relapse.

Treatment of RRMM is complex, as it has to be individualized based on several patient-related (e.g., age, ECOG PS, comorbidities, patient preference), treatment related (e.g., prior therapies, depth- and DoR to prior therapies, toxicity from prior therapies, refractoriness to anti-myeloma agents), and disease-related factors (e.g., cytogenetic risk status, relapse characteristics [biochemical vs. clinical, early vs. late], presence or risk of side effects) [Durer, 2020]. The second-line treatment options with EMA marketing authorization are shown in the table below:

Table 4 2nd Line MM Treatments

Abbreviation	Medications	
DVd	Daratumumab, bortezomib, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/darzalex
PVd	Pomalidomide, bortezomib, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/imnovid-previously-pomalidomide-celgene
Cilta-cel	Ciltacabtagene autoleucel	https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti
DKd	Daratumumab, carfilzomib, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/kyprolis#overview
DRd	Daratumumab, lenalidomide, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/darzalex
EloRd	Elotuzumab, lenalidomide, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/empliciti
IsaKd	Isatuximab, carfilzomib, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/sarclisa
IxaRd	Ixazomib, lenalidomide, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/ninlaro
Kd	Carfilzomib, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/kyprolis#overview
KRd	Carfilzomib, lenalidomide, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/kyprolis#overview

Abbreviation	Medications	
SVd	Selinexor, bortezomib, dexamethasone	https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio

BCMA-therapies such as CAR-T and bispecifics are present in the treatment landscape. Bispecifics teclistamab, talquetamab and elranatamab are currently approved as monotherapies for patients who have received 4 or more lines of therapy but in future may also be available for earlier lines [Tecvayli SmPC, 2022; Elrexfio SmPC, 2024; Talvey SmPC, 2023]. CAR-T cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel) have received approval for earlier treatment lines; 3rd and 2nd line treatment relapsed and refractory multiple myeloma respectively [Abecma SmPC, 2024; Carvykti SmPC, 2024].

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 progresses to multiple myeloma or related malignancy at a rate of 1% per year [Kyle, 2018] and more than half of individuals who are diagnosed with MGUS have had the condition for over 10 years prior to the clinical diagnosis [Therneau, 2012]. MGUS can progress to a more advanced pre-malignant stage referred to as smoldering multiple myeloma (SMM). SMM progresses to multiple myeloma at a rate of approximately 10% per year over the first 5 years following diagnosis, 3% per year over the next 5 years, and 1.5% per year thereafter [Rajkumar, 2022].

The prognosis of MM varies due to its heterogenous manifestations and the response to the various possible treatments. Patients with MM generally survive for a median of approximately 5 years (Leieu, 2020; Lopez-Munoz, 2023; Ruotsalainen, 2024). The median age of death for patients with MM is 76 years with approximately 80% of deaths in those over 65 (SEER, 2024).

Key indicators for poor prognosis in patients with MM include high proliferation rate and tumor burden, usually measured by high levels of C-reactive protein and beta-2 microglobulin (over 6 mg/L), and certain cytogenetic abnormalities. Other factors of poor prognosis include the presence of hypercalcemia, and kidney impairment (Shah, 2022). Most patients die due to complications or progression of the disease (Mai, 2018).

Infections following treatment are among the most common causes of death in MM (15.3% to 22%) in the first year of diagnosis. In fact, the risk of both bacterial infections such as meningitis, septicemia, or pneumonia, and viral infections such as herpes zoster and influenza, was estimated to be seven times higher in patients with MM than in matched controls without the disease (Blimark, 2015). Other prevalent causes of death include renal disorders (12.9%), and cardiac disorders (6.7%) (Shah, 2022).

MM has a substantial patient burden, with both symptoms and treatments impacting quality of life (QoL). In a qualitative study of patients in the UK, Germany and France, symptoms of pain and fatigue as well as adverse effects of treatments including peripheral neuropathy, diarrhea and constipation were cited as the most disruptive to quality of life [He. 2021] Patients with MM also report more symptoms and poorer QoL than non-MM patients [Kamal, 2021] and QoL scores decrease as treatment lines increase [Despiegel, 2019; Nielsen, 2017; Hatswell, 2019; Engelhardt, 2021]. In a cross-sectional, multicenter study conducted in France in 2016 [Despiegel, 2019], including 402 patients with MM, EORTC QLQ-C30 and Quality of Life Multiple Myeloma module (QLQ-MY20) scores decreased significantly with treatment line. In particular, all patient functioning domains (ie, physical, role, emotional, cognitive, social) statistically significantly worsened as the line of therapy increased from first line to fourth or greater.

In 2022, GLOBOCAN estimated 121,388 patients died from MM, representing an age-standardized mortality rate (ASMR) of 1.1 per 100,000 (Ferlay, 2024). Mortality of MM was estimated to be 1.5 per 100,000 in Europe and 1.6 per 100,000 in Northern America. Data of mortality from MM between 1980-2019 from 48 countries showed a generally decreasing mortality trend, and this trend was more evident women than men (Huang, 2022). The decrease in mortality can be largely attributed to advances in therapies and better diagnostic techniques.

Table 5 World age-standardized mortality rates in multiple myeloma per 100,000 people in 2022

Geographic region	Mortality rate
World	1.1
Northern America (US and Canada)	1.6
South America	1.4
Central America	0.98
Europe	1.5
Northern Europe	1.8
Western Europe	1.6
Southern Europe	1.6
Eastern Europe	1.3
Asia	0.87
Western Asia	1.6
Eastern Asia	0.75
South-Central Asia	0.94
South-Eastern Asia	0.82
Oceania	1.7
Australia and New Zealand	1.8

Geographic region	Mortality rate
Polynesia	1.9
Micronesia	1.0
Melanesia	0.82
Africa	0.96
Southern Africa	1.8
Northern Africa	1.1
Middle Africa	0.84
Eastern Africa	0.84
Western Africa	0.71

SI.1.4 Important co-morbidities

Patients with multiple comorbidities are at higher risk for poor outcomes. Renal disease is among the most frequent MM presenting clinical symptoms, but it is also associated with disease progression. Failure to achieve renal response during treatment has been widely reported as a significant risk factor of progression [Jeryczynski, 2021; Yadav, 2016].

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]. Studies from the Surveillance, Epidemiology and End Results (SEER) cancer program and the Optum healthcare administrative databases in the US show rates of peripheral neuropathy of 11-17% [He, 2021, Chari, 2020]. The prevalence of hypertension and diabetes among RRMM patients were reported by other observational studies to range from 20-43% and 8-13% in Sweden and France, respectively [Sverrisdottir, 2021, Touzeau, 2021].

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 which have the MMAF payload and which were not represented well in nonclinical species with belantamab mafodotin [Eaton, 2015]. The reason for the greater sensitivity of the 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.

Nephrotoxicity

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.

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.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Cumulatively in all clinical trials, as of 27 February 2024 (DSUR data cut off), a total of 1707 subjects with RRMM, NDMM or Lymphoma have been exposed to at least one dose of belantamab mafodotin either as a single agent (n=783) or as part of combination regimens (n=924).

Table 6 Summary of Exposure Across the Clinical Development Program

Indication/ Study Designs / Treatment	Number of Subjects Exposed to Belantamab Mafodotin [1]
Relapsed/Refractory Multiple Myeloma	
Study BMA117159 / DREAMM-1	
Belantamab mafodotin	73
Total	73
Study 205678 / DREAMM-2	
Belantamab mafodotin (Frozen)	194
Belantamab mafodotin (Lyophilized)	24
Total	218
Study 207504 / DREAMM-11	
Belantamab mafodotin	15
Total	15
Study 208465	
Belantamab mafodotin	6
Total	6
Study 207495 / DREAMM-3	
Belantamab mafodotin	217
Total	217
Study 209626 / DREAMM-12	
Belantamab mafodotin	29
Total	29

Indication/ Study Designs / Treatment	Number of Subjects Exposed to Belantamab Mafodotin [1]
Study 209627 / DREAMM-13	
Belantamab mafodotin	0
Total	0
Study 209628 / DREAMM-14	
Belantamab mafodotin	177
Total	177
Study 205207 / DREAMM-4	
Belantamab mafodotin + Pembrolizumab	41
Total	41
Study 208887 / DREAMM-5	
Belantamab mafodotin	37
Belantamab mafodotin + GSK3174998 (SS1)	9
Belantamab mafodotin + Feladilimab (SS2)	25
Belantamab mafodotin + Nirogacestat (SS3)	69
Belantamab mafodotin + Dostarlimab (SS4)	4
Belantamab mafodotin + Isatuximab (SS5)	30
Belantamab mafodotin + Nirogacestat + Lenalidomide + Dexamethasone (SS6)	20
Belantamab mafodotin + Nirogacestat + Pomalidomide (SS7)	14
Total	208
Study 207497 / DREAMM-6	
Belantamab mafodotin + Bortezomib + Dexamethasone	107
Belantamab mafodotin + Lenalidomide + Dexamethasone	45
Total	152

Indication/ Study Designs / Treatment	Number of Subjects Exposed to Belantamab Mafodotin [1]
Study 207503 / DREAMM-7	
Belantamab mafodotin + Bortezomib + Dexamethasone	281
Total	281
Study 207499 / DREAMM-8	
Belantamab mafodotin + Pomalidomide + Dexamethasone	172
Total	172
Study 218670 / DREAMM-20	
Belantamab mafodotin	5
Total	5
Total (Relapsed/Refractory Multiple Myeloma)	1594
Transplant Ineligible Newly Diagnosed Multiple Myeloma	
Study 209664 / DREAMM-9	
Belantamab mafodotin + Bortezomib + Lenalidomide + Dexamethasone	107
Total	107
Total (Transplant Ineligible Newly Diagnosed Multiple Myeloma)	107
Lymphoma	
Study BMA117159 / DREAMM-1	
Belantamab mafodotin	6
Total	6
Total (Lymphoma)	6
Total exposed to belantamab mafodotin across all studies	1707

[1] The number of subjects exposed to belantamab mafodotin represents the cumulative number of subjects in ongoing and completed studies. For ongoing clinical trials, the cumulative exposure is estimated using the enrolment as of 27-Feb-2024 and the randomization ratio for the study.

Note: Subjects are listed under all treatments that they received.

Exposure for Belantamab mafodotin, Bortezomib and Dexamethasone (BVd) Combination: 207503 (DREAMM-7)

In DREAMM-7, treatment continued in both arms until progressive disease (PD), death, unacceptable toxicity, withdrawal of consent or end of study, whichever occurred first.

In the 2.5 mg/kg BVd group, subjects were exposed to belantamab mafodotin in combination with Bortezomib and Dexamethasone for a median of 15.9 months. Subjects received a median of 9.0 treatment cycles with a median dose intensity of 1.27 mg/kg per 3-week cycle.

Table 7 Summary of Exposure (DREAMM-7 Safety Population)

	Belantamab Mafodotin Q3W 2.5 mg/kg (N=242)
Number of cycles	
Patients n Mean ± SD Median (range)	242 11.7 ± 10.19 9.0 (1 to 55)
Dose intensity (mg/kg/3 weeks)	
Patients n Mean ± SD Median (range)	242 1.40 ± 0.76 1.27 (0.2 to 2.6)
Time on study treatment (months)[a]	
Patients n Mean ± SD Median (range)	242 17.07 ± 12.13 15.9 (0.7 to 40.2)

207503 Source Tables 3.0011 and 3.0012
a. The time on study drug does not exclude dose delay.
Note: 81 (33%) subjects, in the BVd arm of the DREAMM-7 study, remained ongoing as of the cut-off date of 2 October 2023

In the 2.5 mg/kg BVd group, 47% of subjects were female, the median age was 65 years, and 79% of subjects were White – White/Caucasian/European Heritage.

Table 8 Summary of Demographic Characteristics (DREAMM-7 Intent-to-Treat Population)

	Belantamab Mafodotin Q3W 2.5 mg/kg (N=243)
Sex, n (%)	
n	243
Female	115 (47)
Male	128 (53)
Age group (years) [0]	
18 to <65	121 (50)
65 to <75	85 (35)
>=75	37 (15)
Ethnicity	
n	243
Not Hispanic or Latino	213 (88)
Hispanic or Latino	30 (12)
Race detail	
White - White/Caucasian/European Heritage	193 (79)
Asian - East Asian Heritage	21 (9)
White - Arabic/North African Heritage	13 (5)
Black or African American	8 (3)
Asian - Japanese Heritage	3 (1)
Asian – South/East Asian Heritage	3 (1)
Missing	1 (<1)
Asian - Central/South Asian Heritage	1 (<1)
Mixed Asian Race	0
Mixed White Race	0

207503 Source Table 1.0009

[0] Age is imputed when full date of birth is not provided

Exposure for Belantamab mafodotin, Pomalidomide and Dexamethasone (BPd) Combination: 207499 (DREAMM-8)

In DREAMM-8 study treatment continued in both arms until confirmed PD, unacceptable toxicity, death, start of a new anti-myeloma therapy, withdrawal of consent or study end, whichever occurred first.

Participants in the BPd group received a median of 16.0 cycles of study treatment overall (where at least 1 non-zero, non-missing dose of any component of treatment was administered); the median total duration of exposure was 16.542 months. Participants in the BPd group received a median of 6.0 cycles of belantamab mafodotin over a median treatment duration of 13.19 months. The overall median dose intensity of belantamab mafodotin in the BPd group was 1.04 mg/kg/cycle.

Table 9 Exposure to Belantamab Mafodotin (DREAMM-8 Safety Population)

	Belantamab Mafodotin (N=150)
Total duration of exposure (months)[a]	
Median (min, max)	13.19 (0.9, 35.1)
Number of cycles	
Median (min, max)	6.0 (1, 23)
Cumulative dose	
Median (min, max)	12.21 (2.5, 44.1)
Average daily dose	
Median (min, max)	1.99 (1.6, 2.5)
Dose intensity	
Median (min, max)	1.04 (0.4, 2.5)[b]
Relative dose intensity (%)[d,e]	
Median (min, max)	52.50 (18.9, 100.4)

207499 Source: Table 3.0010; 3.0020
a. Treatment duration=([last date of the study drug] – [first dose date of the study drug]) + 1.
b. Dose intensity was the cumulative actual dose/(treatment duration/4 weeks).
d. Relative dose intensity=(dose intensity/planned dose intensity)*100.
e. Planned dose intensity=(cumulative planned dose in actual dosing cycles)/(number of actual dosing cycles) - only actual dosing cycles up to last dose of component were considered.
Note: Belantamab mafodotin dose measured in mg/kg; dose intensity measured in mg/kg/cycle; cumulative dose in mg/kg; average daily dose in mg/kg/day.

In the BPd group, participants were predominantly White (86%) with a median age of 67.0 years, 36% of participants were female and participants ≥75 years of age accounted for 12% of study participants.

Table 10 Summary of Demographic Characteristics (DREAMM-8 ITT Population)

	BPd (N=155)
Sex, n (%)	
Female	56 (36%)
Male	99 (64%)
Age group (years)[a] n (%)	
19 to <65	64 (41%)
65 to <75	72 (46%)
>=75	19 (12%)
Ethnicity	
Not Hispanic or Latino	145 (94%)
Hispanic or Latino	10 (6%)
Race detail	
White - White/Caucasian/European Heritage	124 (80%)
Asian - East Asian Heritage	16 (10%)
White - Arabic/North African Heritage	9 (6%)
Asian - Japanese Heritage	3 (2%)
Asian - Central/South Asian Heritage	1 (<1%)
Native Hawaiian or Other Pacific Islander	1 (<1%)
Mixed Race	1 (<1%)
Black or African American	0
American Indian or Alaska Native	0
Asian – South East Asian heritage	0
Mixed Asian race	0
Mixed White race	0

207499 Source: Table 1.0090

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

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

Exclusion from clinical trials has not resulted in a safety concern for the product.

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 11 Exclusion criteria

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Renal impairment: Patients with active renal conditions or severe renal impairment were not allowed to enrol in GSK sponsored clinical trials; however, patients with an eGFR of ≥30 ml/min/1.73 m2 were allowed to enrol in DREAMM-2 (205678), DREAMM-3 (207495), DREAMM-7 (207503), and DREAMM-8 (207499).	Patients with multiple myeloma have an increased risk of renal impairment, and at the time the DREAMM-2, 3, 7 and 8 protocols were written there was insufficient information on belantamab mafodotin use in renal impairment. Therefore patients with active renal conditions or severe renal impairment were not eligible for inclusion into belantamab mafodotin clinical trials.	No	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. Mild, moderate and severe renal impairment were not found to significantly affect belantamab mafodotin or cys-mcMMAF pharmacokinetics in a dedicated renal impairment study 209626 (DREAMM-12). Study 209626 (DREAMM-12) which is now complete.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
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.	No	Mild hepatic impairment (National Cancer Institute-Organ Dysfunction Working Group [NCI-ODWG] classification) was not found to be a significant factor accounting for interindividual variability in belantamab mafodotin or cys-mcMMAF pharmacokinetics.
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 preexisting 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. Corneal examination findings (including keratopathy), with or without changes in visual acuity, blurred vision, and dry eye is included as an important identified risk in Section SVII.3.1.
Patients with active infection requiring treatment **Patients with known HIV infection, hepatitis B, and hepatitis C unless specific criteria are met**	There is a potential risk of immunosuppression and neutropenia with belantamab mafodotin. Patients with multiple myeloma (MM) are frequently immunodeficient due to the underlying condition.	No	Pneumonia and Upper respiratory tract infection are very commonly reported adverse events included in the belantamab mafodotin prescribing information.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Patients with significant cardiovascular risk factors	There is a potential risk of cardiac findings related to a systemic inflammatory response with belantamab mafodotin treatment.	No	Preclinical findings suggest a potential for cardiac findings related to a systemic inflammatory response. However, to date there is no evidence of systemic inflammatory response or cardiotoxicity in the belantamab mafodotin clinical programme.

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

The clinical development program is unlikely 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.

Table 12 Limitations to detect adverse reactions in clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Fertility, pregnancies and pregnancy outcomes.	Implications are low since patients with RRMM are not typically of child-bearing age. In addition, contraception is advised in the product labelling.
Due to prolonged exposure	Secondary primary malignancies	Limited number of patients on treatment long term and in addition, patients with RRMM are typically of older age and have had prior treatments and confounding comorbidities.

Due to cumulative effects	Dependent upon the effect size and determining a possible drug related effect from comorbidities in confounded population.	Limited number of patients on treatment long term, significant prior treatments, and confounding comorbidities.
Which have long latency	Secondary primary malignancies	Limited number of patients on treatment long term and in addition, patients with RRMM are typically of older age and have had prior treatments and confounding comorbidities.

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

Table 13 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
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 and current unstable hepatic and biliary disease	**Exposure based on DREAMM-2/3 Monotherapy ISS Safety Population:** Mild hepatic impairment 2.5 mg/kg: n=38 (12%) subjects Moderate hepatic impairment 2.5 mg/kg: n=3 (<1%) subjects Source: ISS Source Table 1.2100
Patients with renal impairment	**Exposure based on DREAMM-2/3 Monotherapy ISS Safety Population:** Mild renal impairment: 2.5 mg/kg: n=144 (47%) subjects Moderate renal impairment: 2.5 mg/kg: n=83 (27%) subjects Severe renal impairment: 2.5 mg/kg: n=6 (2%) subjects

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td></td><td>
End Stage Renal Disease:
2.5 mg/kg: n=2 (<1%) subjects
(Baseline eGFR <15 reported as renal impairment status unknown)

Source: ISS Source Table 1.2100

Study 209626 (DREAMM-12) Interim Study Report:

Part 1 enrolled participants with normal or mildly impaired renal function (Group 1) and severe renal impairment (Group 2). Belantamab mafodotin dosing for both groups is 2.5mg/kg every 3 weeks.

Belantamab mafodotin exposure was comparable in Group 1 and Group 2. Overall, participants received a median (min-max) of 2.0 treatment cycles (1-8), and the median (min-max) dose intensity was 2.461 mg/kg (0.62-2.64) per Q3W.

Exposure to belantamab mafodotin (Part 1) (Safety Analysis Set)
<table>
<tr><th></th><th>Group 1 (N=10)</th><th>Group 2 (N=9)</th><th>Other (N=4)</th><th>Total (N=23)</th></tr>
<tr><td>Number of cycles, n</td><td>10</td><td>9</td><td>4</td><td>23</td></tr>
<tr><td>Mean (SD)</td><td>3.2 (2.44)</td><td>3.8 (2.64)</td><td>3.0 (1.83)</td><td>3.4 (2.35)</td></tr>
<tr><td>Median (min-max)</td><td>2.0 (1-8)</td><td>3.0 (1-8)</td><td>3.0 (1-5)</td><td>2.0 (1-8)</td></tr>
<tr><td>Dose intensity (mg/kg/3 weeks)[a], n</td><td>10</td><td>9</td><td>4</td><td>23</td></tr>
<tr><td>Mean (SD)</td><td>1.886 (0.8692)</td><td>2.207 (0.4449)</td><td>2.069 (0.8448)</td><td>2.043 (0.7075)</td></tr>
<tr><td>Median (min-max)</td><td>2.463 (0.62-2.64)</td><td>2.442 (1.29-2.50)</td><td>2.485 (0.80-2.50)</td><td>2.461 (0.62-2.64)</td></tr>
</table>
a. Dose Intensity is the cumulative actual dose divided by the number of potential 3 week cycles whilst on treatment ([cumulative actual dose]/[treatment end date−treatment start date+21]/21).
Source: Table 3.0010
</td></tr>
<tr><td>Patients with cardiovascular impairment</td><td>Patients with severe cardiovascular impairment were not included in the clinical development programme</td></tr>
<tr><td>Immunocompromised patients</td><td>Multiple myeloma patients can have a weakened immune system due to the disease and past treatment. Patients with prior allogenic stem cell transplant and/or active infection requiring treatment are excluded from clinical trials. Absolute neutrophil count must be ≥1.0 x 10^9/L to be included in clinical trials.</td></tr>
<tr><td>Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Patients with a disease severity different from inclusion in clinical trials were excluded from clinical trials</td></tr>
</table>

Type of special population	Exposure
Population with relevant different ethnic origin	Participants were predominantly White in the DREAMM-7 (85%) and DREAMM-8 (86%) studies.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme
Patients with known HIV infection, hepatitis B, and hepatitis C	Not included in the clinical development programme unless specific criteria are met.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorization exposure

GSK received its first approval for belantamab mafodotin on 05 August 2020 in the US for MM. Belantamab mafodotin was subsequently approved in all EEA countries on 26 August 2020. On 23 February 2024, the European Commission endorsed the CHMP recommendation not to renew the conditional Marketing Authorization for belantamab mafodotin. GSK voluntarily withdrew the Marketing Authorization for belantamab mafodotin in the US and in Switzerland due to the inability to provide confirmatory evidence to fulfil the conditions to convert to full approval.

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for belantamab mafodotin.

SV.1.1 Method used to calculate exposure

The algorithm used to derive post-approval exposure for belantamab mafodotin monotherapy is based on the assignment of a median of two vials per patient per month, since vials are not shared or re-used. Using this estimate, the exposure in patient months = [(total sales units÷2) ÷12], where 12 = months, 2 = vials per patient

SV.1.2 Exposure

Post-approval (non-clinical trial) exposure for belantamab mafodotin is provided below.

Overall estimation of post-approval exposure:

Data utilized to calculate estimated exposure is purchased by GSK from a vendor, IQVIA. The data is collected by IQVIA from participating markets on a quarterly basis and sent to GSK up to 60 to 90 days after the end of each quarter. For this reason, there is a lag in the availability of exposure data. At the time this current report was prepared, only data up to December 2023 (Q4 2023) was available.

Based on the available sales data and algorithm described the estimated cumulative exposure to belantamab mafodotin is 2271 patient months of treatment (available data time period April 2020 to December 2023).

Exposure from four ongoing Compassionate Use Programs (CUPs):

As of 04 February 2024, approximately 2790 had patients received belantamab mafodotin in four ongoing CUP/EAP programs.

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

- Nephrotoxicity
- Pulmonary toxicity (Pneumonitis)
- Thrombocytopenia
- Infusion-related reactions (IRR)
- Elevated transaminases
- Immunosuppression

The identified risks of thrombocytopenia, infusion-related reactions, and elevated transaminases and the potential risks of nephrotoxicity, pulmonary toxicity (pneumonitis) and immunosuppression have been classified as risks not considered important for inclusion in the list of safety concerns in the EU-RMP for the following reasons:

REASON FOR NOT INCLUDING AN IDENTIFIED OR POTENTIAL RISK IN THE LIST OF SAFETY CONCERNS IN THE RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Nephrotoxicity: Non-clinical safety studies demonstrated dose-dependent and reversible primary glomerular injury and tubular degeneration, and single cell necrosis of the kidney and bladder urothelium. Of note renal impairment may occur in the setting of multiple myeloma disease progression. Amongst pooled monotherapy data from 312 patients who received belantamab mafodotin in DREAMM-2/DREAMM-3 studies, 47% (144) had mild, 27% (83) moderate and 2% (6) severe renal impairment at baseline. Increasing levels of proteinuria (albuminuria) have been reported in participants receiving belantamab mafodotin not indicative of disease progression. Albuminuria is listed as a common adverse reaction in section 4.8 Undesirable effects in the Belantamab Mafodotin SmPC. When comparing pooled monotherapy data from DREAMM-2/DREAMM-3 studies to data from DREAMM-7 and DREAMM-8 studies, albuminuria is reported at a low frequency:

Table 14 Albuminuria Events in DREAMM-2/3 monotherapy pool, DREAMM-7 & 8

Preferred Term	Mono ISS (D2/D3)	D7		D8	
		BVd	DVd	BPd	PVd
Albuminuria	1 (<1%)	0	0	0	0
Albumin urine present	1 (<1%)	1 (<1%)	0	0	1 (<1%)
Urine albumin/creatinine ratio increased	2 (<1%)	8 (3%)	0	5 (3%)	0
Microalbuminuria	0	5 (2%)	2 (<1%)	0	0

Belantamab mafodotin is a prescription only medicine and its use restricted to physicians experienced in the use of anticancer medicinal products and the necessary safety monitoring requirements. The risk of nephrotoxicity will continue being monitored with routine pharmacovigilance.

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 was based on non-clinical findings. 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.

Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin, although a causal association has not been established.

Two (<1%) grade 3 serious cases of pneumonitis considered to be possibly related to study treatment by the investigator were reported with belantamab mafodotin monotherapy in the DREAMM-2/DREAMM-3 pooled monotherapy data. Both cases were confounded by antibiotic treatment therefore an infectious cause was unable to be ruled out. The events resolved. In the DREAMM-7 study, there were no cases of pneumonitis reported in the BVd arm and there was one case of radiation pneumonitis in the DVd arm. In the DREAMM-8 study, there was one case of pneumonitis reported in each arm (BPd: 1 (<1%) vs. PVd 1 (<1%)).

The belantamab mafodotin SmPC section 4.4 Special warnings and precautions for use advises on new or worsening unexplained pulmonary symptoms (e.g., cough, dyspnoea) and suspected / confirmed Grade 3 or higher pneumonitis.

Routine pharmacovigilance is deemed appropriate for this potential risk.

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization 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 authorized):

Thrombocytopenia: This identified risk was based on available literature for auristatin with ADCs [Donaghy, 2016], nonclinical studies, as well as observations within the DREAMM-1 and DREAMM-2 monotherapy studies. Thrombocytopenic events (Grades 1 to 4) are among the most common AEs associated with belantamab mafodotin. Patients with RRMM frequently present with thrombocytopenia. In pooled data from DREAMM-2 and DREAMM-3 monotherapy studies, 31% of patients (21% Grade 3 or 4) developed treatment emergent thrombocytopenia. In DREAMM-7, thrombocytopenia events were reported in 87% of patients. In DREAMM-8, 55% of patients experienced a thrombocytopenia event. The bleeding risk (Grade 2 or greater) in those with concomitant Grade 3 or 4 thrombocytopenia was balanced in both arms for the DREAMM-7 and DREAMM-8 studies.

Table 15 Thrombocytopenia & bleeding DREAMM-2/3 monotherapy pool, DREAMM-7 &8

	Pooled DREAMM-2 / DREAMM-3		DREAMM-7				DREAMM-8			
	2.5mg/kg (N=312) N (%)		BVd (N=242)		DVd (N=246)		BPd (N=150)		PVd (N=145)	
	All Grades	Grade >=3	All Grades	Grade >=3	All Grades	Grade >=3	All Grades	Grade >=3	All Grades	Grade >=3
Thrombocytopenia AESI	136 (44%)	87 (28%)	211 (87%) EA 50.2	176 (73%) EA 40.2	160 (65%) EA 40.7	113 (46%) EA 29.0	82 (55%) EA 39.586	57 (38%) EA 27.517	60 (41%) EA 44.19	42 (29%) EA 30.933
Any Gr3/4 platelet count decreased	84 (29%) – from lab data		178 (74%) – from lab data		118 (48%)- from lab data		60 (40%) – from lab data		PVd 43 (30%)- from lab data	
Concomitant Gr3/4 platelet count decreased and Gr2 or above bleeding event	N/A	15 (5%)	16 (7%)		14 (6%)		4 (3%)		5 (3%)	

Belantamab mafodotin is a prescription only medicine and its use restricted to physicians experienced in the use of anticancer medicinal products, who are familiar with the management of thrombocytopenia. Thrombocytopenia is listed as a very common adverse reaction in the product labelling, which provides guidelines for dose interruption and modification in the event of thrombocytopenia. This risk is being monitored with routine pharmacovigilance. Labelling is considered sufficient to communicate the risk of thrombocytopenia and is supported by the consistent safety profile observed over 2271 patient months of cumulative patient exposure to belantamab mafodotin in post-marketing use (April 2020 to December 2023).

Routine pharmacovigilance is deemed appropriate for this identified risk and no additional pharmacovigilance or additional risk minimization measures are required.

Infusion-related reactions (IRRs): This identified risk was 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 for pooled monotherapy (DREAMM-2/DREAMM-3), IRRs were reported in 58 / 312 (19%) of the 2.5 mg/kg dose group. In the DREAMM-7 study IRRs were reported commonly (5 [2%]) as well as in the DREAMM-8 study (11 [7%]). This risk will be managed through routine risk minimisation which includes messaging in the belantamab mafodotin 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.

Routine pharmacovigilance is deemed appropriate for this identified risk and no additional pharmacovigilance or additional risk minimization measures are required.

Known risks that do not impact the risk-benefit profile:

Transaminase elevations: The risk of transaminase elevations does not warrant inclusion in the list of safety concerns in the EU-RMP for the following reasons.

The incidence of hepatobiliary AEs / SAEs in monotherapy, DREAMM-7, and DREAMM-8 was low and comparable:

- Belantamab mafodotin pooled monotherapy (6% / <1%)
- DREAMM-7: BVd (5% / 0) and DVd (3% / <1%);
- DREAMM-8: BPd (6% / 1%) and PVd (3% / 0)

In DREAMM-7, the incidence of hepatobiliary enzyme elevations (ALT, AST, ALP, GGT, and LDH) was increased with BVd compared with belantamab monotherapy and DVd arm. This is confounded by concurrent bortezomib which is labelled for hepatobiliary events including increases in liver enzymes, hepatitis, acute liver failure and hyperbilirubinemia.

Table 16 Liver enzymes DREAMM-2/3 monotherapy pool, DREAMM-7&8

	Pooled DREAMM-2 / DREAMM-3	DREAMM-7		DREAMM-8	
	Bela 2.5mg/kg (N=312) N (%)	BVd (N=242) N (%)	DVd (N=246) N (%)	BPd (N=150) N (%)	PVd (N=145) N (%)
ALT increased (AE)	19 (6)	47 (19)	29 (12)	23 (15)	13 (9)
ALT increased Gr3+ (AE)	2 (<1)	14 (6)	3 (1)	2 (1)	5 (3)
AST increased (AE)	50 (16)	37 (15)	13 (5)	15 (10)	11 (8)
AST increased Gr3+ (AE)	5 (2)	3 (1)	0	4 (3)	3 (2)
ALT≥3xULN	10 (3)	34 (14)	29 (12)	21 (14)	14 (10)
ALT≥5xULN	1 (<1)	14 (6)	4 (2)	4 (3)	6 (4)
ALT≥8xULN	0	4 (2)	2 (<1)	1 (<1)	2 (1)
ALT≥10xULN	0	4 (2)	0	1 (<1)	2 (1)
ALT≥20xULN	0	1 (<1)	0	0	1 (<1)
ALT ≥3xULN to <5xULN	10 (3)	33 (14)	27 (11)	20 (13)	11 (8)
ALT ≥5xULN to <10xULN	1 (<1)	12 (5)	4 (2)	3 (2)	4 (3)
ALT ≥10xULN to <20xULN	0	4 (2)	0	1 (<1)	2 (1)
Bilirubin≥2xULN	3 (<1)	3 (1)	3 (1)	3 (2)	4 (3)
PHL/Hy's Law	0	2	2	1	2
GGT elevated (AE)	32 (10)	36 (15)	11 (4)	10 (7)	3 (2)
GGT elevated Gr3+ (AE)	9 (3)	22 (9)	4 (2)	2 (1)	1 (<1)
Alk Phos elevated (AE)	16 (5)	13 (5)	4 (2)	8 (5)	6 (4)
Alk Phos elevated Gr3+ (AE)	3 (<1)	2 (<1)	0	2 (1)	1 (<1)

Belantamab mafodotin is a prescription only medicine and its use restricted to physicians experienced in the use of anticancer medicinal products and the necessary safety monitoring requirements. Increased alanine aminotransferase, increased aspartate aminotransferase and increased gamma glutamyltransferase are currently listed in the SmPC section 4.8 Undesirable effects. Labelling is considered sufficient to communicate the risk of transaminase elevations and is supported by the consistent safety profile observed over 2271 patient months of cumulative patient exposure to belantamab mafodotin in post-marketing use (April 2020 to December 2023).

Routine pharmacovigilance is deemed appropriate for this identified risk and no additional pharmacovigilance or additional risk minimization measures are required.

Other reasons for considering the risks not important:

Immunosuppression – Patients with MM are frequently immunodeficient due to the underlying condition, and concomitant hypogammaglobulinemia (assessment of changes in immunoglobulin levels is challenging in patients with MM). As a result, patients with

MM have an increased susceptibility to infections which may result from several risk factors, including older age, disease complications, chemotherapy-induced neutropenia and use of novel agents [Lavi, 2018; Nucci, 2009; Brioli, 2017; Blimark, 2015].

In DREAMM-7, the incidence of infections was similar (70% BVd vs. 67% DVd) and the majority of events resolved in both arms. In the Infections and infestations SOC, the most common AEs by PT (≥10% of participants) in the BVd group were COVID-19 (24%), upper respiratory tract infection (20%), pneumonia (18%), and bronchitis (10%). The most common AEs by PT (≥10% of participants) in the DVd group were COVID-19 and upper respiratory tract infection (20% each). The incidence rate between the BVd and DVd groups for pneumonia were 18% and 9%, respectively. The incidence of Grade ≥3 AEs in the infections and infestations SOC was higher in the BVd group (31%) than in the DVd group (20%).

Further assessment of the individual Grade ≥3 AEs in this SOC showed that these differences were driven primarily by the higher incidence of Grade ≥3 pneumonia AEs in the BVd group compared with the DVd group (12% and 4%, respectively). After adjusting for time on study treatment, the exposure-adjusted rates for Grade ≥3 pneumonia were 8.409 and 3.338 events per 100 person years in the BVd and DVd groups, respectively. The incidence of Grade ≥3 AEs was similar in both the BVd and DVd groups for COVID-19, COVID-19 pneumonia, and sepsis. No participants had Grade ≥3 AEs of upper respiratory tract infection in either treatment group. Fatal infections were low and balanced between arms.

In DREAMM-8, the incidence of AEs in the infections and infestations SOC was higher (82%) in the BPd group than in the PVd group (68%), however, after adjusting for time on study treatment, the EAIRs were lower in the BPd group than in the PVd group (59.379 vs 72.913). The most common AEs by PT (≥10% of participants) in the BPd group were COVID-19 (37%), upper respiratory tract infection (27%), pneumonia (24%), urinary tract infection (15%), and COVID-19 pneumonia (12%). Events falling under the narrow Infective Pneumonia SMQ (v26.1) were reported in 38% participants in the BPd group and 17% participants in the PVd group. After adjusting for time on study treatment, the EAIRs for these events were 27.517 and 17.676 per 100 person-years, respectively.

The incidence of Grade ≥3 AEs in the infections and infestations SOC was higher in the BPd group (49%) than in the PVd group (26%). After adjusting for exposure, the incidence rates were 35.241 vs 27.987 per 100 person-years. Further assessment of the individual Grade ≥3 AEs in this SOC showed these differences were driven primarily by AEs related to pneumonia, COVID-19 pneumonia, and COVID-19.

Belantamab mafodotin is a prescription only medicine and its use restricted to physicians experienced in the use of anticancer medicinal products and the necessary safety monitoring requirements. Pneumonia and upper respiratory tract infections are listed as very common adverse reactions in Section 4.8 Undesirable effects in the belantamab mafodotin SmPC.

Labelling is considered sufficient to communicate the risk of pneumonia/URTI and is supported by the consistent safety profile observed over 2271 patient months of cumulative patient exposure to belantamab mafodotin in monotherapy post-marketing use (April 2020 to December 2023).

Routine pharmacovigilance is deemed appropriate for this identified risk and no additional pharmacovigilance or additional risk minimization measures are required.

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

Important Identified Risk #1: Corneal examination findings (including keratopathy), potentially resulting in vision changes

Scientific evidence for risk to be added in the safety specification

Ocular events are a class effect reported with other MMAF-containing ADCs and have been reported with belantamab mafodotin. Corneal exam findings (including keratopathy) is considered an important identified risk based on the changes in the corneal epithelium frequently observed on ophthalmic examination of patients receiving belantamab mafodotin in the clinical trial program. This finding was commonly associated with blurred vision, dry eyes, photophobia, and changes in visual acuity.

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

Risk Benefit Impact:

The ocular 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 ocular events have been found to be mostly Grade 3 and where follow-up is available, resolve when the drug is held.

In in the context of the proposed risk mitigation (prescriber/patient educational materials, and ophthalmic monitoring), the benefit of belantamab mafodotin both as monotherapy and in combination with bortezomib/dexamethasone, or pomalidomide/dexamethasone outweighs the identified risk of corneal examination findings (including keratopathy), potentially resulting in vision changes, in patients with MM. Ocular adverse events and visual changes can be managed in clinical practice through appropriate monitoring, as well as dose modifications (dose delays and reductions), enabling participants to continue treatment, as evidenced by low rate of withdrawals from treatment due to ocular events. Additional risk minimisation efforts further described in Part V, Section V.2 of this document.

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: Corneal examination findings (including keratopathy), potentially resulting in vision changes

Table 17

Potential Mechanism	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.
Evidence source(s) and strength of evidence	**Pre-Clinical**: Ocular events in the clinic are a class effect reported with ADCs which have the MMAF payload and which was not represented well in nonclinical species with belantamab mafodotin. 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. **Class effects**: Corneal epithelial toxicity is a known class-effect associated with ADCs containing microtubule inhibitor payloads (e.g., auristatins and maytansinoids) [Gan 2018; Goss 2018; Lassman 2019; Reardon 2017; Shapiro 2017; Tannir 2014; Thompson 2018; van den Bent 2017]. These events are most commonly reported with monomethyl auristatin F (MMAF)-containing ADCs and are often described as microcyst-like epithelial keratopathy (MEK). **Clinical**: Changes to the corneal epithelium on ocular examination have frequently been observed in the belantamab mafodotin clinical trial programme. This finding was most commonly associated with blurred vision, dry eyes, and changes in visual acuity. There is no evidence from AE reporting and extensive ophthalmic examinations that eye structures other than the cornea (such as the lens, retina, etc.) are affected by treatment with belantamab mafodotin.

Characterization of the risk

The DREAMM-2 study used the GSK scale to combine/describe corneal exam findings and Best Corrected Visual Acuity (BCVA) into a composite grade. The GSK scale was used as the basis for the Keratopathy Visual Acuity (KVA) scale.

The DREAMM-3, DREAMM-7 and DREAMM-8 studies used CTCAE guidance to grade ocular events in the original protocol. From protocol amendment 1, the KVA scale was used to determine dose modifications and is comprised of two components to determine the overall KVA grade (change in vision based on BCVA and corneal exam findings).

DREAMM-7&8 and DREAMM-2&3 pooled monotherapy: Most Frequent Ocular AEs (CTCAE)

	DREAMM-2 & 3 Pool Belantamab mafodotin monotherapy (n=321)	**DREAMM-7 BVd (n=242)**	**DREAMM-8 BPd (n=150)**
	All Grades	**All Grades**	**All Grades**
Any Event	210 (67%)	191 (79%)	133 (89%)
Vision blurred	108 (35%)	160 (66%)	119 (79%)
Dry eye	75 (24%)	123 (51%)	91 (61%)
Photophobia	53 (17%)	114 (47%)	66 (44%)
Foreign body sensation in eye	57 (18%)	106 (44%)	91 (61%)
Eye irritation	54 (17%)	103 (43%)	75 (50%)
Eye pain	37 (12%)	77 (32%)	49 (33%)
Visual impairment*	16 (5%)	26 (11%)	23 (15%)
Visual acuity reduced*	46 (15%)	14 (6%)	34 (23%)
Corneal epithelial microcysts*	8 (3%)	1 (<1%)	34 (23%)
Punctate keratitis*	24 (8%)	2 (<1%)	34 (23%)
Keratopathy**	92 (29%)	6 (2%)	11 (7%)

*Corneal exam findings reported as AEs predominantly prior to protocol amendment 1
**Corneal exam findings reported as AEs (by design in DREAMM-2, original protocol DREAMM-3)
D7 T3.0034, D8 Table 3.0425 and 3.0435 ISS mono T3.1450

Ocular AESIs in DREAMM-7 BVd Group and DREAMM-8 BPd Group, and DREAMM-2&3 pooled monotherapy: Summary of Characteristics of Ocular Symptoms (CTCAE)

Ocular Symptoms/AESIs (by CTCAE) Characteristics, n (%)	**DREAMM-7 (BVd) (N=242)**	**DREAMM-8 (BPd) (N=150)**	**Pooled Belantamab Mafodotin-Containing Group (N=516)**
Number of participants with event	191 (79%)	133 (89%)	428 (83%)

Number of events	1856	1709	5979
Event characteristics (% based on all participants)[a,b]			
Serious	0/242	1/150 (<1%)[f]	0/516
Related to study treatment	186/242 (77%)	132/150 (88%)	423/516 (82%)
Number of events (% based on all participants)			
One	21/242 (9%)[g]	6/150 (4%)[g]	251/516 (49%)
Two	21/242 (9%)[g]	7/150 (5%)[g]	71/516 (14%)
Three or more	149/242 (62%)[g]	120/150 (80%)[g]	106/516 (21%)
Maximum grade (% based on all participants)			
Grade 1	42/242 (17%)	27/150 (18%)	80/516 (16%)
Grade 2	67/242 (28%)	41/150 (27%)	133/516 (26%)
Grade 3	76/242 (31%)	63/150 (42%)	204/516 (40%)
Grade 4	6/242 (2%)	2/150 (1%)	11/516 (2%)
Action taken (% based on all participants)[a,c]			
Dose not changed	155/242 (64%)	133/150 (89%)	380/516 (74%)
Dose interrupted/delayed or reduced	127/242 (52%)	94/150 (63%)	311/516 (60%)
Dose interrupted/delayed	116/242 (48%)	93/150 (62%)	299/516 (58%)
Dose reduced[d]	50/242 (21%)	7/150 (5%)	90/516 (17%)
Treatment discontinued	8/242 (3%)	6/150 (4%)	18/516 (3%)
Not applicable	28/242 (12%)	25/150 (17%)	47/516 (9%)
Worst outcome (% based on participants with an event)[e]			
Recovered/resolved	92/191 (48%)	74/150 (49%)	199/428 (46%)
Recovering/resolving	6/191 (3%)	10/150 (7%)	28/428 (7%)
Recovered/resolved with sequalae	15/191 (8%)	0/150	9/428 (2%)
Not recovered/not resolved	78/191 (41%)	49/150 (33%)	192/428 (45%)

Note 1: Combination pool includes all treatment-emergent AEs.
Note 2: Participants may have unknown grade.
Note 3: Table includes data of all participants; data for participant with event only can be found m5.3.5, Combination Safety Pooling Table 3.2100.
Note 4: For the combination pool the output is based on ocular symptom, for the individual studies the output is based on ocular AESIs. Ocular Symptoms include PTs under group terms 'keratopathy/keratitis', and symptoms 'vision blurred', 'dry eye', 'photophobia', 'eye pain', 'eye irritation' and 'foreign body sensation' identified by GSK internal review.
a. Participants may be included in more than 1 category for 'Event characteristics' and 'Action taken'.

b. 'Study treatment related' includes responses of 'Yes' and missing responses to the question 'Is there a reasonable possibility that the AE may have been caused by the study treatment?'.
c. Subjects may be included in more than one category for 'Action Taken'. 'Action taken' counts actions related to any of the study treatments.
d. In DREAMM-8, per original protocol, dose reductions were not recommended for belantamab mafodotin. After Protocol Amendment 1, dose reductions were allowed at first Grade ≥2 corneal events (KVA scale).
e. Outcome worst case hierarchy: not recovered/not resolved > recovered/resolved with sequelae> recovering/resolving > recovered/resolved.
f. One participant on DREAMM-8 experienced an SAE of Diplopia more than 70 days after last dose, hence was therefore included in the analysis of all events in the individual studies but not in the analysis of the treatment emergent events in the combination pool
g. For the ocular AESI analysis, many participants experienced additional events that did not fall under the group terms 'keratopathy/keratitis', and symptoms 'vision blurred', 'dry eye', 'photophobia', 'eye pain', 'eye irritation' and 'foreign body sensation'

Source: m5.3.5, Combination Safety Pooling Table 3.2100; m 5.3.5.1, DREAMM-7 CSR Table 3.0028; m 5.3.5.1, DREAMM-8 CSR Table 3.0820

In DREAMM-7, no serious ocular AEs were reported. One participant in the BVd group had a Grade 4 event of infective (Pseudomonas aeruginosa) ulcerative keratitis with stromal involvement of the left eye. The infectious keratitis resolved; however, the participant's visual acuity in the affected eye remained severely affected (20/400 at the last visit, 77 days after the start of the event). The participant withdrew consent and was unable to be followed further.
In DREAMM-8, one serious ocular AE (diplopia) was reported for 1 participant (<1%) in the BPd group, the event resolved spontaneously and was reported as unrelated to belantamab mafodotin. There were no serious ocular AEs in the PVd group. There were 2 Grade 4 ocular AEs reported in the BPd group (and none in the PVd group): 1 event of visual acuity reduced with the worst visual acuity grade lasting for a total of 2 weeks OU, and 1 event of visual impairment in 1 eye due to aggravation of glaucoma, which was reported as unrelated to belantamab mafodotin.

Changes in best corrected visual acuity in Patients with normal BCVA[a] at baseline

DREAMM-7 BVd	**20/50**	**20/200**
Patients, n/N (%)	82/242 (34%)	5/242 (2%)
Time to onset of first event, median (range), days	73.5 (16-753)	105 (47-304)
Duration of first event, median (range), days	22 (6-257)	19 (8-26)
First event resolved,[b] n (%)	80 (98%)	5 (100%)

DREAMM-8 BPd	**20/50**	**20/200**
Patients, n/N (%)	51/150 (34%)	2/150 (1%)
Time to onset of first event, median (range), days	112 (28 – 761)	351 (2-673)
Duration of first event, median (range), days	57 (14 – 451)	57
First event resolved,[b] n (%)	43 (85%)	1 (50%)

	[a] Only patients with baseline visual acuity of 20/25 or better in at least one eye with on-study worsening to 20/50 or 20/200 in each eye at the same visit. [b] "Resolved" was defined as achieving grade 1 or baseline visual acuity.
Risk factors and risk groups	None currently identified
Preventability	Patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional before each of the first 4 doses of belantamab mafodotin, and as clinically indicated thereafter. Physicians should advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment as this may reduce corneal symptoms. For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.
Impact on the benefit-risk balance of the product	In the context of the proposed risk mitigation, the benefit of belantamab mafodotin both as monotherapy and in combination with bortezomib/dexamethasone or pomalidomide/dexamethasone for patients with RRMM outweighs the identified risk of corneal examination findings (including keratopathy), with or without changes in visual acuity, blurred vision, or dry eye. Ocular adverse events and visual changes can be managed in clinical practice through appropriate monitoring, as well as dose modifications (dose delays and reductions), enabling participants to continue treatment, as evidenced by low rate of withdrawals from treatment due to ocular events. Additional risk minimisation efforts are described in Section V.2.
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 Section V.2. If belantamab mafodotin becomes more widely used, this may have resourcing implications, with need for more availability of eyecare specialists, due to the need for ocular monitoring.

SVII.3.2 Presentation of the missing information

Not applicable

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 18 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Corneal examination findings (including keratopathy), potentially resulting in vision changes
Important potential risks	None

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

III.1 Routine pharmacovigilance activities

Other forms of routine pharmacovigilance activities for Corneal examination findings (including keratopathy), potentially resulting in vision changes:

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

- Specific adverse reaction follow-up questionnaires for corneal examination findings (including keratopathy), potentially resulting in vision changes

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

The TFQ is available in Annex 4 of the EU-RMP.

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities required for this product.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Table 19 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 authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There is no post-authorization efficacy study proposed for this product.

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

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 20 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Corneal examination findings (including keratopathy), potentially resulting in vision changes	**Routine risk communication:** The following SmPC sections include information on ocular adverse reactions: • 4.2 Posology and method of administration • 4.4 Special warnings and precautions for use • 4.7 Effects on ability to drive and use machines • 4.8 Undesirable effects The following PIL sections include information on ocular adverse reactions for patients: • 2. What you need to know before you take belantamab mafodotin • 4. Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Warnings & Precautions includes recommendation for ophthalmic examinations, considerations prior to dosing and recommended supportive care • Dosage and Administration includes specific dose modifications for corneal adverse reactions or changes in visual acuity **Other routine risk minimization measures beyond the Product Information:** • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products

V.2. Additional Risk Minimization Measures

Additional risk minimization: Educational Materials for Healthcare Professionals and Patients

Objectives:

To mitigate the risks of corneal examination findings (including keratopathy), potentially resulting in vision changes in patients taking belantamab mafodotin by ensuring patients and prescribers are aware of the importance of eye examinations and the use of preservative-free eye drops.

Rationale for the additional risk minimization activity:

To help oncologists, ECPs and patients understand the ocular 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 ocular risks and potential visual impairment associated with taking belantamab mafodotin. This includes guidance on screening exams as well as prophylaxis 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 ocular risks associated with prescribing belantamab mafodotin and how this risk is best managed and mitigated. They will be encouraged to work closely with the ECP since their treatment plan may be impacted by the ECP's exam findings.

ECPs will receive educational materials to help them understand the ocular 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:

Following approval of the RMP, the Applicant will oversee and follow local processes to ensure implementation of the education materials, which includes submission to the Regulatory Authority as required and will include the proposed tools to be used and a local communication and distribution plan for the predetermined target audience.

Oncologists and ECPs will receive educational materials to help them understand the ocular risks associated with belantamab mafodotin.

Patients taking belantamab mafodotin will receive educational materials from their treating oncologist focusing on the possible risks of corneal examination findings (including keratopathy), 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. Prior to the launch of belantamab mafodotin the RMP materials will be translated into the local language (if applicable).

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

Routine pharmacovigilance: ongoing monitoring of ocular safety data from all sources (spontaneous, clinical trials, post-marketing surveillance) with special attention to nature/severity of reported events, compliance with labelling recommendations, and inclusion of regular updates in aggregate reports.

V.3 Summary of risk minimization measures

Table 21 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk Minimisation Measures	Pharmacovigilance activities
Corneal examination findings (including keratopathy), potentially resulting in vision changes	**Routine risk minimization measures**: The following SmPC sections include guidance for ocular adverse reactions: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects PIL sections: 2. What you need to know before you take Belantamab Mafodotin 4. Possible side effects Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products. **Additional risk minimization measures:** Educational Materials for Healthcare Professionals and Patients	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow-up questionnaire **Additional pharmacovigilance activities**: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for BLENREP (belantamab mafodotin)

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

Belantamab mafodotin's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how belantamab mafodotin should be used.

This summary of the RMP for belantamab mafodotin 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 belantamab mafodotin's RMP.

I. The medicine and what it is used for

Belantamab mafodotin is authorized for the treatment of multiple myeloma:

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

(see SmPC for the full indication). It contains belantamab mafodotin as the active substance and it is given by intravenous infusion.

Further information about the evaluation of belantamab mafodotin’s benefits can be found in belantamab mafodotin’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

ADD LINK TO EPAR SUMMARY

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of belantamab mafodotin, together with measures to minimize such risks and the proposed studies for learning more about belantamab mafodotin’s risks, are outlined below.

Measures to minimize 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 authorized 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 minimize its risks.

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

In the case of belantamab mafodotin, 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 analyzed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of belantamab mafodotin are risks that need special risk management activities to further investigate or minimize 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 belantamab mafodotin. 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	Corneal examination findings (including keratopathy), potentially resulting in vision changes
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important Identified Risk: Corneal examination findings (including keratopathy), potentially resulting in vision changes	
Evidence for linking the risk to the medicine	Corneal examination findings are a class effect reported with other MMAF-containing ADCs and have been reported with belantamab mafodotin. Corneal examination findings (including keratopathy), potentially resulting in vision changes, 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.
Risk factors and risk groups	None currently identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections: 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. PL Sections: 2, 4 • Prescription only medicine • Use restricted to physicians experienced in the use of anticancer medicinal products. **Additional risk minimization measures:** Educational materials for prescribing haematologists/ oncologists, eye care professionals, and patients

II.C Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of belantamab mafodotin.

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

There are no studies required for belantamab mafodotin.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following Targeted Follow-up Questionnaire is provided for the risk ‘corneal examination findings (including keratopathy), potentially resulting in vision changes’:

- Visual disturbances

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):		

Version 1: Effective (October 2020)

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

The educational materials consist of three items which are aimed at helping prescribers (haematologists/oncologists), eye care professionals and patients understand the ocular risks associated with belantamab mafodotin, so that ocular events (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 who are expected to prescribe, or dispense belantamab mafodotin, and patients who receive belantamab mafodotin have access to/are provided with the following educational materials to be disseminated in line with NCA agreed implementation pathways.

Educational Materials for Healthcare professionals (HCP) (haematologists/oncologists/eye care professionals)

To include the following key messages:

- Detailed information on the ocular effects of belantamab mafodotin, including proper grading
- Description of required ocular exams for patients receiving belantamab mafodotin before each of the first 4 doses of belantamab mafodotin, and as clinically indicated thereafter:
    - Slit lamp examination to provide detailed information on the impact of belantamab mafodotin on the eye, including corneal examination, findings such as superficial punctate keratopathy, microcyst-like epithelial changes and haze, with or without changes in visual acuity.
    - Measurement of best corrected visual acuity to provide a measure of the impact of any corneal exam findings on the visual acuity.
- Key messages to convey during patient counselling:
    - Advice to patients that ocular adverse reactions may occur during treatment.
    - 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 ocular adverse reactions occur.

Patient Materials

Patient education materials

To include the following key messages:

- Description of eye related problems reported with belantamab mafodotin which may occur during treatment.
- Eye exams should be performed before each of the first 4 doses of belantamab mafodotin, and as clinically indicated thereafter.
- Basic details on the anatomy and physiology of the eye and a description of eye exams.
- Patients experiencing eye-related problems may require a dose adjustment to their treatment with belantamab mafodotin, which means either reducing the dose or changing the time between the doses. Your doctor might also ask you to see an eye care professional.
- Tell your haematologist/oncologist about any history of vision or eye problems.
- If you experience changes with your vision whilst on belantamab mafodotin, contact your haematologist/oncologist.
- Your doctor will ask you to use eye drops called preservative-free artificial tears during treatment. Administer them as instructed.
- Trackers for eye drops and appointments.

Patient wallet card

The Patient wallet card will contain the following key information:

- Indicates the patient is on treatment with belantamab mafodotin, known to cause serious ocular effects (including keratopathy) and contains contact information for the prescribing haematologist/oncologist and the ECP.
- Present to doctor during regular follow-up visits.
- Patients to present the wallet card to the pharmacist to find preservative-free artificial tears for use as directed.