EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/CHMP/414341/2020 Corr.*
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BLENREP

International non-proprietary name: belantamab mafodotin

Procedure No. EMEA/H/C/004935/0000

Note

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

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* Data in table 30 corrected in line with SmPC

Administrative information

Name of the medicinal product:	BLENREP
Applicant:	GlaxoSmithKline (Ireland) Limited 12 Riverwalk Citywest Business Campus Dublin 24 IRELAND
Active substance:	Belantamab mafotdotin
International Non-proprietary Name/Common Name:	belantamab mafodotin
Pharmaco-therapeutic group (ATC Code):	L01XC39
Therapeutic indication:	BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.
Pharmaceutical form:	Powder for concentrate for solution for infusion
Strength:	100 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

ADA	Anti-Drug Antibody
ADC	Antibody-Drug Conjugate
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under Concentration Curve
BCMA	B Cell Maturation Antigen
BM	Bone Marrow
CBR	Clinical Benefit Ratio
CI	Confidence Interval
CL	Clearance
CMA	Conditional Marketing Authorisation
CMAA	Conditional Marketing Authorisation Application
CMC	Chemistry, Manufacturing, and Controls
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CPV	Continuous Process Verification
CQA	Critical Quality Attribute
CTD	Common Technical Doxument
DAR	Drug-Antibody Ratio
DL	Drug Load
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry
e.g.	*exempli gratia* (for example)
eGFR	Estimated Glomerular Filtration Ratio
ELISA	Enzymo-Linked Immunosorbent Assay
ER	Exposure/Response
EU	European Union
Fc	Fragment chrysallizable
FIHT	First In Human Trial
FTIR	Fourier Transform Infrared
GC	Gas Chromatography
GCP	Good Clinical Practice
HPLC	High Pressure Liquid Chromatography
HR	Hazard Ratio
i.e.	*id est* (that is)
IC	Ion Chromatography
ICD	Immunogenic Cell Death
Ig	Immunoglobulin

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IMWG	International Myeloma Working Group
INN	Interanational Non-proprietary Name
IPC	In Process Control
IRC	Independent Review Committee
IRR	Infusion Related Reaction
ITT	Intention To Treat
IV	Intravenous(ly)
LC-MS/MS	Liquid Chromatography with tandem Mass Spectrometry
LMW	Low Molecular Weight
mAb	Monoclonal Antibody
mc	maleimidocaproyl
mec	microcyst-like epithelial changes
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MMAF	Monomethyl Auristatin F
MoA	Mechanism of Action
MRD	Minimal Residual Disease
MRP	Multi-Drug Resistance associated protein
MTD	Maximum Tolerated Dose
NEI VFQ-25	National Eye Institute Visual Function Questionnaire -25
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer (cell)
OATP	Organi Anion Transporting Polypeptide
ORR	Overall Response Rate
OS	Overall Survival
PC	Plasma Cell
PD	PharmacoDynamic(s)
PFS	Progression Free Survival
P-gp	P-glycoprotein
PI	Proteasome Inhibitor
PI	Product Information
PK	Pharmakokinetic(s)
PR	Partial Response
PT	Preferred Term
Q3W	Every Three Weeks
QTPP	Quality Target Product Profile
R-ISS	Revised International Staging System for Multiple Myeloma
RRMM	Relapsed and/or Refractory Multiple Myeloma
RS	Reference Standard
SAE	Serious Adverse Event
sBCMA	soluble form of B-Cell Maturation Antigen
sCR	stringent Complete Response
SOB	Specific Obligation
SOC	System Organ Class
SPE	Solid Phase Extraction
SW-AUC	Sedimentation-Velocity Analytilcal UltraCentrifugation

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TTE	Time To Event
TTP	Time to Progression
TTR	Time to Response
UHPCL-MS/MS	Ultra-High Pressure Liquid Chromatography with tandem Mass Spectrometry
UPLC	Ultra-High Pressure Liquid Chromatography
WCB	Working Cell Bank
WFI	Water for Injection
VGPR	Very Good Partial Response
WRS	Working Reference Standard

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline (Ireland) Limited submitted, on 18 December 2019, an application for marketing authorisation to the European Medicines Agency (EMA) for BLENREP, through the centralised procedure falling within the Article 3(1) and point 4 of Annex I of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2017.

BLENREP was designated as an orphan medicinal product EU/3/17/1925 on 16 October 2017 in the following condition: Treatment of multiple myeloma.

BLENREP was granted eligibility to PRIME on 12 October 2017 in the following indication: Treatment of relapsed or refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.

Eligibility to PRIME was granted at the time in view of the following:

- Despite available treatments, there is still a need for new options in the intended initial indication for the treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor (PI), an immunomodulatory agent and an anti-CD38 antibody. The unmet medical need was agreed.
- The mechanism of action (MoA) is plausible and nonclinical data were supportive of the proof of principle.
- Preliminary results from the Phase I open-label, dose escalation and expansion study BMA117159 in subjects with relapsed/refractory multiple myeloma were presented. The baseline characteristics showed that the patients were heavily pre-treated, with 94% of treated RRMM subjects in Study BMA117159 had received three or more lines of prior therapy. Further, 89% of patients enrolled in Part 2 were considered double refractory to both immunomodulatory drug and PIs, and 40% had previously received daratumumab. The ORR was of 60% in the overall population and the ORR in patients (n=14) that had received prior daratumumab treatment and in patients that were double refractory to an immunomodulatory agent and PI (n=31) were 43% and 58%, respectively. Most responses (51%) were deep (VGPR or better) and seem to be durable (the 25th percentile for Duration of Response (DoR) is 6.7 months and the median Progression Free Survival (PFS) was 7.9 months).
- Overall, these results appeared promising and supported the product's potential to bring a major therapeutic advantage to relapsed/refractory MM patients that have received prior lines of therapies included immunomodulatory agent, PI and daratumumab.

The applicant applied for the following indication:

BLENREP is indicated as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of BLENREP as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep

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The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0347/2019 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation (CMA) in accordance with Article 14-a of the above-mentioned Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance belantamab mafodotin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

PRIME support

Upon granting of eligibility to PRIME, Tuomo Lapveteläinen was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 23 March 2018. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures: proposed scientific advice on comparability and proposed quality data package, recommendation to seek scientific advice on the quality data to be included in MAA for the intermediate chemical substance of the Antibody-Drug

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Conjugate (ADC), overview of nonclinical data package for MAA, proposed scientific advice on long-term toxicity studies, clarification on antibody half-life, immunogenicity assessments, overview of clinical pharmacology studies and proposed future scientific advice on clinical pharmacology, overview of clinical development and proposed scientific advice on phase II and III studies, statistical analysis plan and rationale for phase II and phase III studies, MRD endpoint and draft guideline, ocular adverse reactions risk management, orphan designation and maintenance of orphan designation at approval, plans for CMA and PIP strategy.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
18 May 2017	EMEA/H/SA/3559/1/2017/I	Dr David Brown, Dr Odoardo Olimpieri
28 June 2018	EMEA/H/SA/3559/2/2018/PA/PR/III	Prof. Dieter Deforce, Dr Olli Tenhunen
20 September 2018	EMEA/H/SA/3559/3/2018/PR/PA/II	Dr Rune Kjeken, Dr Olli Tenhunen
15 November 2018	EMEA/H/SA/3559/2/FU/1/2018/PA/PR/II	Dr Jens Reinhardt, Dr Olli Tenhunen
31 January 2019	EMEA/H/SA/3559/2/FU/2/2018/PA/HTA/PR/III	Dr Olli Tenhunen, Ms Blanca García-Ochoa Martín
17 October 2019	EMEA/H/SA/3559/2/FU/3/2019/PA/PR/III	Dr Olli Tenhunen, Ms Blanca García-Ochoa Martín

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

Quality development:

- Cell line control strategy.
- Demonstration of analytical comparability and, provided comparability can be demonstrated at quality level, that no additional non-clinical or clinical tests will be needed to qualify the proposed process changes, comparability acceptance criteria, list of potentially critical quality attributes.
- Acceptability of the validation approach for mAb, ADC DS and DP as well as stability.
- Proposed activity and potency assays and their categorization as release and stability or characterization assays for commercialisation.
- API starting materials, agreement that the drug-linker component of the product is a non-biologically derived drug substance. Advice was also sought regarding the tests and acceptance criteria to control the quality of the linker component.

Non-clinical development:

- Acceptability of the overall non-clinical data package for MAA.
- Environmental risk assessment.

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- Acceptability of the nonclinical toxicology package to support a MAA and that no additional genotoxicity or embryo-fetal developmental toxicity studies are needed.

Clinical development:

- Corneal event mitigation strategy.
- Adequacy of the study DREAMM-2 design to support a CMA application, including dosing, primary and key secondary endpoints, proposed statistical analysis plan and immunogenicity analysis plan.
- Adequacy of the phase III monotherapy trial 207495 (DREAMM-3) to convert the CMA to a full approval, in particular regarding the comparator and the statistical analysis plan of the primary and secondary endpoints.
- Agreement of the overall clinical development plan to support a CMA for the proposed indication.
- Acceptability of the proposed specific obligations (SOB) to convert the initial CMA into a full MAA.
- Adequacy of the proposed pharmacokinetic assessments.
- Acceptability of the overall clinical pharmacology package to support the registration of Belantamab mafodotin lyophilized configuration as monotherapy, appropriateness of the pharmacokinetic data analysis approach proposed for the lyophilized configuration and that the clinical data can be submitted during review.
- Acceptability of the risk management plan (RMP) for the initial CMA.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Tuomo Lapveteläinen Co-Rapporteur: Blanca Garcia-Ochoa

The co-rapporteur was only appointed to the application at a very late stage replacing the previous co-rapporteur from the same national competent authority. The appointed co-rapporteur was considered exceptionally justified because the individual had previously been acting as coordinator for Protocol assistance on the development relevant for the indication subject to the present application.

The appointed rapporteur had no such prominent role in protocol assistance relevant for the indication subject to the present application.

The application was received by the EMA on	18 December 2019
Accelerated Assessment procedure was agreed-upon by CHMP on	14 November 2019
The procedure started on	30 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	31 March 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	10 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 April 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to	17 April 2020

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CHMP during the meeting on	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 April 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	11 June 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	23 June 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to BLENREP on	23 July 2020
The CHMP adopted a report on similarity of BLENREP with Darzalex, Farydak, Imnovid, Kyprolis, and Ninlaro of the authorised orphan medicinal products on	23 July 2020

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2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

BLENREP was proposed to be indicated as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent.

2.1.2. Epidemiology

Multiple myeloma (MM) is a rare and incurable disease of the plasma cells which typically affects adults who are more than 60 years of age (median age is at diagnosis is ~ 70 years). It is the second most common haematological malignancy (after non-Hodgkin's lymphoma [NHL]), representing 1% of all cancers and 2% of all cancer deaths. In 2018, the estimated annual, age-standardised, MM incidence rate worldwide was 1.7 per 100,000 (Ferlay, 2019). Progress has been made over the last 15 years in the treatment of multiple myeloma, such that survival of patients with newly diagnosed multiple myeloma has increased from approximately 3 years in the years 1985 to 1998 (Kyle 2003) to 6 to 10 years (Moreau 2015).

2.1.3. Biologic features

Multiple myeloma is characterized by marrow plasmacytomas (plasma cell tumours) and overproduction of monoclonal immunoglobulins (IgG, IgA, IgD or IgE) or Bence-Jones protein (monoclonal K or h light chains), while the production of normal immunoglobulin is impaired.

Based on karyotype, MM is classified as nonhyperdiploid and hyperdiploid, with the latter accounting for 50% to 60% of cases and characterized by trisomies in odd-numbered chromosomes. MM has a heterogeneous progression pathway, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the evolution of drug-resistance clones [Laubach, 2014]. Thus, drug resistance to prior regimens in patients with relapsed/refractory (RR) MM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008). Therapies with a multi-modal MoA, that both target MM cells and elicit an immunogenic response are expected to minimise development of drug resistance in MM.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The clinical features of MM are varied and can arise from the effects of the tumour itself, or the toxicity of the tumour products, or the host's own immune response.

The most common symptoms include persistent skeletal pain (especially pain in the back or thorax), pathological fractures and vertebral collapse, anaemia, renal impairment, hypercalcaemia and recurrent or persistent bacterial infections. Approximately 20% of patients are asymptomatic at the time of diagnosis.

The most common criteria used in diagnosis of symptomatic MM is the presence of neoplastic plasma cells comprising greater than 10% of BM cells or presence of a plasmacytoma; paraprotein (M-protein) in the serum and/or urine; and evidence of related organ or tissue impairment due to plasma cell disorder.

The International Staging System (ISS) is used for prognosis and it was revised by The International Myeloma Working Group (IMWG) including cytogenetics by fluorescence in situ hybridization (FISH) and lactate dehydrogenase (LDH, Revised International Staging System for Multiple Myeloma, R-ISS), and is now widely accepted (Palumbo, 2015). At the time of diagnosis, patients are typically categorized according to R-ISS, their age, comorbidity and their suitability for intensive treatment.

Despite advance in therapy, MM remains incurable. All patients eventually relapse and with each successive relapse, the chance of response and duration of response typically decreases and ultimately the disease becomes refractory and results in cumulative end organ damage (e.g., renal, cytopenia’s, infections and bone complications).

2.1.1. Management

Current treatment of MM includes glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell transplantation (ASCT), proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs, such as daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat.

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After the approval of daratumumab and its wide use in combinations in earlier lines of treatment, a new population of patients has emerged, referred to as triple-class refractory, encompassing those patients with disease refractory to at least 1 PI, 1 immunomodulatory agent and an anti-CD38 mAb. These patients have generally been exposed to all 5 drugs that have demonstrated single-agent effect (with or without glucocorticoids), including bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. Most of these patients have already received alkylating agent therapy, other anti-MM drugs, as well as multiple courses of glucocorticoids, they also have numerous comorbidities and receive multiple concomitant medications. There is a clear unmet medical need for new therapies because the treatment options are very limited and their median overall survival is around 3-5 months (Usmani, 2016; Gandhi, 2019; Mikhael, 2020).

About the product

Belantamab mafodotin is a humanised IgG1κ mAb conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF). Belantamab mafodotin binds to cell surface B Cell Maturation Antigen (BCMA) and is rapidly internalised. Once inside the tumour cell, the cytotoxic agent is released disrupting the microtubule network, leading to cell cycle arrest and apoptosis. The antibody enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis induced by belantamab mafodotin is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells (SmPC, section 5.1).

The applicant initially requested approval for the following indication:

BLENREP is indicated as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent.

The final indication applied for by the applicant following CHMP review of this application is: BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 antibody, and who have demonstrated disease progression on the last therapy.

The recommended dose is 2.5 mg/kg of belantamab mafodotin administered as an intravenous infusion once every 3 weeks (SmPC, section 4.2).

It is recommended that treatment should be continued until disease progression (SmPC, section 4.2).

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered of major public health interest. This was based on the clinical studies submitted for belantamab mafodotin. The product had shown promising treatment effect in 196 multiple myeloma patients (DREAMM-2) previously treated with a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 mAb ; ORR assessed by an independent review committee was 31% for 2.5 mg/kg dose cohort and 34% for the 3.4 mg/kg dose cohort. The intended patient population does not have specifically approved treatment options available, and the expected PFS and OS are dismal.

The applicant requested consideration of its application for a CMA in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

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- It is likely that the applicant will be able to provide comprehensive data. The Applicant confirmed its intention to provide the following data as specific obligation covert the initial CMAA to a full approval:

    1. Provision of the end of study report for DREAMM-2 (Study 205678): This will provide long-term safety and efficacy data in the indicated patient population.

    2. Provision of randomised data from DREAMM-3 (Study 207495): This will include mature safety and efficacy data (PFS) of belantamab mafodotin monotherapy in a third line plus RRMM patient population.

- Unmet medical needs will be addressed, as there is currently no EU approved treatment for patients with RRMM double refractory to a PI and an immunomodulatory agent and are failing on an anti-CD38 therapy. Belantamab mafodotin has shown significant benefit in terms of improved clinical efficacy (ORR) and addresses the unmet medical need in terms of deep and durable clinical responses compared to historical data and an improvement in patient-reported disease-related symptom as reported in DREAMM-2.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Belantamab mafodotin is indicated for a subset of MM patients with a dismal prognosis and limited approved treatment options. Based on the positive benefit: risk demonstrated in DREAMM-2, immediate availability of belantamab mafodotin would provide these patients with an important and novel therapeutic option whist additional data are being generated to confirm safety and efficacy of belantamab mafodotin in a randomised Phase III study (DREAMM-3).

2.2. Quality aspects

2.2.1. Introduction

The active substance (INN: belantamab mafodotin) is an antibody-drug conjugate (ADC) composed of a recombinant, human (IgG1) afucosylated mAb (belantamab) conjugated to cytotoxic microtubule-disrupting agent, monomethyl auristatin F (MMAF). Belantamab is partially reduced and conjugated with SGD-1269 active substance intermediate at the interchain cysteine residues, resulting into belantamab mafodotin active substance, which has a target drug-antibody ratio (DAR) of four (4).

Belantamab mafodotin binds specifically to the anti-B-cell maturation antigen (BCMA) and kills multiple myeloma (MM) cells expressing BCMA via a multi-modal mechanism including delivery of cytotoxic MMAF inducing apoptosis, enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death.

The finished product is presented as powder for concentrate for solution for infusion containing 100 mg of belantamab mafodotin as active substance.

Other ingredients are: sodium citrate, citric acid, trehalose dihydrate, disodium edetate and polysorbate 80. Belantamab mafodotin is reconstituted in sterile water (2 mL) to provide a concentration of 50 mg / mL.

The product is available in Type 1 glass vials sealed with bromobutyl rubber stopper and aluminium overseal with a plastic removable cap containing 100 mg powder, as described in section 6.5 of the SmPC.

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Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

2.2.2. Active Substance

2.2.2.1. Belantamab antibody intermediate

General Information (belantamab antibody intermediate)

Belantamab (Figure 1) is a recombinant afucosylated humanized IgG1κ mAb specific for B-cell maturation antigen (BCMA). The functional protein consists of two kappa light chains (LC) and two IgG1 heavy chains (HC) with a total of 1330 amino acids. There are 451 amino acids in each heavy chain and 214 amino acids in each light chain. The heavy chains are connected to each other by two interchain disulfide bonds and a light chain is attached to a heavy chain by a single interchain disulfide bond. The light chain has two intrachain disulfide bonds and the heavy chain has four intrachain disulfide bonds. The antibody is N-linked glycosylated on each heavy chain at asparagine (Asn) N301 with afucosylated structures composed of N-acetyl-glucosamine, mannose, and galactose. The major glycans present are afucosylated bi-antennary structures with varying amounts of terminal galactose and low levels of sialic acids. The polypeptide molecular mass is 146 kDa and the carbohydrate molecular mass is approximately 3 kDa resulting in a total estimated molecular mass of 149 kDa for belantamab.

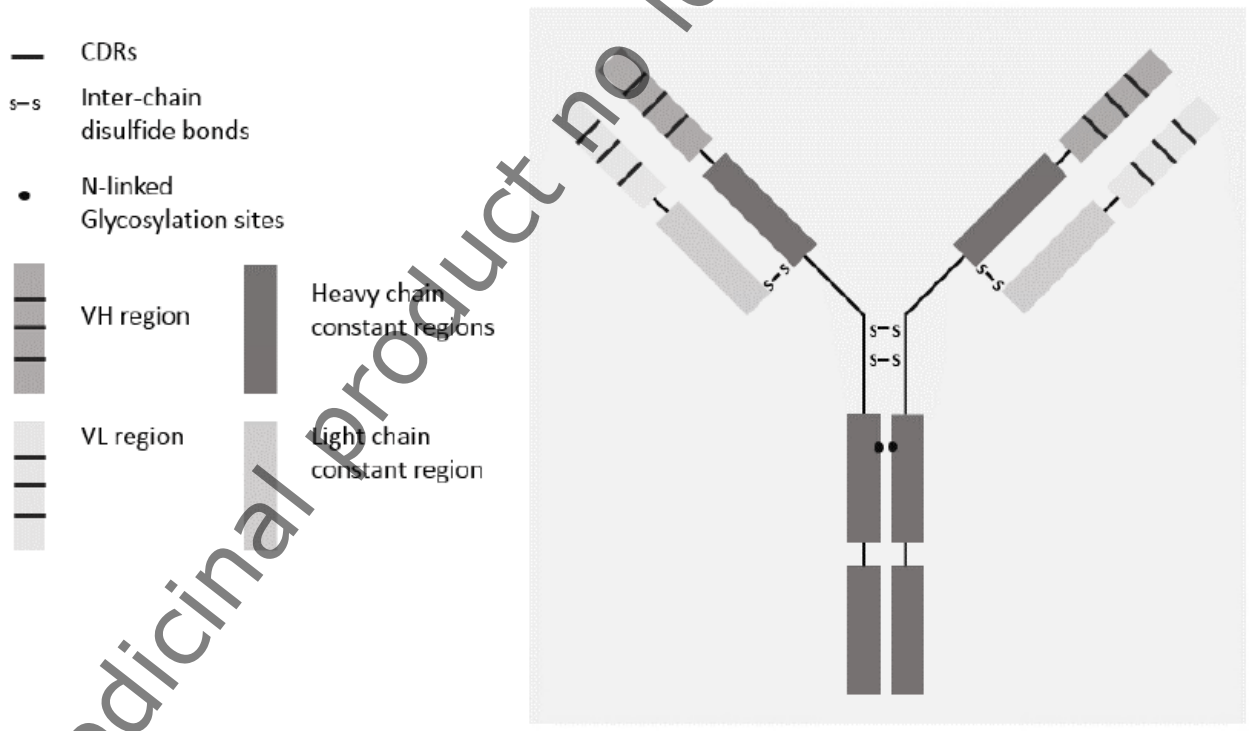

Figure 1: Schematic representation of belantamab

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Manufacture, process controls and characterisation (belantamab antibody intermediate)

Description of manufacturing process and process controls

The commercial belantamab Process 3 is a conventional mAb production process that starts by thawing of one WCB vial followed by a serial of cell culture expansion steps in shake flasks and two seed bioreactors until the production bioreactor step is reached. Belantamab is purified from the harvest through centrifugation followed by depth filtration and membrane filtration, Protein A chromatography, low pH virus inactivation, flow-through ion exchange chromatography, and virus filtration as well as an ultrafiltration/diafiltration steps. The applicant has described the batch manufacturing system, including reprocessing or manufacturing multiple batches from a single working cell bank vial. The batch size is the mass of the mAb produced from a single scale bioreactor.

Four processes have been used for belantamab manufacture: 1 process for non-clinical studies, 2 processes for clinical studies and 1 process for clinical and commercial studies. The applicant has sufficiently described the process changes made during development of belantamab manufacturing process. These include increase of the process scale, implementation of working cell bank (WCB), change of the media supplement, virus filter and ultrafiltration/diafiltration membrane change and manufacturing site change. The intended commercial process material is manufactured using Process 3.

QP declarations for the manufacturing sites have been provided. Valid GMP certificates have been provided for the mAb intermediate manufacturing sites.

To support the process changes extensive comparability assessments have been performed to demonstrate comparable process performances and analytical comparability for belantamab. These studies have included process comparability, extended characterization, forced degradation studies, comparability of stability results and batch analyses.

The process control strategy for belantamab manufacturing process has been described in detail. Manufacturing process hold times are indicated in the process flow diagrams.

Reprocessing is allowed for virus filtration and final filtration step in case of filter integrity test failure or other operational deviation not associated with excursions from microbiological control action limits, studies supporting the reprocessing have been provided. In process hold times for Clarified Unprocessed Bulk (CUB) and purification intermediates have been validated by studying the biochemical and microbiological stability.

Raw materials are presented in tables for cell culture and for purification processes. Most of the raw materials are of compendial grade referred to USP, EP, NF or JP. In addition, specifications for all non-compendial raw materials are provided. No raw materials of animal or human origin have been used in the manufacture of belantamab cell banks or during belantamab manufacture. Sufficient information on the raw materials used in the cell culture and purification process are presented.

Control of critical steps and process intermediates

As part of the development of the control strategy, a series of risks assessment have been performed on each stage of the process to identify the process parameters (PPs) that impact on critical quality attributes (CQAs). The acceptable ranges for the process parameters were established in characterization studies using qualified small-scale models.

Characterisation

Information on the structural, biochemical, and biological characteristics of belantamab was obtained through characterization tests performed on the primary reference standard (PRS) lot 172405900, manufactured by Process 2.

The characterisation studies included physicochemical characterisation to address primary structure (amino-acid sequence of H- and L-chain) by peptide mapping, liquid chromatography-mass

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spectroscopy/mass spectroscopy (LC-MS/MS) analysis, intact and reduced mass analysis (LC-MS: masses of the intact molecule and H- and L- chains), disulfide-bond pattern and free sulfhydryls (LC-MS/MS), secondary structure (fourier transform infrared, FTIR), tertiary structure (near ultraviolet circular dichroism, near-UV-CD), temperature-induced unfolding (differential scanning calorimetry, DSC), glycosylation on both HCs at N301 (ultra-high pressure liquid chromatography (UPLC), capillary gel electrophoresis (CGE), LC-MS/MS). In addition, belantamab specific binding activity to antigen, FcgRIIIa, FcRn was determined by surface plasmon resonance (SPR). Data of binding to FcγRI, FcγRIIa, and FcγRIIb by SPR were also include in the characterization exercise. Potency determination by an ADCC reporter bioassay was carried out. CDC activity is not considered to be a significant MoA.

Process related impurities remain at acceptable levels for daily exposure based on risk assessment and ability of the manufacturing process to reduce process-related impurities. Clearance of host cell protein (HCP), host cell DNA and Protein A by the belantamab manufacturing process to acceptable levels has been shown through successful manufacture.

Product-related impurities and substances include charge variants, aggregates, and fragments. Purity profiles were generated using Capillary Isoelectric Focusing (cIEF) for charge variants, CGE for fragments, and Size Exclusion Chromatography (SEC) for fragments and aggregates. Belantamab exists primarily in its monomeric form with low levels of dimeric aggregates. The levels of aggregates are controlled at release and stability. Fragmentation studies showed that belantamab size variants result from various combinations of the heavy chain and light chain subunits, i.e., fragments of belantamab HC and LC species, disulfide and non-disulfide linked covalent variants, and truncated HC and LC. These variants are considered in the control strategy.

Process validation

Appropriate validation studies have been performed for belantamab manufacturing Process 3. The Applicant has applied a three-staged approach: Process Design, Process Performance Qualification (PPQ) and Continued Process Verification (CPV). Ongoing/ Continued process verification is covered by EU GMP.

Five consecutive commercial scale PPQ batches have been manufactured. All batches were successfully processed through upstream process and downstream process steps. The release specification criteria were met for the five belantamab batches. Data from PPQ campaign shows that the manufacturing process can consistently produce belantamab that meets its predefined acceptance criteria. Based on the provided results the process is able to remove impurities to acceptable low levels for HCP, hcDNA, bioburden, endotoxins, retroviruses and other putative viruses and media components.

A risk assessment concluded that the risk of extractables and leachables is low in the belantamab manufacturing process as there are effective purge point for any potential leachable and extractables in the manufacturing of belantamab mafodotin process.

Resin lifetimes have been validated using small scale models of Protein A and Ion Exchange chromatography. The established resin lifetimes will be verified at full scale during commercial manufacturing. Cleaning validation employed for the chromatography resins has been performed. Commercial scale results of the resin cleaning validation studies showed no carry-over of protein.

Shipping validation reports have been provided, showing that belantamab packaging and shipping process is reliable, repeatable and robust.

Generation of cell substrate and Cell banking system

The applicant described in detail the origin of the gene sequences encoding the two chains of belantamab. Also, a detailed description and rationale is provided of the gene constructs and the two expression plasmids. Appropriate information on the gene construct, producer cell line, and establishment of cell

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banks is provided. A conventional two-tiered cell banking system has been established and tested for adventitious agents, cell viability, identity, integrity of expression construct, and gene copy number. Genetic stability of the producer cells was demonstrated using cells at the limit of *in vitro* cell age. Specification and qualification are presented for manufacture and testing of new WCB. Cell banks (MCB, WCB and EPCB) have been sufficiently characterised and shown to be free from non-viral and viral adventitious agents.

Specification, analytical procedures, reference standards, batch analysis, and container closure (belantamab antibody intermediate)

The specification for belantamab follows the requirements of present guidelines and Ph. Eur. "monoclonal antibodies for human use" monograph (01/2012:2031). For the non-compendial methods the principles of the analytical procedures have been described. Specifications are based on process- and product understanding, including batch release results from Process 1, Process 2, Process 3, including clinical lots, PPQ lots and post-PPQ lots.

The agreed belantamab specification is considered suitable. Appropriate method descriptions and method validations have been provided for all analytical methods.

During the procedure cIEF has been added to the belantamab release and shelf life specification. The Applicant has agreed to tighten the belantamab release and shelf life specification acceptance limits for % Main and %Acidic by cIEF.

Reference standards

The applicant has adequately described the reference standards (RS). Four RS have been manufactured during the development of belantamab using material from GSK development process, non-clinical Process 1, clinical Process 2 and clinical Process 3. A two-tiered system consisting of primary RS (PRS) and working RS (WRS) is used. The PRS is representative of the material used in clinical studies.

The PRS and WRS have been appropriately qualified through release testing and additional characterisation. For future WRS, qualification protocol consisting of release testing, additional characterisation and acceptance criteria is presented. Stability of the reference standards is monitored in the ongoing stability program.

Belantamab batch analytical data

Batch analytical data of 29 belantamab batches manufactured by processes 1, 2 and 3 is presented.

Stability (belantamab antibody intermediate)

The design of the stability studies follows the ICH Q5C guideline. Stability data are presented for nine belantamab batches, these include process registration batches (3), clinical batches (3), and Process Performance Qualification batches (3).

No trends were observed in any of the parameters tested for the duration of the study of frozen belantamab. Process 2, Process 3 and PPQ batches stored at the long-term storage conditions show consistent results.

Based on the stability results under long term storage condition, results from accelerated and stress studies the proposed shelf-life for belantamab antibody intermediate is acceptable.

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2.2.2.2. Drug substance intermediate SGD-1269 (linker-drug intermediate)

General Information (linker-drug intermediate)

SGD-1269 is composed of monomethyl auristatin F and maleimide functionality linked by caproic acid. The maleimide moiety reacts with the antibody in the conjugation reaction to belantamab mafodotin. SGD-1269 contains 9 stereogenic centres. General information was provided for solid state form, melting point, moisture sorption, solubility, optical rotation and UV-visible absorption.

Full information for the active substance intermediate SGD-1269 was provided in the dossier. No INN has been assigned, other common names are maleimidocaproyl monomethylauristatin F and mc-MMAF.

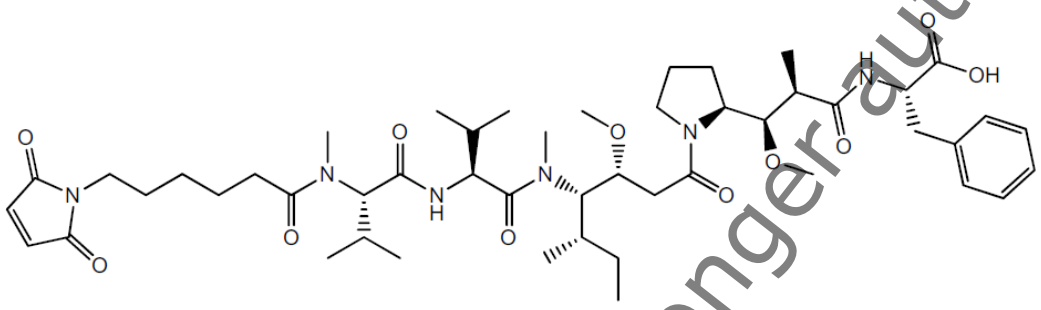

Figure 2: SGD-1269 linker-drug intermediate structural formula

Manufacture, process controls and characterisation (linker-drug intermediate)

The manufacturing process of SGD-1269 is a six-stage convergent synthesis. The synthesis includes starting materials and isolated intermediates. The manufacturing process of SGD-1269 was described in sufficient detail, including all reagents, reaction temperatures and solvents. The overall control strategy is based on specifications of the starting materials, intermediates and after purification steps. No routine reworking or reprocessing is included in the process.

The starting materials for the synthesis of SGD-1269 were agreed in the EMA Scientific Advice (Procedure No: EMEA/H/SA/3559/2/FU/1/2018/PA/PR/II). All starting materials have defined chemical properties and structure and are incorporated as significant structural fragments into the structure of the active substance. All starting materials undergo several chemical transformations and purifications. The synthetic routes of the starting materials were described, and typical impurities were determined using validated analytical methods. Appropriate specifications were set for the starting materials and batch data from each supplier complied with the specifications.

The criticality of the process parameters was evaluated on the basis of stretching the parameters and examining the effect on SGD-1269 purity and yield.

The intermediates are controlled by specifications that include tests for identification and assay. These intermediates do not contain impurities that could be carried on to SGD-1269. The specifications of intermediates also include tests for related impurities. Appropriate validated methods were used.

The pharmaceutical development followed Quality by Design principles outlined in ICH Q8, Q9, Q10 and Q11 using a risk management approach.

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Identity, assay and purity were identified as critical quality attributes. The overall control strategy was based on setting appropriate specification limits for all starting materials and intermediates. The origin and fate of each observed and potential related impurity was discussed thoroughly and examined by stretching studies of the manufacturing process, spiking experiments and determining the purge factors of the impurities.

The cytotoxic moiety of belantamab mafodotin, is expected to be genotoxic in mammalian systems given it is a microtubule disrupting agent. The SGD-1269 related impurities sharing a similar structure are expected to have similar toxicity as the SGD-1269 molecule. The known and reasonably predicted impurities present in SGD-1269 have been assessed to be non-mutagenic.

The structure of SGD-1269 was characterized by 1H and 13C NMR, MS of the protonated molecule and fragment ions and IR. The used methods are appropriate for structure elucidation of SGD-1269. An exhaustive list of observed and potential impurities was provided. The origin and fate of the related impurities was thoroughly discussed.

Specification, analytical procedures, reference standards, batch analysis, and container closure (linker-drug intermediate)

The specification of SGD-1269 includes tests for description, identification by IR, assay, purity and related impurities by HPLC, [solvent] content by ion chromatography (IC), water content by Karl-Fischer -titration (KF) and residual solvents by gas chromatography (GC). Validated analytical methods were used.

The HPLC method for assay, purity and related impurities is considered appropriate.

Different analytical methods were used at different stages of development for the determination of related impurities. All batches complied with the specification at the time of analysis.

The proposed specification limit for assay was justified.

As outlined in the guidance "Information on nitrosamines for marketing authorisation holders" (EMA/189634/ 2019) and Questions and answers on "Information on nitrosamines for marketing authorisation holders" (EMA/CHMP/428592/2019 Rev. 2), Marketing Authorisation Holders of products on the European market need to perform a risk assessment with respect to potential formation of nitrosamine impurities and the potential for cross-contamination for all their medicinal products. Following this assessment, it was concluded that there is no risk identified for the presence of nitrosamines.

Stability (linker-drug intermediate)

The stability studies were conducted according to ICH guidance. No significant changes or trends were observed in stability indicating parameters.

Based on the stability results under long term storage condition, results from accelerated and stress studies the proposed retest period for SGD-1269 linker-drug intermediate is acceptable.

2.2.2.3. Belantamab mafodotin active substance

General information

Belantamab mafodotin is an antibody-drug conjugate that includes belantamab (IgG1) monoclonal antibody which has 16 disulfide bonds, including four 4 interchains. Belantamab is partially reduced

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and conjugated with SGD-1269 at the interchain cysteine residues, resulting into belantamab mafodotin active substance, which has a target drug-antibody ratio (DAR) of four (4).

Manufacture, process controls and characterisation

The sites involved in the manufacture, packaging, testing, and release of belantamab mafodotin active substance are found acceptable.

Description of manufacturing process and process controls

The belantamab mafodotin manufacturing process is composed of five steps. The process starts with (1) thawing of the belantamab and solution preparation for reduction, (2) partial reduction of disulfide bonds for conjugation of belantamab with SGD-1269 and quenching of the process, (3) concentration of the belantamab-SGD-1269 conjugate and removal small molecular weight impurities by buffer-change step, (4) formulation and final filtration, (5) filling of active substance in containers and freezing. The manufacture is designed to be operated sequentially, without hold points or critical processing times.

A risk assessment was performed on each process step to identify process parameters with impact on CQAs.

Acceptable ranges, and associated CQAs for the manufacturing process are provided with rationale, justifications and supportive data for all relevant manufacturing steps. The process control strategy includes in-process controls (IPCs), Process Parameters (PPs) and Critical Process Parameters (CPPs) with acceptable ranges.

Raw Materials

Adequate information on the raw materials used in the belantamab mafodotin active substance manufacturing process is presented. Most of the materials are of compendial grade referred to in Ph.Eur, USP-NF or JP. Specifications for non-compendial raw materials used in the manufacturing processes are given. The non-compendial raw materials are tested per local specification and they are required and verified to meet the specifications reported by the vendor on the Certificate of Analysis (CoA). No raw materials of animal or human origin are used.

Manufacturing Process Development

The history, development and control strategy of the belantamab mafodotin manufacturing process has been sufficiently described. Belantamab mafodotin has been manufactured by process1 and 2 using belantamab antibody from Process-1, -2 and -3. Initial belantamab mafodotin manufactured by Process 1 active substance was used in non-clinical and clinical studies. Modifications were made to Process 2 to accommodate the finished product change of frozen solution presentation to lyophilized powder and increase of active substance concentration. Further changes were introduced to optimize the process and scale-up to commercial scale manufacturing. The number of process stages (5) has remained the same for belantamab mafodotin Processes 1 and 2. No changes were made to the conjugation stage between Process 1 and Process 2.

Comparability Assessment of belantamab mafodotin DS Process 1 and Process 2

Extensive studies have been performed to support the comparability of belantamab mafodotin active substance manufactured by Process 1 and Process 2 using belantamab batches from Process 1, 2 and 3. These studies have included extended characterization, forced degradation, stability comparability and comparison of batch analytical results. The provided results support the comparability of the belantamab mafodotin manufactured by Process 1 and Process 2.

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Characterisation

Extensive characterisation studies of belantamab mafodotin have been conducted.

Process-related impurities

The applicant has evaluated the clearance of process-related impurities that result from the coupling of belantamab with SGD-1269. The Applicant has performed a risk assessment showing that the maximum expected levels of the process-related impurities remain below the permitted daily exposure supporting the safety conclusion.

Product related impurities

The Applicant has identified product-related impurities of belantamab mafodotin, these include acidic- and basic-charge variants, aggregates, fragments, and drug load (DL) variants.

Process validation

The manufacturing process for belantamab mafodotin was validated using a three step approach. In stage1 small-scale studies were performed to determine acceptable ranges for parameters and to establish attributes for PPQ studies. In stage2, three Process Performance Qualification batches were manufactured to demonstrate consistency in process performance and production of the active substance meeting established quality criteria. For stage3, the Applicant has planned ongoing/continued process verification (CPV) to monitor performance attributes and process parameters, and to accumulate trend data to provide assurance that the process remains in a state of control during routine commercial manufacturing.

Three commercial scale batches of belantamab mafodotin were manufactured during the PPQ studies. The provided data show that the manufacturing process can consistently produce the active substance fulfilling the pre-defined quality criteria. Clearance of process-related residuals and impurities has also been validated demonstrating consistent clearance of both impurities.

The information provided concerning the process validation is found acceptable.

Container Closure System

The chosen container closure system is adequate, complies with relevant standards and has been described in sufficient detail.

Specification

The agreed belantamab mafodotin active substance specification is considered suitable. For establishing acceptance criteria, clinical ranges, risk to overall product efficacy and safety, historical ranges, process capability and expected method variability, assurance of stability have been taken into consideration.

At the request of CHMP the Applicant has reviewed and revised the active substance release and shelf-life acceptance criteria.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

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Batch analysis data on 21 belantamab mafodotin active substance batches manufactured by Process 1 and Process 2 were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

A two-tiered reference standard (RS) system is used. Primary RS is representative of the material used in clinical studies and will be used for the qualification of new working RS. Working RS will be used as a reference for the release of DS and during stability testing. The primary and working RS have been appropriately qualified and characterised. A protocol describing the qualification of future reference standards is included.

Stability

Stability data have also been presented on accelerated and stressed storage conditions. All batches included in the stability studies are representative of the commercial manufacturing process.

No trends were observed in any of the parameters tested for the duration of the study of frozen belantamab mafodotin active substance.

Based on the stability results under long term storage conditions, results from accelerated and stress studies the proposed shelf-life for belantamab mafodotin is acceptable.

Photostability study showed that belantamab mafodotin is light sensitive and should therefore be protected from light. Based on results from freeze/thaw studies, the active substance can tolerate up to five cycles of freezing and thawing with no changes in quality.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Belantamab mafodotin for injection, 100 mg finished product is a powder for concentrate for solution for infusion. It is supplied as a sterile, preservative-free, white to yellow lyophilized powder in a single dose vial, manufactured from a bulk drug product (BDP) solution containing 50 mg/mL belantamab mafodotin. Other ingredients include sodium citrate/citric acid, trehalose, disodium edetate and polysorbate 80. Belantamab mafodotin finished product is filled and lyophilized in Type 1 untreated clear glass vials. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Belantamab mafodotin finished product is reconstituted with 2.0 mL of sterile water for injection (WFI). The lyophilized powder after reconstitution forms a clear to opalescent and colourless to yellow to brown solution that is essentially free from visible particulates. The sterile WFI used for reconstitution of belantamab mafodotin finished product is not supplied by the Applicant.

Pharmaceutical development

The main objective of the formulation development was to achieve long-term stability of critical quality attributes and to find a finished product presentation to meet the quality target product profile (QTPP).

Two different finished product presentations of belantamab mafodotin were used in clinical studies: a 20 mg/mL solution for infusion and a 100 mg powder for solution for infusion. Only the powder for

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solution for infusion is proposed for commercialization and therefore it is emphasized that the liquid presentation is not assessed or approved within this submission.

The Applicant has conducted comparability assessments to evaluate the impact of manufacturing process changes between the liquid and lyophilized finished product processes. Pre-determined acceptance criteria were used to determine comparability. Detailed description on setting the acceptance criteria was not provided and no justification for the set criteria was located. However, as the analytical test results were provided the data can be evaluated regardless of the comparability acceptance criteria. Based on the provided results, it can be agreed with the Applicant's overall conclusion that manufacturing process changes have not impacted the quality or biological activity of belantamab mafodotin.

The formulation and manufacturing process were developed to minimize product degradation as a result of exposure to stresses such as freeze-thaw/temperature cycling, exposure to light, time out of cold storage, and shear stresses and to produce a product that meets the product quality attributes.

Process characterization studies were performed on each unit operation of the process to mitigate the identified risks, evaluate process parameter impact on product quality, understand the risk and criticality of process parameters, to define proven acceptable ranges, and set in-process controls. The commercial manufacturing controls were established using the process understanding attained from lab-scale process, characterization studies, the production-scale process capability, and finished product quality data obtained from the engineering batch and clinical manufacturing.

No significant changes were made to the manufacturing process after establishing process conditions with an engineering batch, with the exception of the removable cap colour and the primary drying time during lyophilization. The selected manufacturing process consists mainly of active substance thaw, pooling, dilution and mixing of the active substance, sterile filtration and aseptic filling into vials, partial stoppering, lyophilization and stoppering followed by capping.

The primary packaging is Type 1 glass vials sealed with bromobutyl rubber stopper and aluminium overseal with a plastic removable cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Description of manufacturing process and process controls

The sites involved in the manufacture, packaging, testing, and release of belantamab mafodotin finished product are appropriately provided. Valid GMP certificates have been provided for all listed finished product manufacturers.

The Applicant has provided a batch formula representing the intended batch size range.

A clear step-by-step description and a flow chart of the belantamab mafodotin finished product manufacturing process including CPPs and IPCs were provided. The process starts with thawing of active substance and involves preparation of diluent solution, pooling the active substance and compounding of the BDP, sterile filtration, filling and partial stoppering, and lyophilization followed by capping. After capping, the vials are externally washed, inspected, packaged in bulk, and stored at 2-8°C at the manufacturing site. There are no re-processing steps. The manufacturing process has been sufficiently described.

The critical process parameters (CPPs) and in-process tests (IPTs) with their associated acceptance criteria or limit or acceptable ranges have been presented for all relevant manufacturing steps.

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Rationale and justification for the classification of process controls applied in finished product manufacture was provided. Overall, the presented process controls are appropriate and the proposed control strategy for the finished product manufacturing process is acceptable.

Process validation

The belantamab mafodotin finished product manufacturing process was validated at the proposed commercial manufacturing site through controlled process parameters and performance parameters with predetermined acceptance criteria. Three consecutive commercial scale PPQ batches were produced for the studies. The validation studies included: Process performance qualification, Validation of the sterilization processes, Media fill trials, and Shipping validation. In addition, a verification of the total BDP solution hold time was conducted during the PPQ batches.

Overall, all PPQ batches satisfactorily met the pre-determined acceptance criteria for all controlled process parameters, in-process tests and release tests. The Applicant has confirmed that the media fills and SIP process meet GMP requirements as defined in EudraLex Vol 4 Annex 1.

Product specification

The agreed finished product specification is considered suitable for control of the finished product. A difference in acceptance criteria between release and shelf life specifications is proposed for residual moisture. Overall, the test parameters proposed to be included in the specification are considered relevant and in line with current guidance. The specification includes tests for appearance, identity, purity, potency, quantity and general tests.

The majority of methods are used to control both the active substance and finished product and have been discussed in the active substance part of the report.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated Inductively coupled plasma-mass spectroscopy (ICP-MS) method was provided. The information on the control of elemental impurities is satisfactory.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data on 20 batches of different scales of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The same product-specific reference standard is used for release and stability testing of belantamab mafodotin bulk active substance and belantamab mafodotin finished product. Refer to the relevant part of the report for details.

Stability of the product

The Applicant has provided data on stability studies performed at the long-term storage condition at the accelerated storage condition and at the stress storage conditions. All evaluated long-term stability parameters met the acceptance criteria.

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The proposed shelf-life specification differs from release specification for residual moisture, and for stability studies container closure integrity is tested instead of sterility.

Based on the provided data, the proposed shelf-life of 18 months, when stored at 2 – 8°C, for belantamab mafodotin finished product is acceptable.

In-use microbiological study, and in-use stability study for reconstituted and diluted finished product support the in-use storage conditions proposed in the SmPC: *i.e.*, reconstituted solution can be stored for up to 4 hours at room temperature or stored in a refrigerator (2°C to 8°C) for up to 4 hours, and the diluted solution can be stored in a refrigerator (2ºC to 8ºC) prior to administration for up to 24 hours. In the SmPC it also stated that "Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulfone (PES) based filter is recommended". Data to support the use of the PES based filter has been provided.

Adventitious agents

The Applicant has addressed both non-viral and viral contaminants.

In the manufacturing process of belantamab mafodotin no material from animal or human origin is used and therefore the risk of TSE contamination from the raw materials used is considered negligible. The Applicant has also provided a risk assessment for all raw and starting materials.

In-process testing is in place to ensure safety from bioburden and mycoplasma and cell banks have been tested to be free from non-viral (sterility and mycoplasma) and viral adventitious agents. Release of belantamab production batches requires testing of unprocessed bulk for the presence of adventitious viruses. A tabulated summary of the analytical qualification/validation results of these analytical procedures should be provided.

The viral clearance validation (VCV) studies were performed in accordance with requirements in ICH Q5A(R1) to demonstrate the capacity of belantamab Process 3 to remove and/or inactivate viruses. The Applicant has provided appropriate details on the methods and method qualification/validation.

The manufacturing process for belantamab includes steps specifically designed to remove viruses (virus filtration) and inactivate viruses (low pH viral inactivation) and additionally the chromatography steps contribute to the overall virus clearance. Overall, the inactivation/removal of different types of viruses is considered to be sufficiently demonstrated.

GMO

Not relevant.

Post-approval change management protocol (PACMP)

Belantamab mafodotin finished product

The PACMP for belantamab mafodotin finished product describes the transfer of the finished product manufacturing process and vial inspection.

Overall the proposed analytical testing program is considered sufficient and acceptable for comparability evaluation for the proposed technology transfer. The Applicant has justified the statistical approach used to determine the acceptance criteria and committed to follow possible trends in the analytical test results. The Applicant's proposal to submit the data report upon completion of the

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technology transfer activities as a Type IB variation, if all specified criteria are met, is considered acceptable. In case significant changes are planned to the PACMP described here, the Applicant commits to submit the changes to EMA for review and approval before implementation.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to suggested studies and review of documentation once more manufacturing experience is obtained. These points are put forward and agreed as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The Applicant is recommended to review, and if found appropriate, to revise the acceptance limits for cIEF, Binding by SPR and cell growth inhibition assay.
- The Applicant is recommended to carry out additional studies on the MCB and WCB as part of the qualification of the new WCBs which is expected to be completed in 3-7 years.

2.3. Non-clinical aspects

2.3.1. Introduction

Primary and secondary pharmacology studies described in this section were conducted in accordance with accepted practice for these study types and in general agreement with the principles of Good Laboratory Practice (GLP). The single *in vitro* safety pharmacology study was conducted according to GLP regulations, furthermore safety pharmacology evaluations [cardiovascular and/or respiratory] were incorporated into the GLP repeat dose toxicology studies in rats and monkeys. All GLP studies were carried out in an Economic Co-Operation and Development (OECD) member country in accordance with the OECD Test Guidelines.

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Selected evaluations were conducted with cys-mcMMAF, the active cytotoxic moiety, and GSK2857914, the parent, unconjugated afucosylated anti-BCMA antibody, to further characterize the overall nonclinical profile of belantamab mafodotin.

Two different DS presentations have been used during nonclinical development: solution and powder for solution (which is proposed for commercialization).

All definitive toxicology studies supporting the development of belantamab mafodotin were conducted in full compliance with Good Laboratory Practice (GLP) regulations and were conducted in an Organisation of Economic Cooperation and Development (OECD) member country in accordance with the OECD Test Guidelines. Other studies were performed in accordance with accepted scientific practice and in general agreement with the principles of GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

- *In vitro* studies

BCMA binding and internalisation, fragment chrysallizable (Fc-R) binding

Belantamab mafodotin binds with high nanomolar affinity to human rBCMA (Kd 1.1 - 1.6 nM at 25°C and 3.1 nM at 37°C). Supporting the selection of cynomolgus monkey as a species for toxicological evaluation, comparable affinity to monkey BCMA (Kd 0.7 nM at 25°C and 8.4 nM at 37°C) was shown, and no binding to mouse or rat BCMA.

Conjugation or afucosylation did not affect the binding affinity of belantamab mafodotin to hBCMA. Afucosylation improved binding to FcγRIIIa (human and monkey of origin) by 10- to 20-fold. The afucosylation or conjugation did not affect the binding affinity for the other Fc-receptors (human or monkey of origin), including the FcRn.

Unconjugated parent anti-BCMA Mab (GSK2857914) neutralised binding of BCMA ligands BAFF and APRIL to BCMA in a cell-free plate assay with IC50 values of 749 ng/mL and 617 ng/mL, respectively, and inhibited BAFF- and APRIL-induced NFκB signalling in NCI-H929 cells with IC50 values of 1.84 µg/mL and 1.56 µg/mL, respectively.

Binding and internalisation of belantamab mafodotin and unconjugated GSK2857914 to the BCMA on cell surface was shown with flow cytometry and confocal microscopy on human MM NCI-H929 cells. Upon binding BCMA on MM cells, belantamab mafodotin was internalised within 1 hour out to 7 hours and active cytotoxic drug (cys-mcMMAF) was released via lysosome mediated degradation of the ADC.

ADC-mediated Cytotoxicity

G2/M arrest and apoptosis induced by belantamab mafodotin was shown in a concentration and time dependent manner in MM cell lines using cell viability assays and flow cytometry assays for cell cycle analysis and cleaved caspase 3/7 expression. Belantamab mafodotin at 0.01 to 10 µg/mL concentration had cytotoxicity potency against MM cells with IC50 values ranging from 6 to 70 ng/mL. Belantamab mafodotin decreased viability of patient-derived primary CD138+ MM cells of the whole bone marrow mononuclear cells together with MM patient plasma mimicking the tumour microenvironment.

The kinetics of belantamab mafodotin -induced cell death was directly affected by number of BCMA receptors. The growth inhibitory activity was achieved even in the presence of physiologically relevant concentrations of soluble BCMA or the BCMA ligand APRIL.

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Belantamab mafodotin did not have by-stander killing effect on BCMA-negative bone marrow stromal cells and various effector cells.

Antibody-Dependent Cellular Cytotoxicity (ADCC)/ Antibody-Dependent Cellular Phagocytosis (ADCP) activity

Afucosylation of the antibody moiety of belantamab mafodotin was shown to enhance the interaction with Fc gamma receptors (FcγRs) present on primary immune cells (e.g. natural killer [NK] cells and macrophages), and lead to ADCC- and ADCP -mediated killing of MM cells. Belantamab mafodotin (and unconjugated afucosylated GSK2857914) had ADCC activity with an IC50 value of 1.8 ng/mL and a maximal cytotoxicity of 70% at 100 ng/mL when assessed on human PBMNC effector cells (E) and BCMA-positive ARH77-10B5 leukaemia target cells (T) at an E:T ratio of 50:1. Both donor and cell line variability was noted, with the EC50 ranging from 0.57 ng/mL to 111 ng/mL. Belantamab mafodotin induced ADCC in primary BM derived CD138+ cells from MM subjects. Belantamab mafodotin was active in both the allogeneic setting (using healthy donor PBMCs) and in autologous setting (using PBMCs derived from the same patient as the CD138+ MM cells). EC50 values were estimated to be approximately 100 ng/mL. Belantamab mafodotin was active against the plasmablasts with the mean EC50 value was 98 ng/mL.

Belantamab mafodotin at 2 and 10 µg/mL promoted ADCP in human macrophages derived from M-CSF–stimulated monocytes and MM cell lines at an E:T ratio of 4:1.

Induction of immunogenic cell death

Belantamab mafodotin induced a wide range of immunogenic cell death markers (incl. ATP, HMGB1, CRT) indicative of early phase (ER stress), mid-phase (modulation of immune response) and initiation of the inflammatory reaction as well as late phase (apoptosis and necrosis) in NCI-H929 MM cells. Dolastatins (a family of natural toxins from which MMAF is derived from), have been shown to induce immunogenic cell death (ICD), leading to an enhancement of dendritic cell maturation and T cell priming.

Immune-modulatory effects

Belantamab mafodotin had minimal immunomodulatory effects on human PBMC-derived CD4+ and CD8+ T cell activation and no significant effect on IFNγ and IL-4 production in both CD4+ and CD8+ T cells. The study in immature dendritic cells showed that belantamab mafodotin may have an effect on activation/maturation of immature DCs.

In vitro activity in combination with other agents used in MM therapies

The apoptotic and ADC-mediated cytotoxicity (ADCC) activity of belantamab mafodotin *in vitro* in MM cell lines and MM patient samples was enhanced when combined with a proteasome inhibitor (i.e. bortezomib), immunomodulatory agents (i.e. lenalidomide and pomalidomide), as well as gamma secretase inhibitors.

- *In vivo studies*

Anti-tumour activity in mouse xenograft, orthotopic and immune competent syngeneic models

In xenograft mice bearing NCI-H929 human multiple myeloma cell tumours, a complete tumour regression that was maintained for the whole 60 days, was achieved with 4 mg/kg dose of belantamab mafodotin administered twice weekly for 4 weeks. At this dose varying the drug-antibody ratios (DAR) from 3.5 to 4.6 had no effect on anti-tumour activity. For clinical batches the DAR was 4. Anti-tumour activity (decreased necrosis, increased infiltration of leucocytes into the tumour, decreased markers for cell proliferation and apoptosis) was confirmed in histology.

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In xenograft mice bearing OPM-2 tumours with two total doses of 100 µg (4 mg/kg) belantamab mafodotin dosed twice weekly resulted in near complete tumour eradication out to 36 days in 3 of 5 mice.

In mouse orthotopic MM1Sluc tumour graft model and in EL4-hBCMA syngeneic model (expressing human BCMA), belantamab mafodotin significantly reduced tumour growth and increased survival. Full tumour regression was obtained with 30 mg/kg. The results showed that belantamab mafodotin toxin-induced ICD can result in an adaptive immune response resulting in complete tumour regression. CD4+ and CD8+ T cells had significant impact in the anti-tumour activity of belantamab mafodotin in EL4-hBCMA syngeneic tumour model. Anti-tumour activity, such as increased tumour necrosis and presence of tumour infiltrating lymphocytes, was confirmed by immunohistochemistry.

PD study in cynomolgus monkey

Reduction of BCMA expressing plasma cells in blood and bone marrow were observed in cynomolgus monkeys after treatment with a 1 mg/kg IV-dose of belantamab mafodotin or GSK2857914. Treatment with belantamab mafodotin had no effects in absolute counts of CD4+ T cells, CD8+ T cells, CD14+ monocytes, granulocytes or NK-like cells (CD3-/CD4-/CD8+). There was an initial drop in the level of free soluble BMCA which then increased, whereas the level of complexed sBCMA increased initially increased and then started to decrease at 4 days until undetectable when the drug level had reduced below the detection level.

The impact on the IgE levels was the highest while IgG, IgA and IgM levels were reduced. Levels of IL-10, IL-12, IL-1β and IL-8 were variable between the animals but trended to small increase towards the end of the study. IL-6 levels showed a small peak 6 hours post dosing in all animals in both treatment groups. The effects on Ig levels and cytokines were in general comparable for belantamab mafodotin and GSK2857914.

In vivo activity in combination with other agents used in MM therapies

Belantamab mafodotin enhanced anti-tumour activity and/or prolonged survival in combination with agents such as lenalidomide and bortezomib, but not with pomalidomide, dexamethasone.

Secondary pharmacodynamic studies

GSK2857914 neutralization of BAFF and APRIL ligand binding to BCMA (Report 2011N125952)

GSK2857914 completely neutralized both BAFF and APRIL ligand binding to BCMA in a plate-based assay while the control mAb palivizumab was inactive. The antibody potency was compared in a cell-based assay to evaluate the effects on cell signalling. GSK2857914 was found to completely neutralize BAFF induced NF-κB cell signalling. In addition, GSK2857914 completely neutralized APRIL induced NF-κB cell signalling in the absence of soluble BCMA. BAFF induced cell signalling was reduced in the absence or presence of soluble BCMA. Isotype control antibodies were inactive in the assay.

GSK2857914-induced agonism (Report 2013N175851)

No agonism was observed with GSK2857914 at ≥100 µg/mL in NCI-H929, OPM-2 or JJN3 cells. However, GSK2857914 cross-linked with an anti-human IgG significantly increased NF-κB cell signaling greater than GSK2857914 antibody alone by approximately 2 and 5-fold in NCI-H929 and OPM-2 cells with EC_{50} values of approximately 1.2 and 1.13 µg/mL, respectively, but no change was noted in JJN3 cells. There were small (<1.1-fold) but significant differences in NF-κB induction in NCI-H929 cells when plate immobilized GSK2857914 is compared to control IgG.

Selective in vitro cytotoxicity of belantamab mafodotin (Reports 2013N176111 and 2014N224675)

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Belantamab mafodotin did not affect viability of isolated PBMCs, NK cells, CD14+ monocytes, or BMSCs. Belantamab mafodotin at 500 ng/mL or 5000 ng/mL had no significant effect on normal human bone marrow derived myeloid progenitor or on patient bone marrow derived MM progenitors cell numbers, respectively. Plasmacytoid dendritic cells from healthy donors and myeloma subjects were also shown to express low levels of BCMA. However, limited cell killing activity was observed in these cells relative to killing levels observed in MM cells.

The effect of belantamab mafodotin on various CD4+ and CD8+ T cell functions was evaluated by measuring T cell proliferation (Report 2014N224675). Following treatment with belantamab mafodotin there were no negative effects on the function of activated CD4+ or CD8+ T cells (proliferation, activation, and cytokine production) based on multiple blood donors.

Safety pharmacology programme

Standalone safety pharmacology studies were not conducted with belantamab mafodotin, instead the cardiovascular and/or respiratory function endpoints were included in the repeat dose toxicity studies in rats and monkeys. Additionally, a single *in vitro* hERG assay assessing the potential for delayed ventricular repolarization was conducted with the active cytotoxic drug, cys-mcMMAF. Safety pharmacology evaluations (cardiovascular and/or respiratory) were incorporated into the GLP repeat dose toxicology studies in rats and monkeys.

Belantamab mafodotin

In the 3 week repeat dose toxicity study with belantamab mafodotin in the cynomolgus monkey (Report 2013N158643), ECGs from the females in each group were collected continuously for approximately 1 minute at baseline, prior to the second weekly dose on Day 8, and at approximately 30 minutes after dosing on Day 8. ECGs from the males in each group were collected continuously for approximately 1 minute at baseline, for approximately 24 hours on Day -7 or -4 and again on Day 8, after dosing. Quantitative assessments conducted on ECGs from males following the second weekly dose (Day 8) showed no apparent belantamab mafodotin-related effects on heart rate or RR, PR, QRS, QT or QTc interval durations. All ECGs evaluated in this study were qualitatively considered normal for the cynomolgus monkey and, based on their sporadic occurrence and/or low frequency, none of the findings were considered to be related to belantamab mafodotin. There were no abnormal ECG findings detected from the administration of belantamab mafodotin.

In the 13 weeks repeat dose toxicity study with belantamab mafodotin in the cynomolgus monkey ECG recordings were performed using a non-invasive telemetry system (Report 2018N375127]. Recordings were performed once prior to the start of dosing for all animals at baseline for approximately 27 hours. In Week 5 (Day 29) and Week 12 (Day 78) ECGs were collected approximately 3 hours immediately prior to the daily dosing and approximately 24 hours after the daily dosing. ECGs were assessed, and the following parameters reported: Heart rate, PR, QRS and QT intervals, QTc. An increase in heart rate was noted during Week 5 from 4 to 18 hours post dose in males administered 10 mg/kg/week. No effects on heart rate or ECG parameters were observed at the end of the off-dose period in animals previously administered 3 mg/kg/week.

Serum cardiac troponin I was measured in the rat and monkey 3 week studies and no treatment-related effects were observed (Reports 2013N174857 and 2013N158643).

Detailed cage-side clinical observations following dosing were performed in the 3 and 13 week IV rat and monkey toxicology studies with belantamab mafodotin, and although no formal assessment of effects on the central nervous system was undertaken no clinical observations indicative of neurobehavioral effects

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were observed in any of the studies (Reports 2013N174857, 2018N374327, 2013N158643, 2018N375127).

cys-mcMMAF

The potential of cys-mcMMAF to inhibit hERG tail current was measured by whole cell patch clamping in HEK293 cells stably transfected with hERG cDNA (Report 2018N376608). Current arising from hERG channel operation was measured prior to and following exposure to cys-mcMMAF (0, 10 and 100 µM). Cys-mcMMAF inhibited hERG current by (Mean ± SEM) 1.2 ± 0.7% at 10 µM and 3.4 ± 0.4% at 100 µM versus 1.1 ± 0.6% in control. The IC_{50} for the inhibitory effect of cys-mcMMAF was estimated to be greater than 100 µM. Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by (Mean ± SD) 87.5 ± 1.3%. Thus, cys-mcMMAF has no inhibitory effect on hERG channel.

Evaluation of ECG, blood pressure, respiratory rate and heart rate was performed in the 5 day repeat dose toxicity study in the cynomolgus monkey study with cys-mcMMAF (Report 2013N177530). All animals received an ECG examination prior to dosing, at 1 to 2 hours after dosing Day 1, and on Days 7 and 18. Standard ECGs were recorded, RR, PR, and QT intervals and QRS duration were measured, and heart rate was determined. The systolic, diastolic, and mean arterial pressure, heart rate, and respiratory rate were also measured at each interval. There was no effect on qualitative or quantitative ECG parameters or respiratory rate following IV administration of cys-mcMMAF. There was a dose-related trend towards increased systolic, diastolic and mean blood pressure readings on Day 1 and Day 7 when the pooled data were evaluated. These changes were not statistically significant when the data were assessed by sex.

No clinical observations indicative of neurobehavioral effects was observed in the toxicology studies with cys-mcMMAF (Reports 2013N177527 and 2013N177530).

GSK2857914 (Mab)

ECGs were recorded from each animal once prior to the start of dosing and on Day 15 of the 4 week repeat dose toxicity study in cynomolgus monkey with GSK2857914 (Report 2012N150466). During the treatment period ECG recordings were made prior to dosing and at the approximate T_{max} (48 hours after dosing). All ECGs were within normal limits.

Pharmacodynamic drug interactions

No pharmacodynamic (PD) drug interaction studies with belantamab mafodotin have been submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

The pharmacokinetics (PK), absorption, distribution and excretion of belantamab mafodotin (ADC), GSK2857914 (the parent, unconjugated anti-BCMA antibody) and cys-mcMMAF (the active cytotoxic moiety released from belantamab mafodotin) have been investigated through a series of *in vivo* intravenous (IV) studies and a single intraperitoneal (IP) study to mice, rats and cynomolgus monkeys. Additionally, toxicokinetics (TK) of belantamab mafodotin, GSK2857914 and cys-mcMMAF were evaluated in single and repeat dose toxicity studies.

The results of the PK studies of belantamab mafodotin or GSK2857914 following single IV and single IP dose to mice are presented in ***Table 1***.

Table 1 Absorption after a single intravenous or intraperitoneal dose (Mouse)

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Report No. (Study No.):	2013N175927 (DT/Mouse/PK/2011/007)			2013N176011 (BD/2012/M005)	
Gender (M/F)/No. of Animals:	12M/group			3M	
Vehicle/Formulation:	Not stated in the report			Not stated in the report	
Method of Administration:	Intravenous			Intraperitoneal	
Dose (mg/kg):	1			4	
Sample:	Serum			Blood	
Sampling time points:	0.25, 3, 6, 24, 48, 72, 96, 168, 240, 336, 408, and 504 hours			0.25, 3, 6, 24, 48, 72, 96, 168, 240, 336, 408, and 504 hours	
Assay:	Gyrolab based immunoassay			Gyrolab based immunoassay	
Analyte:	GSK2857914	Belantamab mafodotin[a]		Belantamab mafodotin[a]	
		Total mAb	ADC	Total mAb	ADC
PK Parameters					
C_{max} (µg/mL)	20.7	18.3	19.6	24.1	23.5
T_{max} (h)	3	3	3	24	24
AUC_{0-t} (µg.h/mL)	2430	1810	1530	5120	4820
AUC_{inf} (µg.h/mL)	3190	2160	1770	NC	5790
$t_{½}$ (h)	319	214	204	NC	182
MRT (h)	154	156	140	NC	174
Cl (mL/h/kg)	0.313	0.463	0.564	NC	0.692
V_{ss}(mL/kg)	109	122	129	NC	183

Additional Information: There was no evidence of in vivo instability of the conjugated mcMMAF, as the pharmacokinetics of ADC and total mAb were similar. Relative bioavailability for the IP route was approximately 80%.

a = For bioanalytical purposes, belantamab mafodotin is quantified as belantamab mafodotin (ADC) and belantamab mafodotin (total mAb). belantamab mafodotin (ADC) is defined as GSK2857914 conjugated to one or more mcMMAF groups (DAR >0) and belantamab mafodotin (total mAb) is defined as GSK2857914 with or without conjugated mcMMAF (DAR≥0).
AUC = area under the serum or blood concentration time curve; BCMA = B-cell maturation antigen; Cmax = Maximum observed serum or blood drug concentration. Cl = clearance; MRT = Mean residence time; NA = Not available; NC = Not calculated; PK= Pharmacokinetics; SCID = Severe combined immunodeficiency. t½ = Terminal elimination half-life; Tmax = Time at which Cmax occurred; Vss = Volume of distribution at steady-state.

The results of the PK studies of belantamab mafodotin or GSK2857914 following single IV dose to rat and monkey are presented in ***Table 2***.

Table 2 Absorption after a single intravenous dose (Rat and Monkey)

Report No. (Study No.):	2012N140200 (NA)			2013N157994 [in life phase and sample acquisition (A113598)] 2012N143303 [sample analysis (A113598)]		
Gender (M/F)/No. of Animals:	3M/group			3M/group		
Vehicle/Formulation:	Not stated in the report			Phosphate buffered saline/Solution		
Method of Administration:	Intravenous			Intravenous		
Dose (mg/kg):	1			1		
Sample:	Serum			Serum		
Sampling time points:	0.25, 3, 6, 24, 48, 72, 96, 168, 240, 336, 408, and 504 hours.			0.08, 0.5, 1, 3, 6, 24, 48, 72, 96, 120, 168, 336, 504, 672, 1008, 1176, 1344, and 1680 hours[c]		
Assay:	Gyrolab fluorescent immunoassay			Gyrolab fluorescent immunoassay		
Analyte:	GSK2857914[a]	Belantamab mafodotin[b,d]		GSK2857914	Belantamab mafodotin[d]	
		ADC	Total mAb		ADC	Total mAb
PK Parameters:						
C_{max} (µg/mL)	27	33.3	32.7	30.7	29.2	26.8
T_{max} (h)	0.25	0.25	0.25	0.22	0.08	0.08
AUC_{0-t} (µg.h/mL)	2670	2400	3380	1600	912	1040
AUC_{inf} (µg.h/mL)	3460	3050	NC	1630	944	NC
$t_{½}$ (h)	255	252	NC	96.1	102	NC
MRT (h)	180	160	NC	105	81.7	NC
Cl (mL/h/kg)	0.289	0.333	NC	0.616	1.07	NC
V_{ss} (mL/kg)	97.6	103	NC	70	105	NC

a = Due to rapid decline in serum concentrations from 504 hours in two of the animals dosed with GSK2857914 the PK parameters for GSK2857914 are based on the data from only one animal.
b = Data dose normalised as belantamab mafodotin dosed at 0.6 mg/kg.
c = Samples also taken at 4800 hours, but not analysed
d = For bioanalytical purposes, GSK2857916 is quantified as GSK2857916 (ADC) and GSK2857916 (total mAb). GSK2857916 (ADC) is defined as GSK2857914 conjugated to one or more mcMMAF groups (DAR >0) and GSK2857916 (total mAb) is defined as GSK2857914 with or without conjugated mcMMAF (DAR≥0). AUC0-t = Area

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under the serum concentration time curve (from time 0 to last time point); AUCinf = Area under the plasma concentration time curve extrapolated to infinity. Cmax = Maximum observed serum drug concentration; Cl = Clearance; mAb = Monoclonal antibody; MRT = Mean residence time; NC = Not Calculated. t½ = Terminal elimination half-life; Tmax = Time at which Cmax occurred; Vss = Volume of distribution at steady-state.

The results of the PK studies of cys-mcMMAF following single IV dose to rat and monkey are presented in ***Table 3***.

Table 3 Absorption after a Single Intravenous Dose (Rat and Monkey)

Report No. (Study No.):	2019N415388 (1019-012)			2019N415363 (1019-013)		
Gender (M/F)/No. of Animals:	6M/group			3M/group		
Vehicle/Formulation:	Phosphate buffered saline/Solution			Phosphate buffered saline/Solution		
Method of Administration:	Intravenous			Intravenous		
Dose (mg/kg):	0.3, 1, 3			0.3, 1, 3		
Sample:	Plasma			Plasma		
Sampling time points:	0.03, 0.08, 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 36 and 48 hours.			0.03, 0.08, 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 36 and 48 hours.		
Assay:	HPLC/MS/MS			HPLC/MS/MS		
Analyte:	Cys-mcMMAF			Cys-mcMMAF		
PK Parameters:						
Dose (mg/kg)	0.3	1	3	0.3	1	3
C_{max} (ng/mL)	867	1880	15000	1560	1750	13900
T_{max} (h)	0.0333	0.0670	0.0443	0.0373	0.0333	0.0333
AUC_{0-t} (ng.h/mL)	124	629	2520	309	595	2390
AUC_{inf} (ng.h/mL)	NR	NR	NR	330	604	2390
$t_{½}$ (h)	NR	NR	NR	8.75	5.42	4.62
Cl (mL/h/kg)	NR	NR	NR	910	1660	1250
V_{ss} (mL/kg)	NR	NR	NR	2050	1960	600

Key:
a = Cys-mcMMAF exists in two isomeric forms, the linear isomer was administered in these studies.
AUC_{0-t} = Area under the plasma concentration time curve (from time 0 to last time point); AUCinf = Area under the plasma concentration time curve extrapolated to infinity.
Cl = Clearance; C_{max} = Maximum observed plasma drug concentration; HPLC/MS/MS = High-performance liquid chromatography with tandem mass spectrometry.
NR = No Result since data were not sufficiently robust to derive PK parameters from the terminal elimination phase.
T_{max} = Time at which C_{max} occurred; $t_{½}$ = Terminal elimination half-life; V_{ss} = Volume of distribution at steady-state.

Belantamab mafodotin was stable when incubated in rat, monkey or human plasma at 37ºC, as less than approximately 3% of the total MMAF conjugated to the antibody was released as free cys-mcMMAF over a 96-hour period. In an incubation of belantamab mafodotin with human serum, maleimide exchange was observed; the transfer of mcMMAF from belantamab mafodotin onto human serum albumin (HSA) to form HSA-mcMMAF.

Following incubation of belantamab mafodotin with HCEC cells and RPTECs, there was evidence for co-location of drug with lysosomes and catabolism to release cys-mcMMAF.

Following a single IV administration of fluorescently labelled belantamab mafodotin or GSK2857914 to rats, the fluorescent signal of both antibodies in liver, kidney and eyes was similar. Both antibodies were associated with connective tissue in the eye and eyelids, extra-orbital lacrimal and harderian glands and liver, as well as muscle in the eyelids but was not observed in the cornea or glands in the eyelids. The fluorescent signal was higher in liver and kidneys compared to the eye. Cys-mcMMAF liberated from belantamab mafodotin was detected at very low levels in liver, bone marrow, kidney, harderian gland and extra-orbital lacrimal gland, but was not detected in the cornea, eyelid or whole eye.

Following IV administration of belantamab mafodotin to rabbits, belantamab mafodotin (ADC and total mAb) and cys-mcMMAF were detected in tear fluid, but no effect on tear production was observed in belantamab mafodotin-treated animals when compared to vehicle control.

The binding of cys-mcMMAF to plasma proteins was investigated at 0.5, 5, and 50 ng/mL in human plasma from 3 donors, using equilibrium dialysis. Cys-mcMMAF exhibited low protein binding in human plasma in a concentration-dependent manner. The unbound percentages in the 3 donors ranged from 49.1 to 61.8% at 0.5 ng/mL, from 68.8 to 70.7% at 5 ng/mL, and from 80.9 to 88.7% at 50 ng/mL.

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Cys-mcMMAF has limited metabolic clearance. *In vitro* (rat, monkey, human) and *in vivo* (rats), the linear isomer of cys-mcMMAF was predominately chemically hydrolysed and dehydrated to the cyclized isomer of cys-mcMMAF, with a very minor amount of Phase I/II enzymatic biotransformations. It is the sum of the linear and cyclized isomers that are measured in the bioanalytical assay for cys-mcMMAF. Following IV dosing of ^{3}H-cys-mcMMAF to rats, radioactivity was excreted in faeces (83%) and urine (13%), predominately as either the cyclized or linear or isomers of cys-mcMMAF, respectively. In rat faeces, the cyclized isomer of cys-mcMMAF (SGD-1462) constituted the major component being 13.8% of the total radioactivity. Cys-mcMMAF was not an inducer neither inhibitor of key CYP enzymes in human hepatocytes. *In vitro*, cys-mcMMAF was not a substrate of transporters OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K, but was a substrate of OATP1B1 and OATP1B3. *In vitro,* cys-mcMMAF was not an inhibitor of transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K. A study was conducted to determine if cys-mcMMAF was either a substrate or inhibitor of the following efflux transporters using vesicular transport assays: P-gp; BCRP; BSEP; MRP1, MRP2, MRP3, MRP4 and MRP5. The studies showed that cys mcMMAF is a substrate of organic anion transporting polypeptide (OATP)1B1 and OATP1B3, multidrug resistance-associated protein (MRP)1, MRP2, MRP3, bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp).

2.3.4. Toxicology

Single dose toxicity

A summary of the single dose toxicity studies is included in ***Table 4***. Single dose toxicity studies were conducted in rats and monkeys with belantamab mafodotin (ADC in the table) or the cytotoxic moiety cys-mcMMAF.

Table 4 Single dose toxicity studies conducted with belantamab mafodotin or cys-mcMMAF

Study ID Test item	Species/ Sex/Number/ Group	Dose (mg/kg) Route	Approx. lethal dose (mg/kg)	Major findings
2012N134122 No GLP ADC	Rat 4/sex/group	10, 30, 100 IV	100	Inflammation in lung, heart, spleen, lymph nodes, kidney, injection site. Atrophy/necrosis in gonads, eyes, bone marrow, liver, skin. Presence of ADAs
2012N133495 No GLP ADC	Monkey 1/sex/group	3, 10, 30 IV	>30	Kidney injury Hemorrhage in heart, skin and stomach Cholestasis Skeletal muscle injury
2013N177526 No GLP Cys-mcMMAF	Rat 3 female/group	2.5, 10, 17.5, 25 IV	HNSTD ≥ 25	↓reticulocyte
2013N177529 GLP Cys-mcMMAF	Monkey 1/sex/group	1, 3, 6, 10 IV	HNSTD ≥ 10	Discoloration of the injection site ↓red cell mass ↑AST, bilirubin

Repeat dose toxicity

Repeat dose toxicity studies (**Table 5**) were conducted to investigate the effects of repeated administration of belantamab mafodotin (ADC below in the table), cys-mcMMAF and GSK2857914 in rats and monkeys.

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Table 5 Repeat dose toxicity studies conducted with belantamab mafodotin, cys-mcMMAF and GSK2857914

Study ID	Species/ Number /Group	Dose (mg/kg/ week) Route	Duration	NOEL/ NOAEL (mg/kg/ week)	Major findings
2013N174857 (R30467G) GLP ADC	Rat 10-16/sex/group	3, 10, 30 mg/kg/week IV	3 weeks	3	Findings were observed in testes, lung, teeth (irreversible), kidney, sternum/bone marrow (reversible). Non adverse changes in lymph nodes, eyes, femur, male mammary gland, epididymides, ovaries, spleen, liver, thymus, injection site.
2018N374327 (R32025G) GLP ADC	Rat 12-28/sex/group	3, 10, 30 (once every 3 weeks) IV	13 weeks	<3	Lung damage at all doses. Adverse findings in testes, teeth, kidney. Non adverse changes in eye, male mammary gland, spleen, liver.
2013N158643 (P70260G) GLP ADC	Monkey 3-5/sex/group	1, 3, 10 IV	3 weeks	1	Systemic inflammatory response: spleen, bone marrow, thymus. ↑CRP, WBC ↓albumin, red cell mass, platelets. Glomerulopathy, nephron degeneration. ↓IgM, IgG, NK cells ↑AST, GLDH, GGT, ALT, bilirubin, cholesterol, triglyceride.
2018N375127 (5002582) GLP ADC	Monkey 3-5/sex/group	1, 3, 10 IV	13 weeks	1	Severe pathological changes at 10 mg/kg/week, 1 death, cessation of dosing after 5 weeks. Likely caused by immune complex disease and ADA. Degeneration and necrosis in kidneys, GI tract, lymph nodes, thymus, spleen, liver, mostly reversible. Reversible increase in macrophages in BM, brain, spleen, thymus. Extramedullary , haematopoiesis in liver and lymph nodes. Systemic inflammation. Seminiferous tubule degeneration.
2013N177527 (1019-010) GLP Cys-mcMMAF	Rat 12/sex/group	1, 5, 10 mg/kg/day IV	5 days	10 mg/kg/day	Corneal opacity. ↑ Lung weight, alveolar histiocytosis, inflammation. ↑AST, ALT, neutrophils.
2013N177530 (1019-009) GLP Cys-mcMMAF	Monkey 3/sex/group	0.5, 2, 5 mg/kg/day	5 days	5 mg/kg/day	↑monocytes, lymphocytes.
2012N150466 (P70204G) GLP GSK2857914	Monkey 3/sex/group	10, 30, 100	4 weeks	> 100	Skin reddening, scabs, epidermal degeneration and necrosis, hyperplasia and inflammation. Microscopic changes in spleen, liver, kidney, bone marrow. ↑ inflammatory cytokines and CRP Systemic inflammation.

Genotoxicity

Table 6 Genotoxicity tests conducted with Cys-mcMMAF or belantamab mafodotin

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results
Gene mutations in bacteria (Ames) Cys-mcMMAF GLP	Salmonella strains TA98, TA100, TA1535, TA1537, and E coli strain WP2 *uvrA*	+/- S9 50-5000 µg/plate	Negative

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Gene mutations in mammalian cells Cys-mcMMAF GLP	Mouse lymphoma L5178Y $TK^{+/-}$ locus	+S9 (4h): 5.34-16.9 µg/mL -S9 (4h): 4-16.9 µg/mL -S9 (24h): 0.475-3 µg/mL	Negative
Chromosomal aberrations in vitro - induction of micronuclei Belantamab mafodotin Non-GLP	Human peripheral blood lymphocytes	-S9 (24h): 577 µg/mL	Positive
Chromosomal aberrations *in vivo* Cys-mcMMAF GLP	Rat, micronuclei in bone marrow 5 males/group	2.5-25 mg/kg IV	Negative

Carcinogenicity

No carcinogenicity studies with belantamab mafodotin were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproduction toxicity studies with belantamab mafodotin were submitted (see discussion on non-clinical aspects).

Toxicokinetic data

The results of the TK of belantamab mafodotin, GSK2857914 and cys-mcMMAF in repeat dose toxicity studies are presented in ***Table 7*** and ***Table 8***:

Table 7 Overview of Toxicokinetics (AUC) data belantamab mafodotin (adc and total antibody) following weekly or every 3 weeks intravenous administration of belantamab mafodotin

Study Numbers:	R30467G[a]		R32025G[b]		P70260G[c]		P71346G[d]		205678[h]
Dose (mg/kg/week)	Rat M	Rat F	Rat M	Rat F	Monkey M	Monkey F	Monkey M	Monkey F	Human Day 1 AUCo-∞ (µg.h/mL)
Plasma ADC AUC (µg.h/mL)[g]									
1	NA	NA	NA	NA	1180	1290	1280 (1050)[e]	1030	5644 at 2.5 mg/kg
3	5660	6240	12700	8350	3590	3922	6570	6870	6495 at 3.4 mg/kg
10	26000	17500	45500	29100	20500	22500	21600[i]	21400[i]	
30	51300	45900	106000	74100	NA	NA	NA	NA	
Plasma Total mAb AUC (µg.h/mL)[g]									
1	NA	NA	NA	NA	1500	1540	1700 (1140)[e]	1370	10268 at 2.5 mg/kg
3	7170	7150	15100	10400	4402	4844	8140	7930	10209 at 3.4 mg/kg
10	30500	21000	50900	34000	24200	27400	30200[i]	28600[i]	
30	60000	54000	125000	89400	NA	NA	NA	NA	

Key: AUC = Area under the curve; NA = Not applicable.
ADC = Belantamab mafodotin (GSK2857916).
a = 3 week (once weekly dosing) in Wistar Han rats [Report 2013N174857, m4.2.3.2]. AUC data from the end of the study ($AUC_{(0-168)}$)
b = 13 week (once every 3 weeks dosing) in Wistar Han rats [Report 2018N374327, m4.2.3.2]. AUC data from the end of the study ($AUC_{(0-504)}$).
c = 3 week (once weekly dosing) in cynomolgus monkeys [Report 2013N158643, m4.2.3.2]. AUC data from the end of the study ($AUC_{(0-167)}$).
d = 13 week (once weekly dosing) in cynomolgus monkeys [Report 2018N375127, m4.2.3.2]. AUC data from the end of the study ($AUC_{(0-t)}$).
e = n=2. The parameter values from Animal No. 2002 was excluded from the mean/median and range calculations due to the sharp decrease in the plasma concentrations (non-quantifiable at later time points). The values in the parenthesis are the mean parameters calculated without data exclusion.
f = Belantamab mafodotin administration at 10 mg/kg/week resulted in a deteriorating condition that necessitated cessation of dosing after 5 doses (Week 5/Day29).
g = For bioanalytical purposes, belantamab mafodotin is quantified as belantamab mafodotin (ADC) and belantamab mafodotin (total mAb). belantamab mafodotin (ADC) is defined as GSK2857914 conjugated to one or more mcMMAF groups (DAR >0) and belantamab mafodotin (total mAb) is defined as GSK2857914 with or without conjugated mcMMAF (DAR≥0).
h = Dosing once every 3 weeks in humans [from clinical study 205678; see m2.7.2, Section 2.1.2]. Data from frozen liquid formulation.
i = Exposure data from Week 4 as animals in this group were terminated early due to findings related to immune complex disease as a result of anti-drug antibodies.

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Table 8 Overview of Toxicokinetics (AUC) data cys-mcMMAF following weekly or every 3 weeks intravenous administration of belantamab mafodotin

Study Numbers:	R30467G[a]		R32025G[b]		P70260G[c]		P71346G[d]		205678[h]
Dose (mg/kg/week)	Rat M	Rat F	Rat M	Rat F	Monkey M	Monkey F	Monkey M	Monkey F	Human Day 1 AUC_{0-t} (µg.h/mL)
Plasma cys-mcMMAF AUC (µg.h/mL)									
1	NA	NA	NA	NA	0.0122	0.0121	NC[e]	NC[e]	0.0793 at 2.5 mg/kg
3	0.252	0.263	NC[f]	NC[f]	0.0856	0.0615	25.1	25.5	0.1136 at 3.4 mg/kg
10	1.13	1.36	0.050	0.0819	0.416	0.285	NA[g]	NA[g]	
30	2.90	2.67	0.413	0.370	NA	NA	NA	NA	

Key: AUC = Area under the curve; NA = Not applicable; NC = Not calculated.
a = 3-week (once weekly dosing) in Wistar Han rats [Report 2013N174857, m4.2.3.2]. AUC data from the end of the study (AUC_{0-t})
b = 13-week (once every 3 weeks dosing) in Wistar Han rats [Report 2018N374327, m4.2.3.2]. AUC data from the end of the study ($AUC_{tau(ss)}$).
c = 3-week (once weekly dosing) in cynomolgus monkeys [Report 2013N158643, m4.2.3.2]. AUC data from the end of the study (AUC_{0-t}).
d = 13-week (once weekly dosing) in cynomolgus monkeys [Report 2018N375127, m4.2.3.2]. AUC data from the end of the study (AUC_{0-t}).
e = AUC could not be calculated as no animal in this group had sufficient plasma concentration values.
f = AUC value could not be calculated in this group due to insufficient data
g = Belantamab mafodotin administration at 10 mg/kg/week resulted in a deteriorating condition that necessitated cessation of dosing after 5 doses (Week 5/Day 29), no data presented.
h = Dosing once every 3 weeks in humans [from clinical study 205678; see m2.7.2, Section 2.1.2]. Data from frozen liquid formulation.

Local Tolerance

No separate local tolerance studies have been conducted with belantamab mafodotin. IV injection sites were inspected in the toxicology studies. Clinical and histopathological analysis of injection sites were performed following IV administration of belantamab mafodotin as liquid and lyophilized formulations to rats and monkeys as part of the repeat dose studies (Reports 2012N134122, 2012N133495 and Reports 2013174857, 2013N158643, 2018N374327, 2018N375127).

In the rat 3-week study and the single dose toxicity studies in rat and monkey, injection site changes and inflammatory response indicative of local irritancy were noted at ≥3 mg/kg/week (dose concentrations of ≥0.3 mg/mL). Findings included localized epidermal hyperplasia, mild perivascular haemorrhage and/or inflammation/inflammatory cell infiltrate and occasional skeletal muscle degeneration/necrosis together with changes in plasma AST, aldolase and creatine kinase.

Thirteen weekly doses in the monkey, up to 10 mg/kg (up to a dose concentration of 2.5 mg/mL) and four doses administered 3 weeks apart in the rat, up to 30 mg/kg (up to a dose concentration of 3 mg/mL), did not result in treatment-related changes at the injection site.

Other toxicity studies

- *Mechanistic Ocular Toxicity*

In vitro studies (Reports 2019N410329, 2019N410330)

To investigate the potential for belantamab mafodotin to cause cytotoxicity in human corneal epithelial cells three primary human corneal epithelial cell (HCEC) lines and a primary human renal proximal tubule cells (RPTEC), as a comparator epithelial cell type, were used. All cell lines were confirmed by qPCR to have negligible or no expression of BCMA (Report 2019N410329).

To investigate the potential for belantamab mafodotin to cause cytotoxicity in HCECs and to examine the mechanism of uptake that plays a role, simple monolayer models using primary HCECs were established (Report 2019N410330). GSK2857914 was used as a negative control to demonstrate the antibody alone did not induce cytotoxicity. Vinblastine sulphate was used as a comparator tubulin inhibitor. Experiments to investigate the role of macropinocytosis in belantamab mafodotin-mediated cytotoxicity were conducted using EIPA to inhibit the pathway of non-specific uptake. Cytotoxicity was assessed by

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monitoring Caspase 3/7 markers for apoptosis, the pathway through which MMAF induces cell death, and cell viability in HCECs and RPTECs.

The results indicated that belantamab mafodotin exposure results in significant concentration-dependent increases in apoptosis *in vitro***.** The effects were observed in multiple donors for each cell type and there is a trend for HCECs being slightly more sensitive than RPTECs when assessing the lowest tested concentrations that caused a significant increase in apoptosis.

In the presence of the macropinocytosis inhibitor EIPA pre/co-treatment with EIPA significantly reduced belantamab mafodotin-mediated apoptosis in RPTECs and there was a similar trend in HCECs. Treatment with GSK2857914 showed no significant cytotoxicity, measured as apoptosis or cell viability, for both cell types. Treatment with vinblastine sulphate resulted in no effect on apoptosis, although a trend for decreased cell viability was observed in HCECs.

- *In vivo rabbit Tolerability and Ocular Toxicity (Report 2018N385412)*

A study was conducted to determine the tolerability and ocular toxicity of belantamab mafodotin in the New Zealand white rabbit following two or four IV doses each given 7 days apart. Female rabbits (n=3/group) were given belantamab mafodotin at 0 [vehicle], 15, or 30 mg/kg/week by IV (bolus) injection for two (0 or 30 mg/kg/week) or four weeks (0, 15 or 30 mg/kg/week).

No observations were noted after 2 weekly administrations up to 30 mg/kg/week. After four doses of 30 mg/kg/week, corneal epithelial single cell necrosis (minimal or mild) in all 3 rabbits, potentially associated with superficial corneal haze in 1 rabbit on Days 27 and 30, was observed. Increased mitoses (minimal) in the corneal epithelium in 2/3 rabbits given 15 mg/kg/week for four weeks, was also seen. There was no belantamab mafodotin-related effect on tear production when compared to vehicle control. Following ophthalmologic examination, bilateral striations observed in the retina of a single animal, administered 15 mg/kg/week for 4 weeks, were of uncertain relationship to treatment; this observation did not correlate with any microscopic findings in the retina following examination of multiple (n=6) sections containing the retina from this animal.

- *Tissue cross-reactivity (Report 2013N169796, Report 2013N176627)*

A non-GLP pilot study was conducted to identify a suitable positive control for use with the belantamab mafodotin and GSK2857914 and to determine the cross-reactivity profile of belantamab mafodotin and GSK2857914 in a limited set of human cell lines and human and cynomolgus monkey tissues by IHC analysis (Report 2013N169796).

Mild to moderate specific staining was observed in monkey and human adrenal, heart, kidney, liver, lymph node, spleen and tonsil, in human adipose/skin and in cynomolgus colon.

Minimal to mild non-specific staining by the BCMA protein absorption control and no antibody negative control was observed in human and cynomolgus goblet cells in the colon. The level of background staining observed in this study did not prevent evaluation for specific staining.

The potential cross-reactivity of belantamab mafodotin (ADC), prepared as a conjugate of belantamab mafodotin and Anti-diotype mAb S389105H11, was assessed in a definitive GLP study (Report 2013N176627). The following tissue specimens were evaluated: adrenal, urinary bladder, blood cells, bone marrow, breast, brain (cerebellum and cortex), endothelium, eye, fallopian tube, GI tract (oesophagus, gastric antrum, gastric body, duodenum, ileum, colon), heart, kidney, liver, lung, lymph node, ovary, pancreas, parathyroid, parotid, peripheral nerve, pituitary, placenta, prostate, skin, spinal cord, spleen, striated muscle, testis, thymus, thyroid, tonsil, ureter, uterus (cervix and endometrium).

Under the conditions of this study, antigen-specific binding of belantamab mafodotin was showed in positive control material (human spleen).

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Specific positive staining was observed with belantamab mafodotin conjugate in several tissues examined and this was generally associated with individual or focal groups of cells, blood vessel walls/perivascular tissue and connective tissue. The majority of specific positive staining observed with belantamab mafodotin was cytoplasmic. In all tissues where specific positive staining with belantamab mafodotin was observed, comparable staining was seen with the positive control article but not with the negative control article. All other observed staining was variable and considered to be non-specific.

2.3.5. Ecotoxicity/environmental risk assessment

Table 9 Summary of main study results

Substance (international non-proprietary name (INN)/Invented Name): belantamab mafodotin			
CAS-number (if available): n/a			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Chemaxon QSAR prediction and published article (Burns et al. Mol Pharm. 2017 p 415-42).	log Kow expected be <4.5	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	No studies conducted	
	BCF	No studies conducted	
Persistence	DT50 or ready biodegradability	No studies conducted	
Toxicity	NOEC or CMR	No studies conducted	
PBT-statement:	For the Cys-mcMMAF moiety of the active ingredient, based on the published data and Chemaxon QSAR prediction, the log Kow is not expected to be >4.5 (Burns et al 2017). Belantamab mafodotin is therefore not PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0025	µg/L	> 0.01 threshold (N)

Belantamab mafodotin PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

Overall, the pharmacodynamics of belantamab mafodotin is adequately characterized. The nonclinical pharmacology data showed the designed mode of action of belantamab mafodotin (anti-tumour activity by ADCC/ADCP activity, ADC-induced apoptosis and cell cycle arrest, ICD) and the selective function targeting both dividing and non-dividing BCMA-expressing tumour cells.

Modifications to the belantamab mafodotin manufacturing process were made during product development, and two different DS presentations have been used during nonclinical development: solution and powder for solution (which is proposed for commercialization). For these, the comparability

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has been demonstrated for the drug substance produced by the earlier manufacturing processes and DS batches used in the nonclinical toxicology studies and in clinical studies, and to commercial DP.

Stability assessments are ongoing for cys-mcMMAF in the presence of belantamab mafodotin at -20°C. Once the stability assessments have been completed, the applicant will make a final assessment of the impact on the cys-mcMMAF dataset. If the maximum storage stability duration is shorter than the time required to support at least 80% of the Study 205678 dataset, the applicant proposes to perform an update of the pharmacokinetic and PK/PD analyses using the data for which storage stability is confirmed and to submit the updated results to the CHMP by 2Q 2021. This was accepted by the CHMP.

Regarding the determination of free soluble BCMA in human serum using ECL the parallelism should be assessed, and the results should be reported. Due to scheduling and staffing complications associated with COVID-19, as well as the lack of suitable incurred samples from study 205678, the assessment has been delayed. The CHMP recommended the applicant to submit the results obtained for the parallelism experiments, when available (Q4 2020).

Belantamab mafodotin functionality was shown for large range of BCMA expression levels on MM cells, at concentrations of belantamab mafodotin hypothesized to be achievable in humans, under conditions designed to mimic the human target cells and microenvironment (MM patient plasma) and with the physiological concentrations of BCMA ligands and shedded BCMA. Belantamab mafodotin induced selective cell death of BCMA-expressing MM cells, with minimal bystander toxicity to non-BCMA expressing cells. Belantamab mafodotin induced durable tumour growth regression in xenograft mice models bearing human multiple myeloma NCI-H929, OPM-2, and MM1Sluc cells, and dependently on the presence of CD8+ T-cells in immune-competent syngeneic mouse expressing human BCMA (EL4-hBCMA). Furthermore, in cynomolgus monkeys a single dose of belantamab mafodotin resulted in reduction in the BCMA-positive plasma cells and IgE levels, and modest reduction in IgG, IgA, and IgM levels.

Belantamab mafodotin was taken up into cells throughout the body by a mechanism unrelated to BCMA receptor expression on the cell membrane (SmPC, section 5.3).

Limited secondary pharmacodynamic effects are expected, related to low potency to induce cell death, which express low levels of BCMA, such as plasmacytoid dendritic cells, and putative payload of non-specific uptake (pinocytosis) into non-target cells. Belantamab mafodotin had no significant effects on cardiovascular, respiratory and central nervous systems in rats and monkeys in safety pharmacology evaluations, but potential to cardiotoxicity related to inflammatory response is listed under RMP, Part II nonclinical safety specifications.

The Applicant has conducted a comprehensive set of *in vitro* and *in vivo* pharmacokinetic studies with each components of the product. No sex differences were observed. The serum t½ of belantamab mafodotin (ADC) in rats was approximately 11 days, which was slightly longer than in mice. Following IV bolus administration of belantamab mafodotin, T_{max} was observed at 0.25 hour in most monkeys; in some animals T_{max} was 3, 6 or 24 hours after dosing during Weeks 1 and 3 for belantamab mafodotin (ADC and total mAb). Belantamab mafodotin was shown to be distributed to connective tissue in eyes, eye lids, extra-orbital lacrimal, Harderian glands, liver, and kidney. Cys-mcMMAF was detected only in the bone marrow but not in the cornea, whole eye or eye lids of the rat. Cys-mcMMAF exhibited low protein binding in human plasma in a concentration dependent manner, from 49.1% at 0.5 ng/mL to 88.7% at 50 ng/mL. Binding of cys-mcMMAF to plasma protein was similar in monkeys and humans, but higher in rats.

The metabolism of cys-mcMMAF was shown to be low and was primarily characterized by non-enzymatic transformations and to a minor degree by oxidative and conjugative metabolism. In *vitro* (rat, monkey, human) and *in vivo* (rats), the maleimide ring was predominantly chemically hydrolysed and dehydrated

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to a cyclized isomeric form of cys-mcMMAF with a very minor amount of Phase I/II enzymatic biotransformation. It is the sum of the linear and cyclized isomers that are measured in the bioanalytical assay for cys-mcMMAF. Cys-mcMMAF was not a sensitive substrate of cytochrome P450 enzymes in vitro. The metabolic pathways of cys-mcMMAF in rat were hydrolysis, beta-lyse, S-methyltransferase, N-acetylation, reductive C-S-cleavage, amino acid conjugation, oxidation and unknown way. There were some differences in the metabolite profiles between the rat, monkey and human. However, this is not of any concern from clinical point of view since the metabolites accounted for less than 5% of the total radioactivity. Furthermore, metabolites unique to human that might have been missed in the toxicity studies conducted in rats and cynomolgus monkeys, were not identified.

The data showed that cys-mcMMAF is predominantly excreted via the hepato-biliary/faecal pathway (83%), and to a lesser amount via renal clearance (13%). Based on available *in vitro* and clinical data, there is a low risk of pharmacokinetic or pharmacodynamic drug interactions for belantamab mafodotin (SmPC, section 4.5).

Radio-profiles of 0- to 8-hour and 8- to 24-hour pooled urine samples showed that unchanged cys-mcMMAF (SGD-1362) was the major component in rat urine, accounting for 9.33% of the radioactive dose (compared to a total of 12.1 % of radioactive dose in the pooled urine samples and 11.6 % of radioactive dose quantitated, 0- to 24-hour post-dose together). Other identified metabolites, including M15, M16, SGD-1462, and M25, each accounted for less than 1% of radioactive dose.

Radio-profiles of 0- to 24-hour and 24- to 48-hour pooled faeces samples showed that the unchanged cys-mcMMAF was a minor component recovered in faeces, accounting for 0.748% of the radioactive dose (compared to a total of 81.4% of radioactive dose in the pooled faeces samples and 40.1% of radioactive dose quantitated, 0- to 48-hour post-dose together, due to low extraction recoveries). SGD-1462, an isobaric analogue of SGD-1362, was the only major metabolite, which accounted for 13.8% of radioactive dose. All other identified metabolites, including M25, M31, and M35 through 48, each accounted for less than 5% of radioactive dose.

In rats a mass balance study with radiolabelled cys-mcMMAF has been performed. Following IV dosing of 3H-cys-mcMMAF to rats approximately 83 % of the dose was excreted in the faeces. Urinary excretion (approximately 13%) was a minor route. Radioactivity was excreted rapidly and 94 % of the administered dose recovered in the first 48 hours after dosing. Total recovery of radioactivity over the 168-hour collection period was 96 %. Radioactivity was excreted predominantly as either the linear or cyclized isomers of cys-mcMMAF.

Non-clinical safety studies have shown dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey) directly related to belantamab mafodotin, accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study. Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with ADA, following 5 weekly doses of 10 mg/kg, led to the early euthanasia of one monkey. Glomerulonephritis associated with immune complex formation is not expected to be reversible. Nephrotoxicity has been categorized as an important potential risk (see RMP).

In general, the toxicological data package for belantamab mafodotin is comprehensive. Repeat dose toxicity evaluation was conducted for belantamab mafodotin, cys-mcMMAF and GSK2857914 in rats and cynomolgus monkeys, and in rabbits focusing on the ocular findings. Of the toxicological species, belantamab mafodotin cross-reacted only with the monkey BCMA target, thus implicating that in rats and rabbits lacking the BCMA binding, not the target specific toxicity, but the off-target or unspecific cytotoxicity via the pinocytosis of the product, has been evaluated. To support the long-term therapeutic use of belantamab mafodotin powder for concentrate for solution for infusion, studies were performed by the IV route of administration for periods of up to 13 weeks in rat (≤30 mg/kg) and monkey (≤10

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mg/kg). The toxicology findings with belantamab mafodotin were primarily related to the safety of the cytotoxic drug conjugate, cys-mcMMAF, which follows the reported safety profiles of other auristatins and microtubule disrupting agents. The tubular degeneration/regeneration in the kidneys, seminiferous tubular changes in the testes, luteinized nonovulatory follicles in the ovaries, degeneration of the incisor ameloblast/odontoblast layers (rat), increased liver enzymes with single cell necrosis, lymphocytolytic and/ or cellularity alterations in the bone marrow, spleen and eye (rat) are considered likely to be related to MMAF. Similar effects have been reported with the auristatins or other microtubule disrupting agents such as colchicine and vinblastine.

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. Increased risk of infections due to immunosuppression and/or neutropenia has been categorized as an important potential risk (see discussion on clinical safety RMP).

Overall, the principal adverse findings (directly related to belantamab mafodotin) in the rat and monkey, at exposures ≥1.2 times of the recommended clinical dose of 2.5 mg/kg, were elevated liver enzymes sometimes associated with hepatocellular necrosis at ≥ 10 and ≥3 mg/kg, respectively and increases in alveolar macrophages associated with eosinophilic material in the lung at ≥3 mg/kg (rat only) (SmPC, section 5.3). Most findings in animals were related to the cytotoxic drug conjugate, the histopathological changes observed in the testes and lung, were not reversible in rats (SmPC, section 5.3).

Although ADA formation was evident in monkey studies, the exposures were generally maintained at low and mid-dose animals and were approximately at the same level in mid-dose animals as the recommended human dose of 2.5 mg/kg, based on ADC area under concentration curve (AUC). The highest non-severe toxic dose in monkeys was 3 mg/kg and the highest dose tested exceeded the clinical dose by 3.8 and 2.5 -fold (ADC and mAb respectively).

Corneal events are one of the most frequently reported AEs associated with belantamab mafodotin in the clinic, and these include keratopathy, blurred vision, dry eyes and photophobia. These corneal events are consistent with those reported in the literature with other MMAF-conjugated ADCs. In nonclinical toxicity studies, corneal effects (bilateral single cell necrosis in the corneal epithelium and/or increased mitoses of corneal epithelial cells) were seen in rats and rabbits, but not in monkeys. Furthermore, in rabbits a finding of bilateral striations in the retina in the 15 mg/kg dose group was reported. Belantamab mafodotin was found in connective eye tissues but not in cornea in rats. The data support the involvement of non-specific macropinocytosis as a mechanism of cellular uptake to the eye and indicate that the ocular adverse effects observed in rats result from unspecific uptake leading to microtubulin inhibition and apoptosis due to the cys-mcMMAF moiety. Regarding the retinal finding in rabbit the cause is unknown. It was postulated that it could be a slight alteration in the alignment of retinal ganglion cells. Finding did not correlate with any microscopic alterations. It did not represent a retinal degeneration or adversely affect the surrounding layers. Thus far similar retinal striations have not been reported in patients after treatment with belantamab mafodotin, and it is sufficient, that the eye alterations are and will be followed critically in patients (see discussion on clinical safety and RMP).

No carcinogenicity or definitive genotoxicity studies have been conducted with belantamab mafodotin (SmPC, section 5.3). Belantamab mafodotin was genotoxic in an *in vitro* screening assay in human lymphocytes, consistent with the pharmacological effect of cys-mcMMAF-mediated disruption of microtubules causing aneuploidy. The absence of carcinogenicity studies is accepted in line with the ICH S9 and S6(R1) guidelines.

No animal studies have been performed to evaluate the potential effects of belantamab mafodotin on reproduction or development. The mechanism of action is to kill rapidly dividing cells which would affect

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a developing embryo which has rapidly dividing cells. There is also a potential risk of heritable changes via aneuploidy in female germ cells (SmPC, section 5.3).

Effects on male and female reproductive organs have been observed in animals at doses of ≥ 10 mg/kg, which is approximately 4 times the exposure of the clinical dose. Luteinized nonovulatory follicles were seen in the ovaries of rats after 3 weekly doses. Findings in male reproductive organs, that were adverse and progressed following repeat dosing in rat, included marked degeneration/atrophy of seminiferous tubules that generally did not reverse following dosing cessation (SmPC, section 5.3). Based on findings in animals and the mechanism of action, belantamab mafodotin may impair fertility in females and males of reproductive potential (SmPC section 4.6). Therefore, women of childbearing potential who may desire offspring in the future should be counselled prior to therapy regarding the option of having eggs frozen before treatment. Men being treated with this medicine are advised to have sperm samples frozen and stored before treatment (SmPC section 4.6).

Based on the mechanism of action of the cytotoxic component monomethyl auristatin F (MMAF), belantamab mafodotin can cause embryo- fetal harm when administered to a pregnant woman. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin has the potential to be transmitted from the mother to the developing fetus (SmPC section 4.6).

BLENREP should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus. If a pregnant woman needs to be treated, she should be clearly advised on the potential risk to the fetus (SmPC, section 4.6).

It is not known whether belantamab mafodotin is excreted into human milk. Immunoglobulin G (IgG) is present in human milk in small amounts. Since belantamab mafodotin is a humanised IgG monoclonal antibody, and based on the mechanism of action, it may cause serious adverse reactions in breast-fed children. Women should be advised to discontinue breast-feeding prior to initiating treatment with BLENREP and for 3 months after the last dose (SmPC, section 4.6).

The pregnancy status of child-bearing women should be verified prior to initiating therapy with BLENREP. Women of child-bearing potential should use effective contraception during treatment with BLENREP and for 4 months after the last dose (SmPC, section 4.6).

Men with female partners of child-bearing potential should use effective contraception during treatment with BLENREP and for 6 months after the last dose (SmPC, section 4.6).

The active substance is composed of a natural substance (monoclonal antibody) conjugated with tubulin polymerization inhibitor mcMMAF. $PEC_{SURFACEWATER}$ of belantamab mafodotin is below the trigger limit of 0.01 µg/L and therefore the product is not expected to adversely affect the aquatic or terrestrial environments.

2.3.1. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.6, 5.1 and 5.3).

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2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with good clinical practice (GCP) as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 10 Clinical studies in the clinical development program supporting the MA

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
m5.3.5.1 Safety and Efficacy Studies: Controlled Clinical Studies						
205678	Safety and Efficacy	Phase II Two-arm, R, OL, PK Exploratory cohort with lyophilized presentation	Patients with RRMM	**GSK2857916:** Frozen Solution **2.5 mg/kg** Cohort: IV infusion over 30 minutes; Day 1 of each 21-day cycle **3.4 mg/kg** Cohort: IV infusion over 30 minutes; Day 1 of each 21-day cycle Lyophilized presentation **3.4 mg/kg** Cohort: IV infusion over 30 minutes; Day 1 of each 21-day cycle	Frozen solution: 2.5 mg/kg: 97 / 37 3.4 mg/kg: 99 / 34 Lyo cohort: 25 / 4	Ongoing (CSR on Final Analysis)
m5.3.5.2 Safety and Efficacy Studies: Uncontrolled Clinical Studies						
BMA117159	Part 1 - Safety and tolerability, and to establish a maximum tolerated dose Part 2 - safety, tolerability, immunogenicity PK, PD, and clinical activity	Phase I NR, OL, DE, PK	Patients with RRMM and NHL	**GSK2857916** Part 1: 60 min IV infusion, dose range 0.03 mg/kg to 4.6 mg/kg, once every 21-days Part 2: 60 min IV infusion, 3.40 mg/kg once every 21 days	Total enrolled (MM): 73 Part 1 MM: 38 / 38 Part 2 MM: 35 / 35 Part 2 NHL: 6 / 6	Concluded (CPSR on Final Analysis)

2.4.2. Pharmacokinetics

The pharmacokinetics of belantamab mafodotin, total mAb (antibody with or without the cys-mcMMAF moiety), and cys-mcMMAF has been evaluated in two clinical studies DREAMM-1 and DREAMM-2 conducted in subjects with RRMM. In addition, a population PK analysis was performed in order to characterize the population PK of belantamab mafodotin in patients with RRMM and identify covariates of clinical interest. The PPK model was subsequently used for exposure-response analyses.

Absorption

Maximum concentration for belantamab mafodotin occurred at or shortly after the end of infusion while cys-mcMMAF concentrations peaked ~24 hours after dosing. Geometric mean belantamab mafodotin Cmax and AUC(0-tau) concentrations were 43 mcg/mL and 4,666 mcg.h/mL, respectively. Geometric mean cys-mcMMAF Cmax and AUC(0-168h) concentrations were 0.90 ng/mL and 84 ng.h/mL, respectively (SmPC, section 5.2).

The dose of belantamab mafodotin was 2.5 mg/kg. Median t_{max} (range) values were 22.83 h (1.92-65.63 h) at Cycle 1 and 23.24 h (0.58-46.08 h) at Cycle 3 for cys-mcMMAF.

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Distribution

The mean steady-state volume of distribution of belantamab mafodotin was 10.8 L (SmPC, section 5.2). Geometric mean value of distribution at steady state for belantamab mafodotin was 4.08 L at Cycle 1 in study BMA117159 (mean 2.9-5.2 L/different dose levels) and 8.0-9.0 L at Cycle 1 in study DREAMM-2.

Belantamab mafodotin binds to the sBCMA in plasma. The assay for quantifying belantamab mafodotin plasma concentrations measures both free and complexed belantamab mafodotin. *In vitro*, cys-mcMMAF exhibited low protein binding in human plasma in a concentration-dependent manner. The unbound percentages in the three donors ranged from 49 to 62% at 0.5 ng/mL, from 69 to 71% at 5 ng/mL, and from 81 to 89% at 50 ng/mL.

Elimination

Belantamab is a large protein which is degraded to small peptides. The antibody-drug compound is not expected to be excreted. As belantamab mafodotin binds to the cell surface, it is internalised and the cytotoxic moiety cys-mcMMAF is released.

Belantamab mafodotin was cleared slowly with total plasma clearance of 0.92 L/day and a terminal phase half-life of 12 days. Over time, clearance was reduced to 0.72 L/day with an elimination half-life of 14 days. Predose cys-mcMMAF concentrations at each dose were typically below the limit of quantification (0.05 ng/mL) (SmPC, section 5.2).

In Part 1 of Study BMA117159, urine was collected for 24 h at each cycle, and aliquots were taken for the determination of cys-mcMMAF concentrations at Cycles 2, 4, 7, 10, 13, and 16. Combining all dose levels at Cycle 2, median cys-mcMMAF fraction excreted into the urine over 24 hours was 0.073% of the administered dose. The median value after Cycle 4 was 0.122 % (n=10; range 0.008 to 0.546%).

Dose proportionality and time dependencies

- *Belantamab mafodotin*

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Table 11 Summary of Belantamab Mafodotin PK Parameters on Cycle 1 (Study BMA117159)

	Treatment Group (Part 1)											Part 2
Parameter	**0.03 mg/kg (N=1)**	**0.06 mg/kg (N=1)**	**0.12 mg/kg (N=4)**	**0.24 mg/kg (N=4)**	**0.48 mg/kg (N=4)**	**0.96 mg/kg (N=3)**	**1.92 mg/kg (N=4)**	**2.50 mg/kg (N=8)**	**3.40 mg/kg (N=3)**	**4.60 mg/kg (N=6)**	**Total (N=38)**	**3.40 mg/kg (N=35)**
AUC(0-τ) (µg.h/mL)	ND	200.5	633.4 (35)	729.4 (91)	2389[3] (51)	4448 (80)	9893[3] (52)	ND	23122[2] (7)	9739 (39)	ND	ND
AUC(0-∞) (µg.h/mL)	ND	215.8	767.3 (50)	632.3[3] (101)	2992[3] (72)	9235[2] (47)	18469[1]	ND	ND	8355[4] (25)	ND	ND
C-EOI (ng/mL)	409	1259	2909 (21)	4227 (20)	11288[3] (15)	17324 (13)	38141[3] (51)	67783 (36)	66486 (23)	114033 (25)	ND	78687[6] (23)
Cmax (ng/mL)	429	1323	2957 (18)	4548 (20)	11876[3] (24)	23050 (23)	43774[3] (45)	ND	68128 (21)	117386 (24)	ND	ND
tmax (h)	2.08	4.08	1.19 (1.00-2.00)	3.09 (2.00-8.78)	1.00[3] (1.00-4.00)	2.05 (2.00-2.08)	1.00[3] (0.50-24.00)	ND	6.92 (2.02-8.78)	1.56 (0.95-2.07)	2.00[7] (0.50-24.00)	ND
Ctrough (ng/mL)	ND	ND	382 (106)	1331[2] (44)	4307[1]	3720 (114)	11421[3] (36)	3727 (50)	28134[2] (36)	2301 (76)	ND	3486[7] (86)
CL (mL/h)	ND	28.3	10.5 (59)	25.0[3] (89)	15.1[3] (75)	8.46[2] (27)	11.7[1]	ND	ND	38.8[4] (38)	17.9[5] (83)	ND
CL (mL/h/kg)	ND	0.274	0.157 (50)	0.377[3] (100)	0.156[3] (68)	0.103[2] (48)	0.104[1]	ND	ND	0.525[4] (28)	0.228[5] (88)	ND
Vss (mL)	ND	5239	2900 (29)	4286[3] (31)	4388[3] (22)	3224[2] (22)	5156[1]	ND	ND	5215[4] (19)	4079[5] (32)	ND
Vss (mL/kg)	ND	50.8	43.4 (17)	64.5[3] (31)	45.3[3] (19)	39.4[2] (4)	46.0[1]	ND	ND	70.5[4] (22)	52.1[5] (29)	ND
t½ (days)	ND	5.26	7.84 (37)	4.91[3] (76)	8.27[3] (50)	11.04[2] (47)	12.85[1]	ND	ND	4.32[4] (17)	6.69[5] (54)	ND

Source: Study BMA117159 CPSR (m5.3.5.2), Table 4.0050, Table 4.0051
Data presented as geometric mean, (%CVb), except tmax, presented as median, (minimum-maximum). n is in column heading unless footnoted
C-EOI = concentration at the end of the infusion; ND = not determined
[1] n=1; [2] n=2; [3] n=3; [4] n=4; [5] n=18; [6] n=32; [7] n=28

Table 12 Summary of Belantamab Mafodotin PK Parameters at Cycle 1 (Study DREAMM-2)

	Belantamab Mafodotin					
Parameter	**2.5 mg/kg (N=95)**		**3.4 mg/kg (N=99)**		**3.4 mg/kg Lyophile (N=24)**	
	n	Value	n	Value	n	Value
AUC(0-τ) (µg.h/mL)	30	4666 (46)	20	5678 (40)	22	5946 (37)
AUC(0-∞) (µg.h/mL)	26	5644 (40)	18	6495 (54)	18	6962 (51)
C-EOI (µg/mL)	91	39.6 (48)	97	49.8 (36)	23	49.5 (18)
Cmax (µg/mL)	32	42.5 (26)	21	52.0 (20)	22	51.3 (18)
tmax (h)	32	0.78 (0.42-2.50)	21	0.70 (0.43-2.15)	22	0.75 (0.48-2.88)
Ctrough (µg/mL)	69	2.43 (52)	71	2.54 (88)	20	3.41 (76)
CL (mL/h)	26	36.1 (42)	18	38.0 (51)	18	37.1 (47)
CL (mL/h/kg)	26	0.443 (39)	18	0.524 (54)	18	0.486 (51)
Vss (L)	26	8.03 (30)	18	8.33 (28)	18	9.04 (26)
Vss (mL/kg)	26	98.7 (30)	18	114.9 (26)	18	118.3 (21)
t½ (days)	29	6.85 (46)	19	6.91 (55)	22	8.18 (41)

Source: Study 205878 CSR (m5.3.5.1), Table 4.0040
Data presented as geometric mean (%CVb), except tmax, presented as median, (minimum-maximum).
C-EOI = concentration at the end of the infusion

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Table 13 Summary of Key Belantamab Mafodotin PK Parameters at Cycle 3 (Study DREAMM-2)

Parameter	Belantamab Mafodotin					
	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)		3.4 mg/kg Lyophile (N=24)	
	n	Value	n	Value	n	Value
CL (mL/h)	19	23.7 (43)	21	22.6 (36)	9	23.8 (41)
CL (mL/h/kg)	19	0.284 (38)	21	0.299 (39)	9	0.288 (46)
Vss (L)	19	6.56 (23)	21	6.94 (28)	9	8.54 (17)
Vss (mL/kg)	19	78.7 (26)	21	91.6 (24)	9	103.5 (22)
t½ (days)	26	8.07 (48)	23	8.93 (46)	11	11.6 (40)

Source: Study 205678 CSR (m5.3.5.1), Table 4.0040
Data presented as geometric mean (%CVb)

- *Total mAb*

Table 14 Summary of Total mAb Pharmacokinetic Parameters on Cycle 1 (Study BMA117159)

Parameter	Treatment Group (Part 1)											Part 2
	0.03 mg/kg (N=1)	0.06 mg/kg (N=1)	0.12 mg/kg (N=4)	0.24 mg/kg (N=4)	0.48 mg/kg (N=4)	0.96 mg/kg (N=3)	1.92 mg/kg (N=4)	2.50 mg/kg (N=8)	3.40 mg/kg (N=3)	4.60 mg/kg (N=6)	Total (N=38)	3.40 mg/kg (N=35)
AUC(0-τ) (µg.h/mL)	ND	160.3	550.3[3] (34)	582.6 (77)	1729[3] (41)	3285 (54)	9028[2] (4)	ND	12973 (39)	12945[5] (39)	ND	ND
AUC(0-∞) (µg.h/mL)	ND	172.9	675.5[3] (45)	678.9 (100)	2032[3] (52)	2949[2] (57)	11372[1]	ND	9559[1]	16222[4] (71)	ND	ND
C-EOI (ng/mL)	408	1413	3013 (16)	4354 (18)	11371[3] (16)	16589 (10)	39969[3] (38)	65014 (25)	75566 (18)	94786 (17)	ND	732077 (24)
Cmax (ng/mL)	476	1440	3046 (16)	4672 (19)	11966[3] (25)	21114 (12)	45231[3] (29)	ND	76289 (18)	96484 (18)	ND	ND
tmax (h)	9.05	2.07	1.60 (1.17-8.88)	2.00 (1.03-2.07)	1.00[3] (1.00-4.00)	4.08 (2.05-9.05)	1.00[3] (0.50-2.00)	ND	1.05 (0.97-2.27)	2.00 (1.00-2.07)	2.00[8] (0.50-9.05)	ND
Ctrough (ng/mL)	ND	ND	391 (68)	808[2] (65)	2473[1]	2103 (112)	5875[3] (42)	7687 (62)	16631[2] (20)	4545 (93)	ND	8493[8] (94)
CL (mL/h)	ND	35.3	12.2[3] (62)	25.0 (79)	22.2[3] (53)	24.3[2] (63)	19.0[1]	ND	21.7[1]	21.6[4] (61)	21.1[6] (58)	ND
CL (mL/h/kg)	ND	0.342	0.180[3] (47)	0.351 (99)	0.230[3] (48)	0.325[2] (57)	0.169[1]	ND	0.356[1]	0.265[4] (72)	0.266[6] (61)	ND
Vss (mL)	ND	4386	3433[3] (38)	4973 (20)	5465[3] (23)	4825[2] (50)	5519[1]	ND	4833[1]	5540[4] (26)	4842[6] (29)	ND
Vss (mL/kg)	ND	42.5	50.8[3] (19)	70.0 (22)	56.4[3] (22)	64.7[2] (44)	49.2[1]	ND	79.2[1]	68.0[4] (13)	61.0[6] (24)	ND
t½ (days)	ND	3.59	8.13[3] (26)	5.76 (73)	7.04[3] (30)	5.83[2] (13)	8.37[1]	ND	6.43[1]	7.60[4] (57)	6.67[6] (44)	ND

Source: Study BMA117159 CPSR (m5.3.5.2), Table 4.0060, Table 4.0061
Data presented as geometric mean, (%CVb), except tmax, presented as median, (minimum-maximum). n is in column heading unless footnoted
C-EOI = concentration at the end of the infusion; ND = not determined
[1] n=1; [2] n=2; [3] n=3; [4] n=4; [5] n=5; [6] n=19; [7] n=32; [8] n=28

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Table 15 Summary of Total mAb Pharmacokinetic Parameters at Cycle 1 (Study DREAMM-2)

Parameter	Belantamab Mafodotin					
	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)		3.4 mg/kg Lyo (N=24)	
	n	Value	n	Value	n	Value
AUC(0-τ) (µg.h/mL)	29	7305 (42)	18	9566 (42)	19	9029 (40)
AUC(0-∞) (µg.h/mL)	16	10268 (66)	10	10209 (65)	9	10170 (75)
C-EOI (µg/mL)	88	43.5 (49)	91	56.4 (39)	22	56.4 (21)
Cmax (µg/mL)	30	48.9 (30)	19	61.1 (27)	20	60.1 (18)
tmax (h)	30	1.75 (0.42-2.50)	19	1.87 (0.50-24.50)	20	0.65 (0.48-2.17)
Ctrough (µg/mL)	66	5.27 (83)	71	5.98 (87)	18	8.13 (101)
CL (mL/h)	16	21.2 (59)	10	25.3 (64)	9	26.0 (59)
CL (mL/h/kg)	16	0.244 (66)	10	0.332 (64)	9	0.333 (76)
Vss (L)	16	7.54 (37)	10	6.77 (29)	9	7.80 (23)
Vss (mL/kg)	16	86.8 (46)	10	88.8 (31)	9	100.0 (29)
t½ (days)	29	10.1 (49)	17	10.5 (70)	19	12.5 (61)

Source: Study 205678 CSR (m5.3.5.1), Table 4.0050
Data presented as geometric mean (%CVb), except tmax, presented as median, (minimum-maximum).
C-EOI = concentration at the end of the infusion

Table 16 Summary of Key Total mAb Pharmacokinetic Parameters at Cycle 3 (Study DREAMM-2)

Parameter	Belantamab Mafodotin					
	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)		3.4 mg/kg Lyo (N=24)	
	n	Value	n	Value	n	Value
CL (mL/h)	10	8.81 (44)	11	10.8 (67)	3	11.8 (124)
CL (mL/h/kg)	10	0.113 (44)	11	0.143 (72)	3	0.128 (130)
Vss (L)	10	5.05 (17)	11	5.59 (30)	3	6.31 (9)
Vss (mL/kg)	10	64.8 (26)	11	74.0 (33)	3	68.8 (15)
t½ (days)	23	14.7 (53)	23	15.5 (50)	11	23.2 (92)

Source: Study 205678 CSR (m5.3.5.1), Table 4.0050
Data presented as geometric mean (%CVb)

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- **Time dependency**

Table 17 Summary of Accumulation Ratios Based on End-of-Infusion Plasma Concentrations (Study BMA117159)

Analyte	Part 1[1]		Part 2	
	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)
Belantamab mafodotin	10	1.14 (86%)	6	1.12 (8%)
Total mAb	10	1.13 (49%)	6	1.36 (16%)
Cys-mcMMAF	7	1.31 (42%)	6	1.42 (55%)

Source: Study BMA117159 CPSR (m5.3.5.2), Table 4.0160, Table 4.0161, Table 4.0170, Table 4.0171; Study BMA117159 Cys-mcMMAF Supplemental Pharmacokinetic Report (m5.3.5.2), Table 9.0190, Table 9.0191

[1] Data combined across dose levels.

Table 18 Summary of Accumulation Ratio Values (Study DREAMM-2)

Parameter	Belantamab Mafodotin					
	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)		3.4 mg/kg Lyophile (N=24)	
	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)
Belantamab mafodotin						
AUC(0-τ) (µg.h/mL)	7	1.69 (50)	4	1.76 (25)	5	1.90 (29)
Cmax (µg/mL)	8	1.09 (20)	5	1.17 (31)	5	1.10 (11)
Total monoclonal antibody						
AUC(0-τ) (µg.h/mL)	7	1.94 (52)	3	1.75 (43)	5	2.64 (35)
Cmax (µg/mL)	8	1.20 (22)	5	1.18 (36)	5	1.31 (24)
Cys-mcMMAF						
AUC(0-168) (ng.h/mL)	1	0.79	1	0.25	1	1.26
Cmax (pg/mL)	6	0.59 (39)	5	0.74 (56)	5	0.68 (81)

Special populations

Impaired renal function

No specific clinical studies were conducted to assess the effects of intrinsic factors on belantamab mafodotin, total mAb, or cys-mcMMAF pharmacokinetics; the inclusion/exclusion criteria for the clinical studies in subjects with RRMM included in the submission allowed the enrollment of subjects with mild or moderate renal impairment or with mild hepatic impairment (NCI-ODWG classification) (Patel, 2004). The effects of renal impairment on the exposure of belantamab were derived from the population PK model which included 47 patients with normal renal, 103 with mild, 60 with moderate, and 7 with severe renal impairment. Baseline calculated estimated glomerular filtration ratio (eGFR) was not found to be a significant factor based on population pharmacokinetic analysis accounting for interindividual variability in belantamab mafodotin or cys-mcMMAF pharmacokinetics with baseline eGFR values as low as 14 mL/min/1.73 m^2 (there were eight subjects with data at baseline eGFR values <30 mL/min/1.73 m^2, seven with severe renal impairment and one with end stage renal disease).

Decrease in GFR from normal to low was seen in 18 % of the patients after dose 2.5 mg/kg and in 15 % of the patients after dose 3.4 mg/kg in study DREAMM-2.

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Impaired hepatic function

No specific clinical studies were conducted to assess the effects of intrinsic factors on belantamab mafodotin, total mAb, or cys-mcMMAF pharmacokinetics; the inclusion/exclusion criteria for the clinical studies in subjects with RRMM included in the submission allowed the enrollment of subjects with mild or moderate renal impairment or with mild hepatic impairment (NCI-ODWG classification) (Patel, 2004).

The effects of hepatic impairment on the exposure of belantamab were derived from the population PK model which included 192 patients with normal hepatic function, and 24 with mild hepatic impairment.

Mild hepatic impairment was not found to be a significant factor accounting for interindividual variability in belantamab mafodotin or cys-mcMMAF pharmacokinetics.

Gender

In population PK analysis, gender was found to be a statistically significant covariate for belantamab mafodotin central volume of distribution, but the impact of gender on predicted exposure parameters was < 15%.

Race

Race was not found to have effect on pharmacokinetics of belantamab mafodotin in the population PK analyses.

Weight

Clearance and volume of distribution of belantamab mafodotin and cys-mcMMAF increased with increasing body weight. Patients with baseline weight between 42.4 and 130 kg were investigated in the two clinical studies. Population PK model-predicted average exposure in the extreme body weights were compared against the exposure in a typical patient (body weight 75 kg). The predicted percent change from a typical patient for ADC Ctau was -20.1% for a 40 kg patient and -10.2% for a 55 kg patient for the lower extreme weight range and +9.97% for a 100 kg patient and +19.5% for a 130 kg patient for the upper extreme weight range.

Elderly

The age of the subjects included in the efficacy and safety studies ranged between 34 and 89 years. Age was not found to affect pharmacokinetics.

Table 19 Patient age distribution by study

Study	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
BMA117159	22/73 (30%)	3/73 (4%)	0
205678	94/218 (43%)	33/218 (15%)	3/218 (1%)
Total	116/291 (40%)	36/291 (12%)	3/291 (1%)

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Pharmacokinetic interaction studies

No *in vitro* or *in vivo* studies on pharmacokinetic drug interactions have been submitted (see discussion on clinical pharmacology).

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Belantamab mafodotin is a humanized immunoglobulin (Ig)G1 immuno-conjugate that binds specifically to B-cell maturation antigen (BCMA). Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell via proteolysis of the mAb component, resulting in cell killing through disruption of the microtubule network and leading to cell cycle arrest and apoptosis. Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells. Immune effector cells can kill tumour cells by antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis (ADCC and ADCP, respectively). Moreover, ADC-induced apoptosis by belantamab mafodotin was shown to be potentially immunogenic, as measured by cell surface externalization of calreticulin (CRT) and secretion of high mobility group box 1 (HMGB1) and ATP. Immunogenic cell death (ICD) induced by belantamab mafodotin resulted in activation of dendritic cells *in vitro* and may contribute to a T cell-mediated anti-tumour response.

Primary and Secondary pharmacology

Primary pharmacology

Free soluble BCMA was explored as a potential marker of response. Target engagement by belantamab mafodotin was indirectly observed by assessing the binding of belantamab mafodotin to sBCMA, observed by reductions in the levels of free sBCMA and increases in the levels of bound sBCMA by the end of the infusion, with return to baseline levels by seven days after dosing.

Study BMA117159

The populations examined included 73 participants from Total Part 1 and Part 2 with valid biomarker data was available, the Biomarker or Pharmacodynamic (PD) Population. In instances where values obtained were outside the limit of quantification and upper or lower limits of detection are known, results were imputed.

BCMA expression in bone marrow aspirate samples was examined by two immunohistochemical (IHC) assays: a single-color BCMA assay with pathological examination, and a BCMA + CD138 dual-colour IHC assay. The dual-colour assay was used to identify myeloma cells by CD138 staining rather than by histology. The single-color BCMA assay showed that patients had moderate BCMA positivity in all bone marrow cells; however, essentially all bone marrow plasma cells examined expressed BCMA. Since there was near uniform expression of BCMA in plasma cells, no relationship was observed with response.

Examination of plasma cell BCMA staining intensity similarly revealed no striking relationship between BCMA expression and response to belantamab mafodotin. Likewise, in the BCMA + CD138 IHC assay,

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myeloma cells (CD138+) had high BCMA expression, with most participants having greater than 80% BCMA positivity in CD138+ cells, with no relationship to response. BCMA Intensity in CD138+ myeloma cells also did not show a relationship with response.

The BCMA receptor was known to be cleaved by gamma-secretase, leading to a release of the extracellular domain of BCMA as sBCMA into the circulation. Since belantamab mafodotin binds sBCMA, the levels of free and belantamab mafodotin-bound sBCMA were measured. Baseline levels of sBCMA were found to be consistent with the MM data observed during the assay validation. The baseline sBCMA levels were compared with response in the dose escalation and expansion cohorts, and no relationships between baseline sBCMA levels and responses were observed.

Examinations of the levels of free and belantamab mafodotin-bound sBCMA prior to and after infusion showed that belantamab mafodotin binds to sBCMA after infusion, as the levels of free sBCMA decrease with an apparent dose-dependent relationship, and the levels of bound sBCMA increase. Consistent, high levels of sBCMA (>90%) engagement were seen in all dose groups ≥ 1.92 mg/kg. A rebound in free sBCMA concentrations and a corresponding decrease in drug-bound sBCMA were also noted between the EOI samples and the subsequent pre-infusion time points. Most patients with data beyond the second treatment cycle showed relatively consistent levels of free and drug-bound sBCMA concentrations, with drug-bound sBCMA concentrations consistently greater than their corresponding free sBCMA levels.

Secondary pharmacology

A concentration-QT interval analysis was conducted on data from two studies in 291 subjects with RRMM (Study BMA117159 and Study DREAMM-2) to assess the potential effect of belantamab mafodotin on cardiac repolarization and to evaluate any relationship between concentrations of belantamab mafodotin, total mAb, or cys-mcMMAF and QT interval.

In total, the analysis dataset contained time-matched ECG and concentration data from 290 subjects, the majority (N=217) from Study DREAMM-2. Within Study DREAMM-2, 11% of subjects (16% of observations from this study) received a lyophilized configuration of belantamab mafodotin. All other Study DREAMM-2 subjects and all BMA117159 subjects received a frozen liquid solution configuration.

Using the estimated slopes and intercepts (where applicable) from the linear regression analyses, the concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF required to result in a 10 msec prolongation in QTc and QTcF were derived. For all three analytes, the derived concentrations required to cause a 10 msec prolongation in QTc were higher than those observed for either starting dose level in Study DREAMM-2.

For both QTc and QTcF, for three analytes, both dose levels and both regression types, the upper 90% CI did not exceed 10 msec. There were no ΔQTc greater than 10 msec corresponding to assumed Cmax of belantamab mafodotin, total mAb, and cys-mcMMAF, based on regression with and without intercept. Consequently, there was a zero probability of the dose levels of belantamab mafodotin studied in Study DREAMM-2 (2.5 and 3.4 mg/kg) prolonging ΔQTc by more than 10 msec. There were no ΔQTcF greater than 10 msec corresponding to assumed Cmax of belantamab mafodotin and cys-mcMMAF, based on regression with and without intercept. For maximal concentrations of total mAb, there was less than a 0.25% chance of prolonging ΔQTcF by more than 10 msec from the dose levels of belantamab mafodotin studied in Study DREAMM-2.

Exposure-response analyses

The population PK models were used to generate individual *post hoc* exposure measures for ADC and cys-mcMMAF. The exposure estimates were simulated for the first dose using the actual dose administered to each subject with their specific demographic and individual eta estimates.

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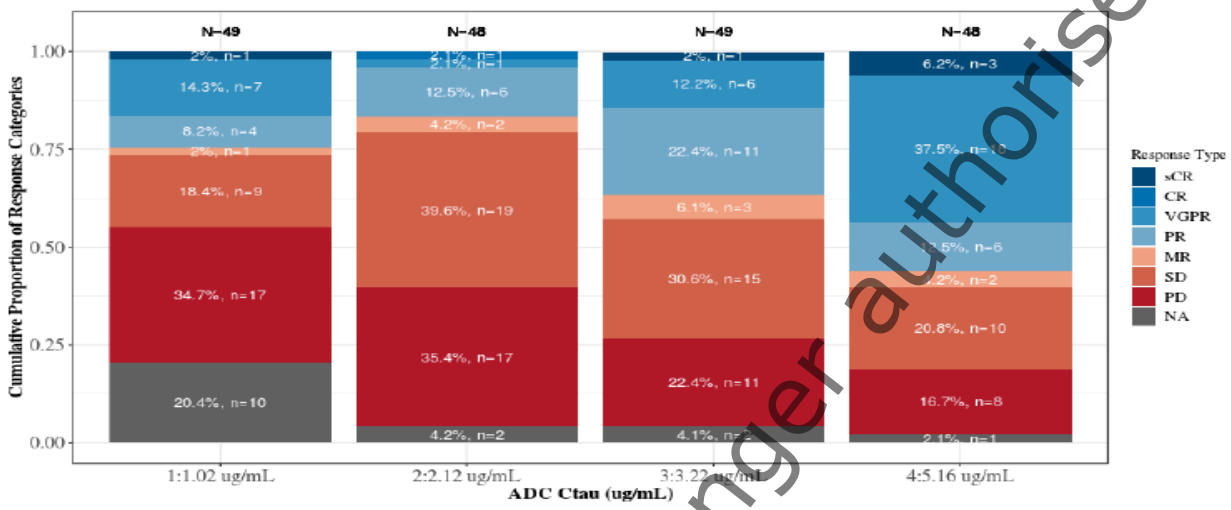
The ER analyses were focused on study DREAMM-2, in which doses 2.5 mg/kg and 3.4 mg/kg every three weeks (Q3W) were used. The figure below presents the best response category achieved for the 194 subjects who received the frozen liquid presentation by quartile of belantamab mafodotin trough concentration (C_{tau}).

Figure 3 Best Response by Cycle 1 belantamab mafodotin C_{tau} (Study DREAMM-2, Frozen Liquid formulation)



sCR = stringent complete response, CR = complete response, VGPR = very good partial response, PR = partial response, MR = minimal response, SD = stable disease, PD = progressive disease, NA =not applicable.

In univariate logistic regression analyses the probability of clinical response seemed to increase with increasing belantamab mafodotin exposure and no clear relationship between plasma concentration of cys-mcMMAF and probability of response was observed. However, the strongest univariate predictor of response was baseline soluble BCMA (sBCMA) level. In multivariate analysis, only baseline sBCMA was found to predict probability of response (***Table 20***).

Table 20 Probability of Response Logistic Regression Analysis Final Model (Study DREAMM-2 - Frozen Liquid Presentation)

Covariate	Beta (β)	SE	95% CI	dOFV	Delta	Odds Ratio (95% CI)
Intercept (β_0)	0.109	0.223	(-0.325,0.551)	NA	-	-
BSBCMA	-0.00608	0.00153	(-0.00937, -0.00335)	26.7	20	0.886 (0.829, 0.935)
Logistic Regression $Ln(p/(1-p)) = \beta_0 + \beta_{BSBCMA} \bullet BSBCMA$						
BSBCMA = baseline soluble BCMA SE = standard error; dOFV = drop in objective function relative previous model.						

In the ER analyses for safety, higher exposure to belantamab mafodotin and lower baseline sBCMA level were identified as predictors of any keratopathy event and grade 2+ keratopathy event in multivariate logistic regression analysis for study DREAMM-2. Belantamab mafodotin and cys-mcMMAF exposure measures were not found to predict blurred vision or dry eye events. In univariate logistic regression analysis for grade 3+ thrombocytopenia baseline platelet count was overall the strongest predictor and natural log of cys-mcMMAF C_{max} was the strongest exposure measure predictor. Both entered the multivariate model for probability of grade 3+ thrombocytopenia (***Table 21***).

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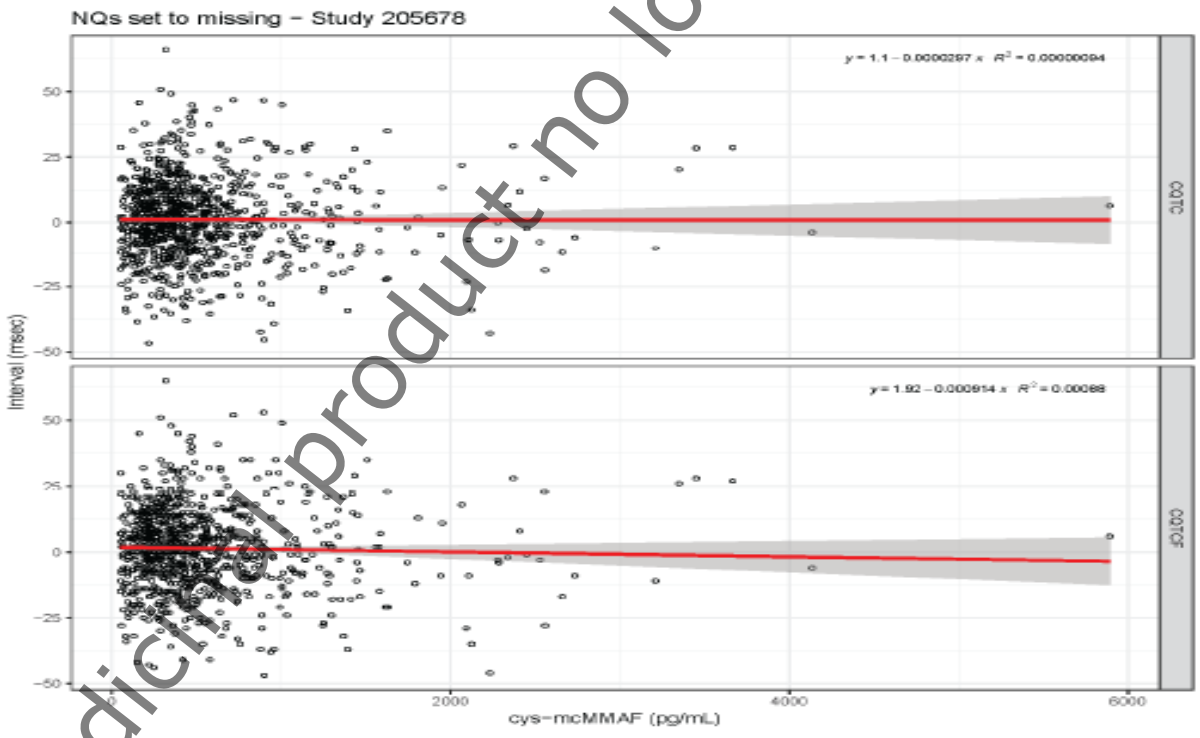
Table 21 Probability of Grade 3+ Thrombocytopenia Event - Regression Analysis Multivariate Results (Study DREAMM-2 - Frozen Liquid Presentation)

Covariate	Beta (β)	SE	95% CI	dOFV	Delta	Odds Ratio (95% CI)
Intercept (β_0)	-8.87	3.41	(-15.9, -2.43)	NA	--	--
BPLAT	-0.0221	0.00375	(-0.03, -0.0152)	59.9	25	0.575 (0.472, 0.683)
LNCMAXM	1.59	0.493	(0.67,2.62)	12.0	0.3	1.61 (1.22, 2.19)
Logistic Regression: $Ln(p/(1-p)) = \beta_0 + \beta_{BPLAT} \bullet BPLAT + \beta_{LNCMAXM} \bullet LNCMAXM$						
BPLAT = baseline platelet count, LNCMAXM = natural log of cys-mcMMAF maximum concentration, SE = standard error, CI = confidence interval, dOFV = drop in objective function relative to previous model with covariate added before it.						

The primary concentration-QTc analysis had time-matched electrocardiogram (ECG,12-lead, in triplicate) and concentration data in 217 subjects from study DREAMM-2.

Figure 4 presents the linear regression analysis of cys-mcMMAF concentration vs ΔQT (using correction factor 0.410 estimated using pre-dose QT and RR values) and ΔQTcF (using the Fredericia correction factor 0.33) for Study DREAMM-2 with both the slope and intercept parameters estimated. Fixing the intercept at 0 did not markedly change the estimated slope. Results were similar when belantamab mafodotin and total mAb concentrations were used as the exposure measure.

Figure 4 Linear Regression of cys-mcMMAF concentration vs ΔQT and ΔQTcF for Study DREAMM-2



2.4.4. Discussion on clinical pharmacology

Pharmacokinetic data for belantamab mafodotin are available from two clinical studies. Most subjects were treated with a frozen liquid formulation; only 24 subjects in study DREAMM-2 were treated with a lyophilized presentation at dose 3.4 mg/kg. The lyophilized presentation is intended for the market. Approximately 1 to 10% differences in average exposure (AUC and Cmax) were observed between the two formulations in noncompartmental analysis; between-subject variability was moderate to high.

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Population PK analysis was used to characterize the PK of the ADC, total mAb and cys-mcMMAF and identify covariates affecting the PK. Biomarkers associated with severe RRMM (high sBCMA and IgG and low albumin levels at baseline) predicted higher clearance of the ADC, which makes exposure-response analyses for efficacy more challenging. The PK model for ADC might be over-parameterised and empirical study effect covariates were implemented in the models. A substantial proportion of observed cys-mcMMAF concentrations were below the lower limit of quantitation (BLQ); an updated model incorporating the BLQ data using the so-called M3 method was requested during the assessment which was considered adequate.

Data following subtherapeutic and supratherapeutic doses is not robust enough to draw conclusion on dose proportionality over the entire investigated dose range (0.03 mg/kg to 4.6 mg/kg). However, it can be concluded that belantamab mafodotin exhibits dose-proportional pharmacokinetics over the recommended dose range with a reduction in clearance over time (SmPC section 5.2).

The estimated clearance and volume parameter values for belantamab mafodotin are in the expected range for an antibody-drug compound. Elimination rate of belantamab mafodotin decreases following repeated dosing, but dose adjustment due to this pharmacokinetic characteristic is not needed. There are sufficient safety data with proposed Q3W dosing. The observed duration of exposure to cys-mcMMAF following IV administration of belantamab mafodotin in clinical studies was long compared with exposure following IV administration of cys-mcMMAF in cynomolgus monkeys. Assuming that the PK in monkey can be extrapolated to human, rate of release of cys-mcMMAF into circulation appears to be slower than rate of elimination.

The protein moiety of the ADC, belantamab, is degraded to small peptides. Further characterisation on elimination of belantamab is not required. It is acknowledged that a mass balance study with radiolabelled cys-mcMMAF in rats was conducted demonstrating that approximately 83 % of the radioactive dose was excreted in faeces and 13 % in urine after an IV dose of 3H-cys-mcMMAF. In human only intact cys-mcMMAF was detected in pooled urine samples. The metabolism, elimination and excretion pathways of cys-mcMMAF in man remain partly unknown. *In vitro* studies indicated maleimide exchange of mcMMAF into human serum albumin. Hypoalbuminemia is however unlikely to have clinical impact through maleimide exchange in patients with multiple myeloma.

No formal studies have been conducted in patients with renal impairment. Renal function was not a significant covariate in population pharmacokinetic analyses that included patients with normal renal function and mild or moderate renal impairment (SmPC, section 5.2).

No dose adjustment is required in patients with mild or moderate renal impairment (eGFR ≥30 mL/min). There are insufficient data in patients with severe renal impairment to support a dose recommendation (SmPC, section 4.2).

No studies have been performed in patients with renal insufficiency, but a phase 1 open label study (209626) of belantamab mafodotin in relapsed/refractory MM patients with renal impairment has been planned to address this issue (see RMP).

No formal studies have been conducted in elderly patients. Age was not a significant covariate in population pharmacokinetic analyses (SmPC, section 5.2). No dose adjustment is required for elderly patients (SmPC, section 4.2).

No formal studies have been conducted in patients with hepatic impairment. Mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or aspartate transaminase [AST] greater than ULN), was not associated with exposure to belantamab mafodotin in the population PK analysis, but increased exposure to cys-mcMMAF was observed. Although data are limited, it is acknowledged that observed safety profiles for patients with hepatic impairment were similar when compared with patients with normal hepatic function. Dose adjustment is not proposed in patients with mild hepatic

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impairment. A phase 1 open label study (209627) in patients with relapsed/refractory MM and hepatic impairment is planned to investigate the effect of moderate or severe hepatic impairment on the pharmacokinetics and safety and tolerability of belantamab mafodotin (see RMP).

Hepatic function was not a significant covariate in population pharmacokinetic analyses that included patients with normal hepatic function or mild hepatic impairment (SmPC section 5.2).

No dosage adjustment is required in patients with mild hepatic impairment. There are insufficient data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment to support a dosage recommendation (SmPC section 4.2).

The proposed dose 2.5 mg/kg is based on body weight. Body weight was a significant covariate in population pharmacokinetic analyses. Belantamab mafodotin Ctau was predicted to be +10% at a body weight of 100 kg (+20% for 130 kg) and -10% at a body weight of 55 kg (-20% for 40 kg) compared to the typical patient (75 kg) (SmPC section 5.2). BLENREP has not been studied in patients with body weight < 40 kg or > 130 kg (SmPC, section 4.2). The CHMP recommended the applicant to explore alternative dosing strategies for patients with body weight > 130 kg to achieve similar exposure as in patients with body weight within 40-130 kg.

Dose adjustment based on age, gender or race is not required.

Based on the *in vitro* studies, in was concluded that interactions between belantamab mafodotin and other drugs are unlikely, so specific interactions studies were not performed. Combined non-clinical and clinical data indicated that release of cys-mcMMAF from the antibody-drug compound is probably the rate-limiting step that determines its concentration in plasma and inhibition of these transporters is not expected to clinically significantly increase the systemic exposure to cys-mcMMAF.

Based on available *in vitro* and clinical data, there is a low risk of pharmacokinetic or pharmacodynamic drug interactions for belantamab mafodotin (SmPC section 4.4).

The exposure parameter values used in the exposure-response analyses were the predicted exposure following the first dose (cycle 1), whereas the response parameters were efficacy and safety observed over multiple treatment cycles. It was not taken into account that a large proportion of patients had dose reduction and/or dose delay. For example, in study DREAMM-2, 29% and 42% of participants had at least 1 dose reduction, and 39% and 48% of participants had 1 or more dose delays among subjects randomized to 2.5 mg/kg and 3.4 mg/kg dose groups, respectively. Results of the ER analyses should therefore be interpreted very cautiously. The effects of baseline characteristics associated with disease severity (sBCMA, IgG, and albumin levels) on the pharmacokinetics of belantamab mafodotin and its time-varying kinetics (reduced clearance over time) also hinder making definite conclusions on relationships between exposure and efficacy. Overall, results of the ER analyses for efficacy did not indicate markedly better clinical response for doses higher than the one proposed. Lack of association between cys-mcMMAF exposure metrics and efficacy endpoints was presumed to be partly due to poor membrane permeability of free cys-mcMMAF.

Higher exposure to belantamab mafodotin was associated with all grade keratopathy and grade 2+ keratopathy events. Exposure to belantamab mafodotin or cys-mcMMAF did not seem to predict blurred vision or dry eye events. Higher exposure to cys-mcMMAF predicted grade 3+ thrombocytopenia events. Baseline platelet count was the most significant predictor of thrombocytopenia, however. No exposure parameters predicted grade 3+ neutropenia or infusion-related reactions. Dose adjustment based on corneal adverse reactions and thrombocytopenia are included in section 4.2 of the SmPC.

Results of the concentration-QTc analysis do not indicate significant potential for prolongation of QTc interval. The analysis had data from patients treated with 3.4 mg/kg dose (*i.e.*, 36% higher than the

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proposed dose). It is also acknowledged that *in vitro*, cys-mcMMAF had no detectable effect on hERG channels. Based on the available data, further investigation on the potential of belantamab mafodotin to prolong the QTc interval is not required.

2.4.5. Conclusions on clinical pharmacology

The PK and PD of belantamab mafodotin have been reasonably well investigated.

2.5. Clinical efficacy

2.5.1. Dose response study

Study BMA117159 (DREAMM-1)

This was an open-label, dose-escalation trial consisted of the following 2 parts: Part 1 dose escalation phase and Part 2 expansion phase for safety confirmation, and clinical activity testing. Subjects were scheduled to be administered belantamab mafodotin via 60 min IV infusion on either once every 3 weeks (21-day cycle) or once weekly schedule.

Table 22 Design of Study belantamab mafodotin

Part 1 Dose Escalation (n=up to 30 subjects) **Population: relapsed/refractory MM** Characterize safety, PK, PD, immunogenicity and establish RP2 dose of GSK2857916 Schedule 1: GSK2587916 once every 3 weeks (21-day cycle) (n=~20) Schedule 2: GSK2587916 once weekly for 3 consecutive weeks, 1-week rest (28-day cycle) (n=~9) Serial PK samples will be collected from all subjects in Part 1
Part 2 Expansion Cohort(s) (n=~50 subjects) **Population:** **1) Subjects with relapsed/refractory MM (up to 40 subjects)** **2) Subjects with lymphomas expressing BCMA (up to 10 subjects)** Cohort Expansion groups: Further evaluate the safety, PK, immunogenicity, and activity of GSK2857916 at the RP2 dose identified in Part 1 A futility analysis based on ORR data will be performed after approximately 15, 22 and 30 subjects have been evaluated for response in MM cohort Both Expansion groups will be analyzed separately Sparse PK samples will be collected from all subjects Genetics research samples will be collected predose from all subjects

BMA117159 Part 1 explored the administration of belantamab mafodotin to humans with RRMM at doses ranging from 0.03 to 4.6 mg/kg. Ocular events and thrombocytopenic events were the most frequent toxicities in Part 1 and these events were the most common reasons for dose modifications. Due to emerging corneal events in the expansion cohort at 3.40 mg/kg, an intermediate dose of 2.50 mg/kg was subsequently added to Part 1.

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No protocol-defined dose-limiting toxicities were observed in Part 1, even at the highest dose tested (4.60 mg/kg), and thus no MTD was established. However, 2 subjects in the 4.6 mg/kg cohort discontinued treatment due to AEs, indicating poor tolerability of this dose.

A dose of 3.40 mg/kg every 3 weeks was identified as the RP2D based on the totality of safety and tolerability data. While the next tested dose of 4.6mg/kg did not result in adverse events fulfilling dose limiting toxicity (DLT) definition, it was felt to be poorly tolerated. In addition, the estimated receptor saturation was at 90% for doses ≥1.92 mg/kg in Part 1. Moreover, clinical activity became apparent at 3.4 mg/kg dose where all 3/3 patients enrolled at this dose level achieved a response. Weekly dosing based on 28 days cycle was not pursued in this study.

In summary there was 1 response out of 8 in the 2.5 mg/kg group and 3/3 responses in the 3.4 mg/kg group. No responses were observed across the lowest doses from 0.03 to 0.48 mg/kg.

The main results of BMA117159 Part 2 (N=35) are as follows:

- The ORR based on confirmed investigator-assessed response was 60% (95% CI:42.1, 76.1), including 54% Very Good Partial Response (VGPR) or better;
- The median time-to-response was rapid at 1.2 months (95% CI: 0.7, 1.4);
- The median duration of response was 14.3 months (95% CI: 10.6, NE);
- Median PFS was 12.0 months (95% CI: 3.1, NE).

Responses were observed in all analysed subgroups.

The DLT was investigated in the Part 1 of the study. No dose-limiting toxicities were observed at any dose level, including the maximum administered dose (4.6 mg/kg). Thus, the maximum tolerated (MTD) was not established.

However, different AEs leading to dose reduction started to occur at doses ≥0.96 mg/kg. There were several AEs related to ocular events, which are uncommon with other current MM treatments options (proteasome inhibitors, immunomodulating agents), leading to dose reductions, dose delays and even permanent discontinuation of study treatment without clear link to the dose (one limbal stem cell deficiency at 1.92 mg/kg dose, one grade 2 keratopathy at 2.5 mg/kg dose). While there seem to be trend with increasing haematological AEs with increasing dose, the trend with ocular events with increasing doses (1.92 to 4.6 mg/kg) is not so clear.

In the part 2 of the study 35 subjects with RRMM received at least one 3.4 mg/kg dose. 43% (15/35) were previously treated with mAb, specifically, 14 subjects had daratumumab.

The median dose intensity reached was 2.89 mg/kg/cycle. Majority of patients experienced dose reductions and dose delays. Similarly, to part 1, many AEs leading to dose intensity less than targeted 3.4 mg/kg/cycle were related to ocular events. The ORR for part 2 was 60% with 54% of patients achieving VGPR or better.

2.5.2. Main study

Study 205678 (DREAMM-2)

Methods

This was a Phase II, open label, randomized, two-arm study to investigate the efficacy and safety of two doses of the belantamab mafodotin in participants with MM who had 3 or more prior lines of

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treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody.

The study included an additional independent cohort of approximately 25 additional participants who received a lyophilized presentation of belantamab mafodotin at 3.4 mg/kg. An ocular sub-study was also included to evaluate the effectiveness of steroid eye drops in up to 30 participants.

Study Participants

The key inclusion criteria were the following:

1. Male or female, 18 years or older (at the time consent was obtained)

2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

3. Histologically or cytologically confirmed diagnosis of MM as defined according to International Myeloma Working Group (IMWG), (Rajkumar, 2015) criteria, AND

a) Had undergone stem cell transplant or was considered transplant ineligible,

AND

b) Had failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and was refractory to an immunomodulatory agent (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib). The number of prior lines of therapy was determined according to the guidelines in Rajkumar, 2014.

Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy.

Nonresponsive disease was defined as either failure to achieve at least minimal response or development of disease progression (PD) while on therapy (Rajkumar, 2011b)

4. Has measurable disease with at least one of the following:

- Serum M-protein ≥0.5 g/dL (≥5 g/L),
- Urine M-protein ≥200 mg/24h,
- Serum Free Light Chain (FLC) assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65).

5. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:

- transplant was >100 days prior to study enrolment,
- no active infection(s),
- participant meets the remainder of the eligibility criteria outlined in this protocol.

6. Adequate organ system functions.

7. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, must be ≤Grade 1 at the time of enrolment except for alopecia and Grade 2 peripheral neuropathy.

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The key exclusion criteria were the following:

1. Systemic anti-myeloma therapy within <14 days, or plasmapheresis within 7 days prior to the first dose of study drug.
2. Symptomatic amyloidosis, active polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes (POEMS) syndrome, active plasma cell leukemia at the time of screening.
3. Prior allogeneic stem cell transplant.
4. Current corneal epithelial disease except mild punctate keratopathy.
5. Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a mAb within 30 days of receiving the first dose of study drugs. Prior BCMA targeted therapy.
6. Evidence of active mucosal or internal bleeding.
7. Any major surgery within the last four weeks.
8. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety).
9. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
10. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.
11. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy.
12. Evidence of cardiovascular risk including any of the following:
    a. QTcF interval ≥470 msecs (the QT interval values must be corrected for heart rate by Fredericia's formula [QTcF]),
    b. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Type II) or 3rd degree atrioventricular (AV) block,
    c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening,
    d. Class III or IV heart failure as defined by the New York Heart Association functional classification system [NYHA, 1994],
    e. Uncontrolled hypertension.
13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916, or any of the components of the study treatment.

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14. Pregnant or lactating female.
15. Active infection requiring antibiotic, antiviral, or antifungal treatment.
16. Known HIV infection.
17. Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb at screening or within 3 months prior to first dose of study treatment.
18. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

Treatments

Belantamab mafodotin was administered at a calculated dose of 2.5 mg/kg or 3.4 mg/kg as an IV infusion on day 1 of each cycle; each cycle was 21 days.

The lyophilized cohort (3.4 mg/kg) was initiated when enrolment had completed in the 2 arms receiving frozen solution and the lyophilized presentation became available.

Patients were treated until disease progression, until unacceptable toxicity, or until confirmed CR.

Objectives

Primary Objective

- To evaluate the clinical efficacy of two doses of belantamab mafodotin in participants with RRMM.

Secondary Objectives

Key Secondary:

- To further evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM.
- To evaluate the safety of belantamab mafodotin in participants with RRMM.
- To evaluate the pharmacokinetic profile of belantamab mafodotin.

Other Secondary:

- To assess ADAs against belantamab mafodotin.
- Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin.
- To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life.
- To assess the safety, efficacy, immunogenicity, and pharmacokinetics of belantamab mafodotin in a lyophilized presentation (n=25).

Ocular sub-study:

- To evaluate the effect of topical corticosteroids on corneal findings in up to 30 participants who will receive monocular topical corticosteroids for the first 4 cycles.

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Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint of the study was overall response rate (ORR), defined as sCR+CR+VGPR+PR, according to 2016 International Myeloma Working Group (IMWG) Response Criteria (Table 29) and as assessed by Independent Review Committee (IRC) based on intention to treat (ITT) population.

Key Secondary Efficacy Endpoints

Duration of Response (DoR) was defined as the time from first documented evidence of PR or better until the earliest date of disease progression (PD) per IMWG, or death due to PD among participants who achieve a response (i.e., confirmed PR or better). Responders without disease progression will be censored at the censoring time point for time to progression (TTP).

Time to response (TTR) was defined as the time between the date of first dose and the first documented evidence of response (PR or better), among subjects who achieve a response (i.e., confirmed PR or better).

Progression free survival (PFS) was defined as the time from first dose until the earliest date of PD per IMWG, or death due to any cause.

Overall Survival (OS) was defined as the time from first dose until death due to any cause.

Other Secondary Efficacy Endpoints

Exploratory minimal residual disease (MRD) negative rate is defined as the proportion of subjects who are negative for MRD at any time point after first dose as determined by the protocol defined testing procedure.

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Table 23 International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (2016)

Response	Standard IMWG Criteria[1]
sCR[2]	• CR as defined below plus normal FLC ratio and absence of clonal plasma cells in bone marrow by immunohistochemistry or 8-color, 2 tube multiparametric flow cytometry
CR[3]	• negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates[3]
VGPR[3]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M-protein plus urine M-component level <100 mg/24 h
PR	• ≥50% reduction of serum M-protein plus reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h • If the serum and urine M-protein are not measurable, a decrease ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in plasma cells is required in place of M-protein criteria, provided baseline bone marrow plasma cell percentage was ≥30%. • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas[4] is also required.
MR	• ≥25% but ≤49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89% • In addition to the above criteria, if present at baseline, 50% reduction in the size of soft tissue plasmacytomas[4] is also required. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
SD	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for CR, VGPR, PR, MR or PD
PD[2]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in 1 or more of the following: • Serum M-protein(absolute increase must be ≥0.5g/dL, ; • Serum M-protein i increase ≥1g/dL, if the lowest M-component was ≥5g/dL; • Urine M-protein (absolute increase must be ≥200 mg/24 h; • In participants without measurable serum and urine M-protein levels, the difference; between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL; • In participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell absolute percentage of baseline status (absolute increase must be ≥10%). • Appearance of new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in longest diameter of a previous lesion >1 cm in short axis. • ≥50% increase in circulating plasma cells (minimum 200 cells per µL) if this is the only measure of disease.

CBR = clinical benefit rate; CR = complete response; FLC = free light chain; IMWG = International Myeloma WorkingGroup; MR = minimal response; ORR = overall response rate; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD=sum of the products of the maximal perpendiculardiameters of measured lesions; VGPR = very good partial response.

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Sample size

The following assumptions were made in the estimation of the required sample size:

Normal approximation of binomial proportion; a response rate of ≥33% in the BCMA arm and ≤15% for the historical control; a 1.25%, 1-sided risk of erroneously claiming superiority of the BCMA arm, in the presence of no true underlying improvement; a ~90% chance of rejecting the null hypothesis when the alternative hypothesis is true.

An interim analysis was conducted after approximately 38% of information was available (i.e., approximately after 25 participants out of the originally planned 65 participants per arm were evaluable for interim analysis), with a futility rule based on a gamma spending function.

The operating characteristics were refined using simulation to account for both within arm futility rule and the comparative futility rule. Based on the simulation results with the planned sample size of 65 participants, there was 86.90% power to reject the null hypothesis within each arm with a 1-sided type I error of 1.23%.

Due to over-enrolment (addressed in Protocol amendment 3), it was estimated that approximately 200 participants (approximately 100 per arm) would be randomized to the frozen liquid solution. At the primary analysis, the null hypothesis would be rejected if the lower bound of 2-sided 97.5% exact CI exceeded the historical control rate of 15%.

With no change to the planned IA (i.e., approximately after 25 participants/arm were evaluable for IA, and same futility boundary), simulation results showed that there was 92.38% power to reject the null hypothesis within each arm with a 1-sided type I error of 0.97% for 100 participants per arm.

Randomisation

Eligible participants in the main study (frozen liquid) were assigned in a 1:1 ratio to receive treatment with either 3.4 mg/kg IV Q3W or 2.5 mg/kg IV Q3W belantamab mafodotin in accordance with the randomization schedule. The following information for stratification was entered into the system to obtain the treatment assignment:

- Number of prior lines of therapy (≤4 vs >4)
- Cytogenetic risk categories (high risk defined as t(4;14), t(14;16), and 17p13del vs non-high risk - all others);

The lyophilized cohort (3.4 mg/kg) was initiated when enrolment had completed in the 2 arms receiving frozen solution and the lyophilized presentation became available.

Blinding (masking)

This was an open-label study.

Statistical methods

Interim analyses were introduced with the first protocol amendment. For each arm (2.5 mg/kg or 3.4 mg/kg), a single futility interim analysis was planned for the primary endpoint ORR after

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approximately 25 participants out of originally planned 65 participants per arm were evaluable. A user-defined gamma spending function (γ=4.2) was planned to be used as a beta-spending function to determine the non-binding futility boundary. With this β-spending function, the stopping boundary in IA was identified as 0.16 on the proportion scale (4 responders out of 25 participants), which is close to the historical control of 0.15. The spending function and associated boundary were chosen to ensure good operating characteristics, specifically, the type 1 error and power.

Trial was designed to provide evidence with respect to ORR to either support the null hypothesis, H0: ORR ≤15%, or reject H0 in favour of the alternative hypothesis, H1: ORR >15%. The hypothesis testing was performed within each dose separately. No hypothesis testing for comparing ORR between the two doses was performed. To control the overall type I error at 5%, alpha was split between two dose cohorts and a dose cohort would be considered statistically superior to the historical control of 15% if the lower bound of 97.5% confidence interval (CI) for ORR is greater than 15%. The historical control comparator of 15% was selected based on the previously reported response rates of 10% to 18% in patients at 4th relapse [i.e., having relapsed after 3 prior lines of therapy].

The following key analysis population were defined:

• The enrolled population included all participants who passed screening and entered the study.

• The ITT population included all participants who were randomly assigned to frozen liquid treatment, whether or not treatment was administered.

• The lyophilized population (Lyo) included all randomized participants who received at least 1 dose of lyophilized study treatment.

• The full analysis population included all randomized participants included in either the ITT or Lyo population.

• The efficacy population consisted of the first 130 ITT participants.

• The evaluable population included all participants who had at least 2 doses of frozen liquid study treatment and completed at least 1 disease assessment after the second dose, progressed, died, or discontinued treatment due to other reasons.

• The safety population included all randomized participants who received at least 1 dose of frozen liquid study treatment and the full safety population included all participants who received at least 1 dose of study treatment (frozen liquid or lyophilized).

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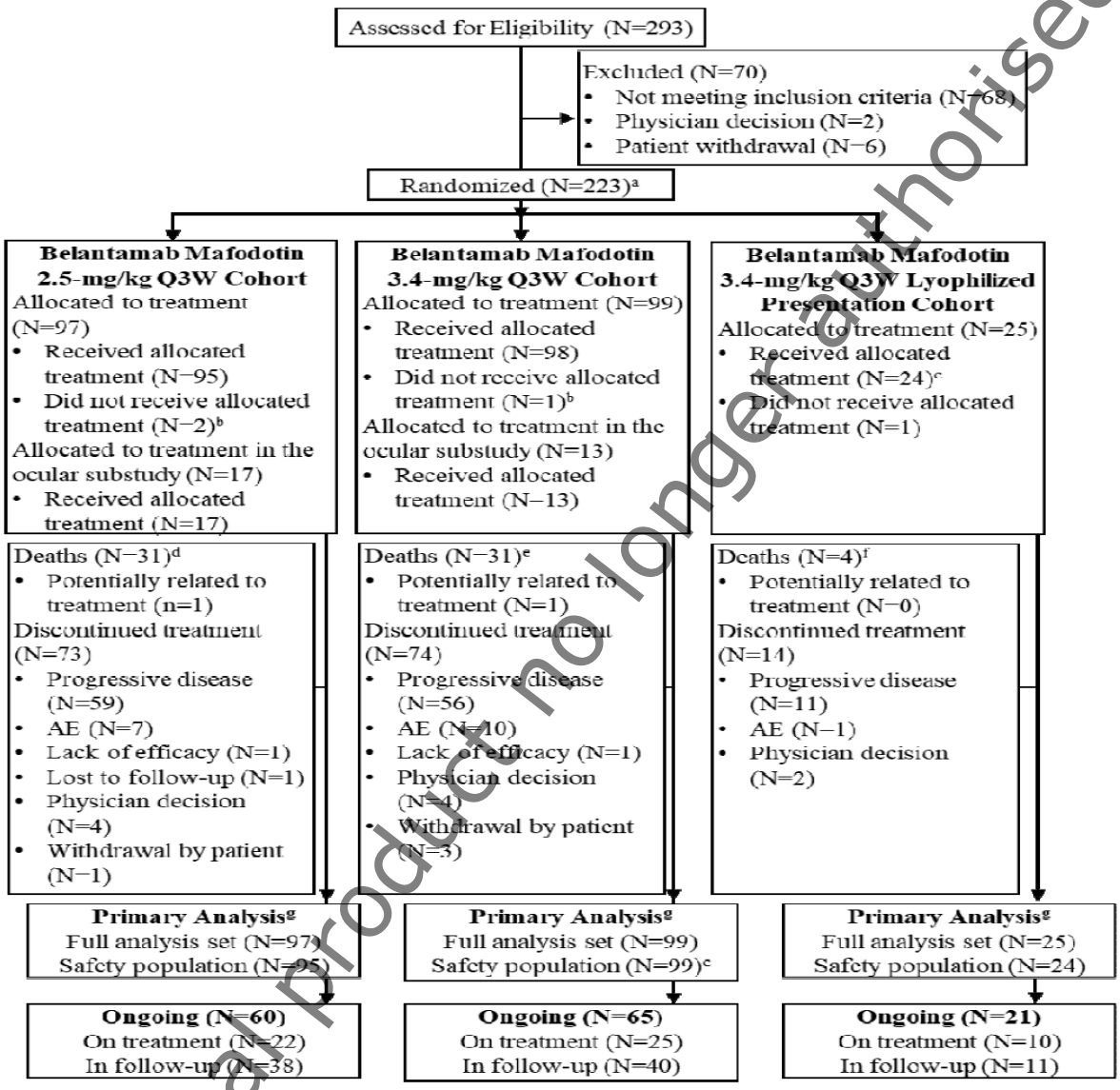
Results

Participant flow

Figure 5 Study Participant flow (Study DREAMM-2)



Recruitment

Patients with RRMM were recruited from 58 centres in 8 countries (Australia, Canada, France, Germany, Italy, Spain, the United Kingdom and the United States).

Study initiation date: first subject was screened on 18 June 2018 and last 2 January 2019.

Conduct of the study

Summary of main protocol amendments

There were 3 amendments to the study protocol. The main changes are described below:

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- Amendment 1 (2 April 2018):

The protocol was amended to address regulatory agency advice. The original single-arm design with 1 dose level (3.4 mg/kg GSK2857916 Q3W) was amended to an open-label, randomized, 2-arm study with 2 dose levels by including the 2.5 mg/kg Q3W dose. In addition, a new exploratory cohort of 25 participants, who will receive a lyophilized configuration of GSK2857916, has been added to gain clinical experience with the lyophilized configuration. To accommodate these main changes, the overall sample size and related analytical methods have been changed.

- Amendment 2 (4 September 2018):

The protocol was amended to address feedback from regulatory agencies, EC/IRB, and investigators. The updates include the addition of exclusion criteria defining the use of high dose steroids, clarification of specific timeframe from last treatment required for systemic anti-myeloma therapy and increase of QTcF criteria. Additional PK sampling timepoints were added to capture the Cmax of the free cytotoxic drug (cys-mcMMAF) and to better define the kinetics of cys-mcMMAF and the elimination phase of ADC and cys-mcMMAF. Soluble BCMA collection timepoints were also added to capture the effect of GSK2857916 administration on soluble BCMA concentrations over time as a marker of pharmacodynamic effect. The dose modifications guidelines for GSK2857916 related Corneal Events clarify dose adjustments for GSK Scale Grade 2 events.

- Amendment 3 (17 December 2018):

The protocol was to address over-enrollment in the frozen liquid solution portion of the study. Due to the over-enrollment, the primary analysis was to be based on all randomized participants (anticipated ~200) enrolled into the frozen liquid solution arms. In addition, a sensitivity analysis based on the first 130 participants was performed to account for the original design.

Protocol Deviations

There were inclusion or exclusion criteria deviations for 6% and 5% of participants who were inadvertently enrolled in the study.

- 5 participants were HBcAb-positive and were recommended to have prophylactic antiviral therapy after stopping study treatment and to be followed for HBV increases or reactivation.
- 2 participants had organ system deviations: 1 participant had a spot urine of <500 mg/g at screening but was >500 mg/g at Cycle 1 Day, and the other participant did not have spot urine or absolute neutrophil count assessments performed at Screening. An absolute neutrophil count was done at Cycle 1 Day 1 prior to dosing.
- 1 participant had measurable disease based on local laboratory, but this result was not confirmed by the central laboratory results.
- 1 participant was enrolled with moderate punctate keratopathy.

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Baseline data

Table 24 Demographic Characteristics (ITT Population, Study DREAMM-2)

	GSK2857916		
	2.5 mg/kg (N=97)	**3.4 mg/kg (N=99)**	**Total (N=196)**
Sex, n (%)	97	99	196
Female	46 (47)	43 (43)	89 (45)
Male	51 (53)	56 (57)	107 (55)
Age (years), n	97	99	196
Mean (SD)	64.1 (10.01)	66.0 (9.09)	65.1 (9.58)
Median (range)	65.0 (39 to 85)	67.0 (34 to 84)	66.0 (34 to 85)
Age Group (years), n (%)	97	99	196
<18	0	0	0
18 to <65	45 (46)	36 (36)	81 (41)
65 to <75	39 (40)	46 (46)	85 (43)
≥75	13 (13)	17 (17)	30 (15)
Race Detail, n (%)	95	99	194
Black or African American	16 (16)	11 (11)	27 (14)
Asian - Central/South Asian Heritage	1 (1)	0	1 (<1)
Asian - East Asian Heritage	1 (1)	0	1 (<1)
Asian - South East Asian Heritage	0	1 (1)	1 (<1)
White - Arabic/North African Heritage	4 (4)	2 (2)	6 (3)
White - White/Caucasian/European Heritage	72 (74)	83 (84)	155 (79)
Mixed Asian Race	0	1 (1)	1 (<1)
Mixed White Race	0	1 (1)	1 (<1)
Multiple	1 (1)	0	1 (<1)
Weight (kg), n	97	99	196
Mean (SD)	78.37 (21.758)	73.90 (14.228)	76.11 (18.435)
Median	75.00	71.80	72.75
(range)	(42.4 to 171.0)	(49.0 to 124.2)	(42.4 to 171.0)

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Table 25 Baseline Disease Characteristics (ITT Population Study DREAMM-2)

	GSK2857916		
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)	Total (N=196)
Stage at screening, n (%)			
I	21 (22)	18 (18)	39 (20)
II	33 (34)	51 (52)	84 (43)
III	42 (43)	30 (30)	72 (37)
Unknown	1 (1)[a]	0	1 (<1)
Type of multiple myeloma, n (%)			
Nonsecretory	0	0	0
Secretory	97 (100)	99 (100)	196 (100)
Myeloma light chain, n (%)			
Kappa Light Chain	54 (56)	64 (65)	118 (60)
Lambda Light Chain	36 (37)	29 (29)	65 (33)
Missing	7 (7)	6 (6)	13 (7)
Myeloma immunoglobulin, n (%)			
IgA	22 (23)	16 (16)	38 (19)
IgG	65 (67)	73 (74)	138 (70)
IgM	2 (2)	0	2 (1)
IgD	0	1 (1)	1 (<1)
IgE	0	0	0
Missing	8 (8)	9 (9)	17 (9)
Extramedullary Disease, n (%)			
Yes	22 (23)	18 (18)	40 (20)
No	75 (77)	81 (82)	156 (80)
Lytic Bone Lesions, n (%)			
Yes	69 (71)	75 (76)	144 (73)
No	28 (29)	24 (24)	52 (27)
Lines of therapy completed at screening, n (%)			
3 Lines	5 (5)	8 (8)	13 (7)
4 Lines	11 (11)	9 (9)	20 (10)
5 Lines	17 (18)	14 (14)	31 (16)
6 Lines	14 (14)	21 (21)	35 (18)
7 Lines	19 (20)	17 (17)	36 (18)
8 Lines	14 (14)	11 (11)	25 (13)
9 Lines	6 (6)	5 (5)	11 (6)
10 Lines	5 (5)	5 (5)	10 (5)
More Than 10 Lines	6 (6)	9 (9)	15 (8)
High Risk Cytogenetics[b] n (%)			
Yes	26 (27)	32 (32)	58 (30)
Other (non-high risk, not done, or missing)	71 (73)	67 (68)	138 (70)

Prior anti-cancer medications are presented in ***Table 26***.

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Table 26 Prior Anti-Cancer Medications by Drug Class of Agents (ITT Population, Study DREAMM-2) (cut-off date of 20 September 2019)

Drug Class	Number (%) of Participants	
	Belantamab Mafodotin Q3W	
	9-Month FU (20Sep19)	
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
Steroids	97 (100)	99 (100)
Immunomodulator	97 (100)	99 (100)
Lenalidomide	97 (100)	99 (100)
Pomalidomide	89 (92)	84 (85)
Thalidomide	29 (30)	39 (39)
Proteasome Inhibitor	97 (100)	99 (100)
Bortezomib	95 (98)	97 (98)
Carfilzomib	74 (76)	64 (65)
Ixazomib	22 (23)	23 (23)
Monoclonal Antibody	97 (100)	99 (100)
Daratumumab	97 (100)	96 (97)
Elotuzumab	15 (15)	13 (13)
Durvalumab	4 (4)	5 (5)
Isatuximab	3 (3)	2 (2)
Pembrolizumab	2 (2)	1 (1)
Investigational antineoplastic agents	1 (1)	1 (1)
Blinatumomab	1 (1)	0
MOR03087	0	1 (1)
Chemotherapy	92 (95)	95 (96)
Stem cell transplant	73 (75)	86 (87)
Other	32 (33)	31 (31)
HDAC inhibitor	11 (11)	9 (9)

Note: Multiple categories per participant was possible, therefore the total may add up to more than 100%.

The refractoriness status of the patients to prior anti-cancer therapies are presented in ***Table 27***.

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Table 27 Participants Refractory to Prior Anti-Cancer Therapy (ITT Population, Study DREAMM-2) (cut-off date of 20 September 2019)

Drug Class	Number (%) of Participants	
	Belantamab Mafodotin Q3W	
	9-Month FU (20Sep19)	
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
Immunomodulator	97 (100)	99 (100)
Lenalidomide	87 (90)	90 (91)
Pomalidomide	86 (89)	79 (80)
Thalidomide	13 (13)	18 (18)
Proteasome Inhibitor	97 (100)	99 (100)
Bortezomib	76 (78)	74 (75)
Carfilzomib	63 (65)	57 (58)
Ixazomib	21 (22)	21 (21)
Monoclonal Antibody	97 (100)	99 (100)
Daratumumab	97 (100)	95 (96)
Elotuzumab	13 (13)	10 (10)
Durvalumab	4 (4)	4 (4)
Isatuximab	3 (3)	2 (2)
Pembrolizumab	2 (2)	1 (1)
Investigational antineoplastic agents	1 (1)	1 (1)
Blinatumomab	1 (1)	0
MOR03087	0	1 (1)
Steroids	95 (98)	92 (93)
Chemotherapy	66 (68)	70 (71)
Stem cell transplant	27 (28)	25 (25)
Other	11 (11)	13 (13)
HDAC inhibitor	11 (11)	8 (8)

Note: Multiple categories per participant was possible, therefore the total may add up to more than 100%.

Numbers analysed

Table 28 Analysis Populations (Study DREAMM-2)

Population, n (%)	GSK2857916	
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
Enrolled	97 (100)	99 (100)
Intent-to-Treat	97 (100)	99 (100)
Efficacy	64 (66)	66 (67)
Safety	95 (98)	98 (99)
Ocular Sub-Study	17 (18)	13 (13)
Full Analysis	97 (100)	99 (100)
Full Safety[a]	95 (98)	98 (99)
Full Pharmacokinetic[a]	95 (98)	98 (99)

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Outcomes and estimation

- *Primary endpoint - Overall Response Rate (ORR)*

Table 29 Best confirmed response based on independent review committee and investigator assessments (ITT Population, Study DREAMM-2) (cut-off date 21 June 2019)

	Belantamab Mafodotin Q3W			
	2.5 mg/kg (N=97)		3.4 mg/kg (N=99)	
	IRC	INV	IRC	INV
Best Response, n (%)				
Stringent complete response (sCR)	2 (2)	2 (2)	3 (3)	1 (1)
Complete response (CR)	1 (1)	6 (6)	0	2 (2)
Very good partial response (VGPR)	15 (15)	12 (12)	17 (17)	18 (18)
Partial response (PR)	12 (12)	9 (9)	14 (14)	10 (10)
Minimal response (MR)	3 (3)	4 (4)	5 (5)	6 (6)
Stable disease (SD)	30 (31)	30 (31)	23 (23)	25 (25)
Progressive disease (PD)	27 (28)	28 (29)	26 (26)	27 (27)
Not evaluable (NE) [a]	7 (7)	6 (6)	11 (11)	10 (10)
Overall Response Rate, n (%)				
sCR+CR+VGPR+PR	30 (31)	29 (30)	34 (34)	31 (31)
97.5% confidence interval	(20.8, 42.6)	(19.9, 41.5)	(23.9, 46.0)	(21.2,42.8)
Clinical Benefit Rate, n (%)				
sCR+CR+VGPR+PR+MR	33 (34)	33 (34)	39 (39)	37 (37)
97.5% confidence interval	(23.5, 45.8)	(23.5, 45.8)	(28.5, 51.1)	(26.6,49.1)

IRC: Independent Review Committee; INV: Investigator

a. NE could be due to response not confirmed or inadequate baseline assessment/no post-baseline assessment.

As of the 9-month FU data (cut-off date of 31 January 2020), the ORR was 32% in the 2.5 mg/kg dose cohort (31/97; 97.5% CI: 21.7, 43.6%). There was a further deepening of response, with 58% of responders achieving VGPR or better, including 2 sCRs and 5 CRs. The median time to best response was consistent with the primary analysis at 2.2 months (95% CI: 1.5, 3.6).

Table 30 Best confirmed response (ITT Population, Study DREAMM-2) (cut-off date of 31 January 2020)

	2.5 mg/kg (N = 97)	3.4 mg/kg (N=99)
Overall response rate (ORR), % (97.5% CI)	32% (22%, 44%)	35% (25%, 47%)
Stringent complete response (sCR), n (%)	2 (2%)	2 (2%)
Complete response (CR), n (%)	5 (5%)	3 (3%)
Very good partial response (VGPR), n (%)	11(11%)	18(18%)
Partial response (PR), n (%)	13 (13%)	12 (12%)
Median duration of response in months (95% CI)	11 [4.2 to Not reached]	6.2 [4.8 to Not reached]
Probability of Maintaining Response at 12 Months (95% CI)	0.50 (0.29, 0.68)	0.42 (0.25, 0.59)
Median time to response in months (95% CI)	1.5 (1.0, 2.1)	1.4 (0.9, 2.1)
Median time to best response in months (95% CI)	2.2 (1.5, 3.6)	3.5 (2.8, 4.3)

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- *Secondary efficacy endpoint- Duration of response*

Table 31 DOR Based on IRC assessment (ITT Population, Study DREAMM-2) (cut-off date 31 January 2020)

	Belantamab Mafodotin Q3W	
	2.5 mg/kg (n=97)	**3.4 mg/kg (n=99)**
Number of participants, n (%)	31	35
Progressed or died due to PD (event)	15 (48)	19 (54)
Censored, follow-up ended	5 (16)	5 (14)
Censored, follow-up ongoing	11 (35)	11 (31)
Event summary		
Death due to PD	0	0
Disease progression	15 (48)	19 (54)
Estimates for DoR (months)		
1st quartile	4.2	4.2
95% CI	(1.4, 10.3)	(2.8, 5.6)
Median	11.0	6.2
95% CI	(4.2, -)	(4.8, -)
Probability of maintaining response		
Time-to-event endpoint at 4 months	0.80	0.86
95% CI	(0.60, 0.90)	(0.69, 0.94)
Time-to-event endpoint at 6 months	0.68	0.56
95% CI	(0.48, 0.82)	(0.38, 0.71)
Time-to-event endpoint at 12 months	0.50	0.42
95% CI	(0.29, 0.68)	(0.25, 0.59)

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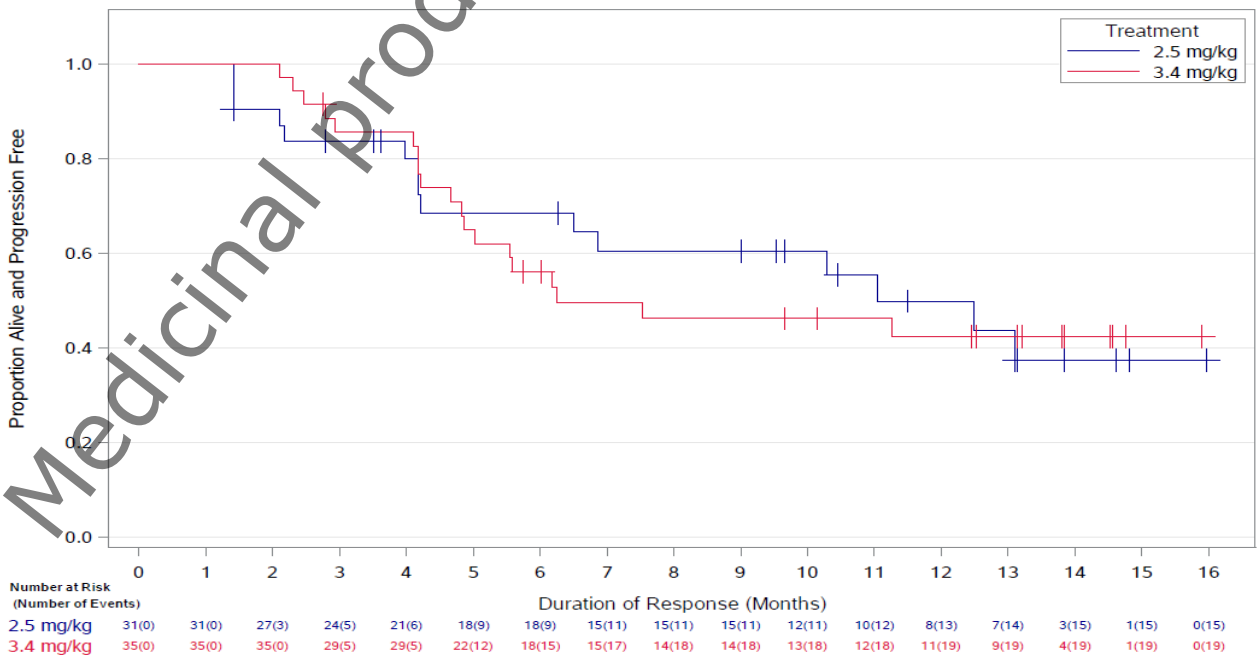
Figure 6 K-M Analysis of IRC-assessed DoR (Study DREAMM-2, 2.5 mg/kg Cohort) (cut-off date of 31 January 2020)



A worst-case sensitivity analysis was conducted based on the assumption that all participants who were censored with follow-up ongoing would progress immediately at the next visit. In this sensitivity analysis the median DoR was 10.3 months (95% CI: 4.2, 12.5) in the 2.5 mg/kg cohort. The estimated probability of having a DoR of ≥ 12 months was 50% in the 2.5 mg/kg cohort and 42% in the 3.4 mg/kg cohort. Among the 31 responders in the 2.5 mg/kg cohort, 11 participants still maintained response with follow-up ongoing, out of whom 6 participants had a DoR of more than 12 months.

- *Secondary efficacy endpoint- Time to Response*

The time to response was short and was similar for both cohorts (median: 1.4 months, 95% CI: 1.0, 1.6; median: 1.4 months, 95% CI: 0.9, 2.1).

- *Secondary efficacy endpoint-Progression-Free Survival*

Table 32 PFS Based on IRC Assessment (ITT Population, Study DREAMM-2) (cut-off date of 31 January 2020)

	Belantamab Mafodotin Q3W	
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
Number of participants, n (%)		
Progressed or died (event)	69 (71)	69 (70)
Censored, follow-up ended	16 (16)	17 (17)
Censored, follow-up ongoing	12 (12)	13 (13)
Event summary, n (%)		
Disease progression	64 (66)	60 (61)
Death	5 (5)	9 (9)
Estimates for time variable (months)		
1st quartile	0.9	0.8
95% CI	(0.8, 1.4)	(0.8, 1.4)
Median	2.8	3.9
95% CI	(1.6, 3.6)	(2.0, 5.8)
3rd quartile	9.7	8.4
95% CI	(4.8, -)	(6.4, -)
Progression-free survival probability		
Time-to-event endpoint at 6 months	0.32	0.39
95% CI	(0.22, 0.42)	(0.29, 0.49)

Furthermore, when adjusting for potential prognostic factors, the HR estimate for the 2 randomized dose cohorts became 0.96 (95% CI: 0.69, 1.35).

Table 33 Cox Regression Analysis of Progression-Free Survival per IRC (Study DREAMM-2, cut -off date of 31 January 2020)

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	13-Month FU (31Jan20)	
	HR (95% CI)	p-value
Without adjustment for covariates		
3.4 mg/kg versus 2.5 mg/kg	0.933 (0.668, 1.303)	0.684
With adjustment for covariates		
3.4 mg/kg versus 2.5 mg/kg	0.964 (0.687, 1.354)	0.835
ISS Staging at Screening: I to II versus III	0.572 (0.405, 0.809)	0.002
Number of prior lines of therapy: 3 to 8 versus ≥9	0.664 (0.434, 1.016)	0.059

ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; IRC: Independent Review Committee; PFS: progression-free survival.

Note: For each covariate, a hazard ratio <1 indicates a lower hazard to experience the event in the first subgroup compared with the second subgroup. Covariates were selected using backward variable selection with exit criteria of alpha=0.10. The dose group (2.5 mg/kg frozen vs. 3.4 mg/kg frozen) was forced in the model. Other covariates include age group ('<65' vs. '>=65'), cytogenetic risk ('Other' vs. 'High'), ISS staging at screening ('I/II' vs. 'III'), type of Myeloma ('Non-IgG' vs. 'IGG'), number of prior lines of therapy ('3-8' vs.'>=9'), ECOG performance status ('0-1' vs.'>=2'), and penta-refractory ('No' vs. 'Yes').

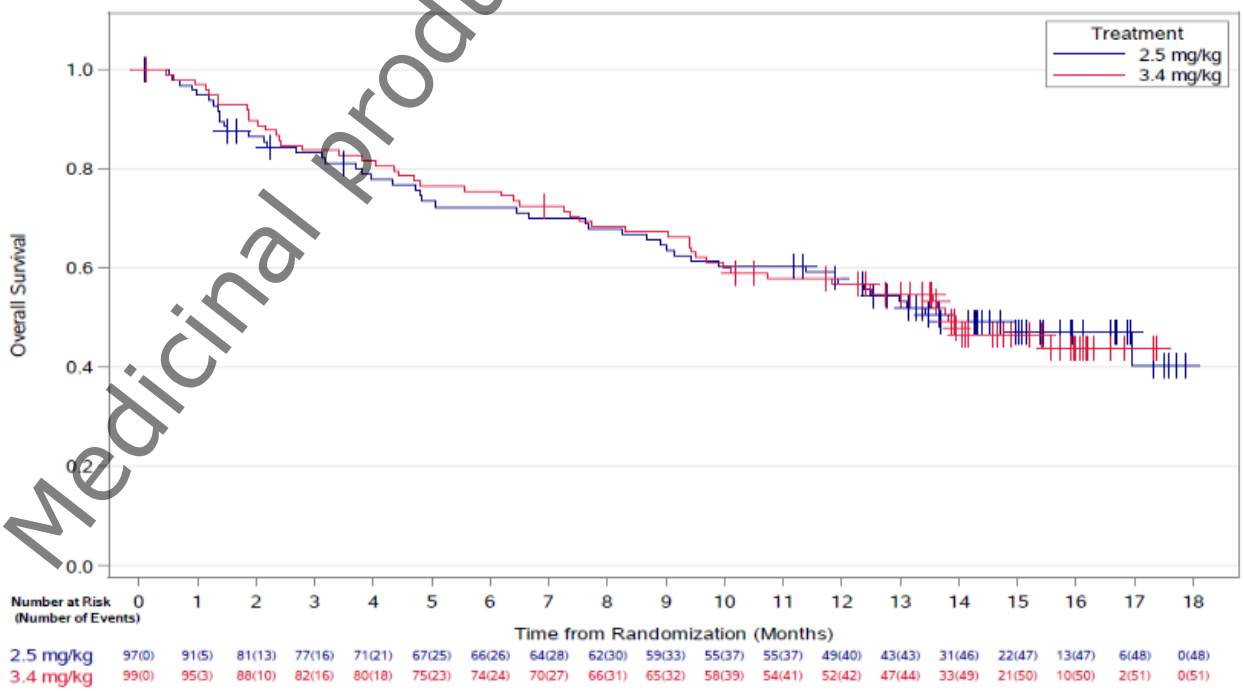
Note: A subject is considered as high risk if the subject has any of the following cytogenetics: t(4;14), t(14;16), and 17p13del. Penta-refractory is defined as refractory to: Bortezomib AND Carfilzomib AND Lenalidomide AND Pomalidomide AND Daratumumab.

- *Secondary efficacy endpoint- Overall Survival*

The OS was not mature at the time of the primary analysis. As of the data cut-off (21 June 2019), the 6-month overall survival rate was 72% and 75% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively.

As of the 13-month FU data (cut-off date of 31 January 2020), OS at 6 months was estimated as 72% in the 2.5 mg/kg cohort. OS at 12 months has been estimated based on the updated data as 57% and the median OS estimate was 13.7 months in the 2.5 mg/kg cohort.

Figure 7 K-M Analysis of OS (Study DREAMM-2, ITT Population) (cut-off date of 31 January 2020)



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- *Secondary efficacy endpoint- Minimal residual disease*

Table 34 MRD negativity rate by best response based on IRC assessment (DREAMM-2, ITT Population)

Best Response	Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		Updated Data (20Sep19)	
	2.5 mg/kg (n=97)	3.4 mg/kg (n=99)	2.5 mg/kg (n=97)	3.4 mg/kg (n=99)
sCR, n MRD negativity rate, n (%) 95% CI	1 1 (100) (2.5, 100)	2 1 (50) (1.3, 98.7)	2 2 (100) (15.8, 100)	1 1 (100) (2.5, 100)
CR, n MRD negativity rate, n (%) 95% CI	0	0	2 1 (50) (1.3, 98.7)	2 1 (50) (1.3, 98.7)
VGPR, n MRD negativity rate, n (%) 95% CI	3 0 (0.0, 70.8)	0	7 1 (14) (0.4, 57.9)	6 1 (17) (0.4, 64.1)
sCR/CR/VGPR, n MRD negativity rate, n (%) 95% CI	4 1 (25) (0.6, 80.6)	2 1 (50) (1.3, 98.7)	11 4 (36) (10.9, 69.2)	9 3 (33) (7.5, 70.1)

Ancillary analyses

The ORR results in demographic and disease-based subgroups based on IRC assessment for the 2.5 mg/kg and the 3.4 mg/kg are presented in Figure 8 and Figure 9.

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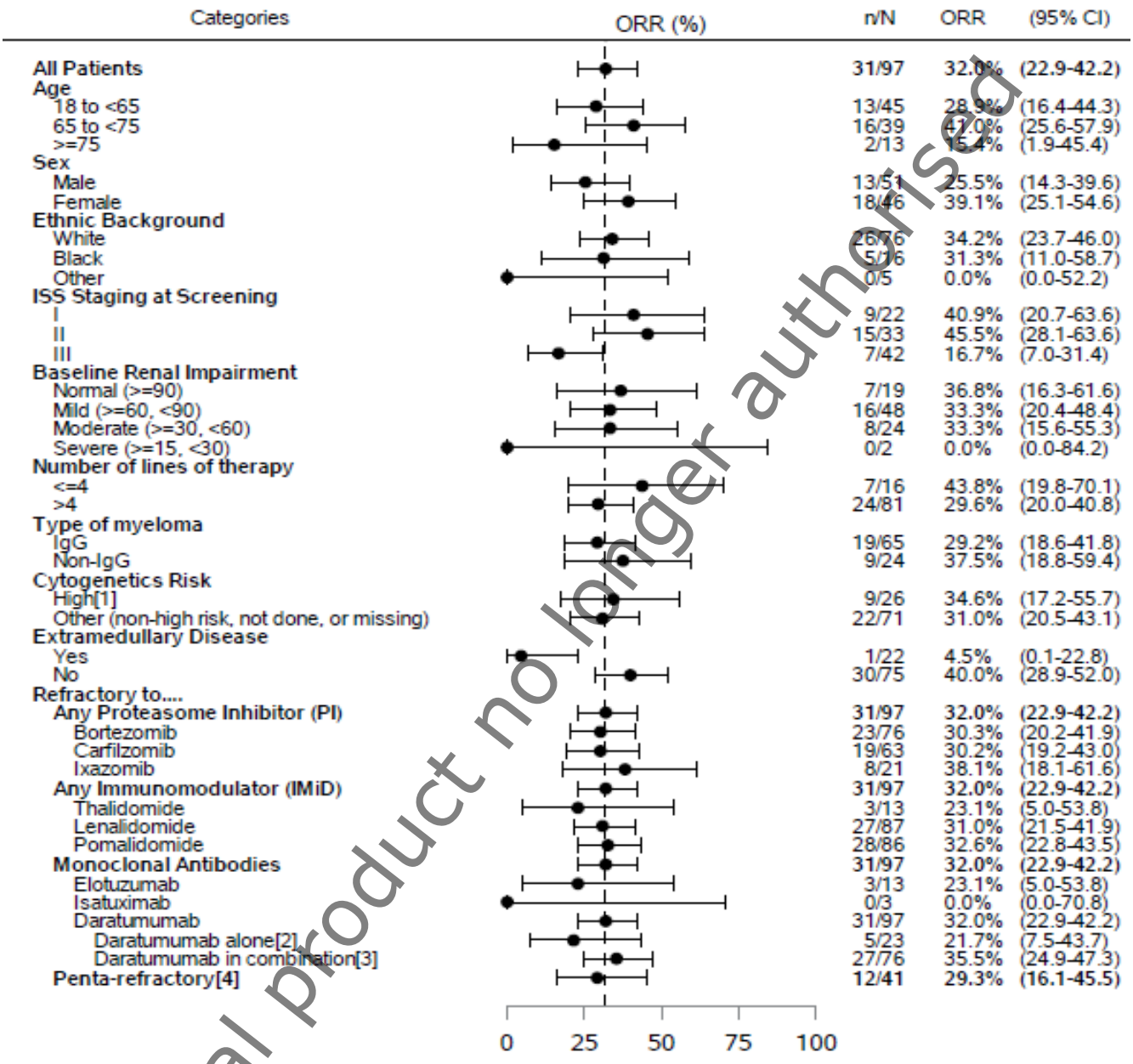
Figure 8 **ORR in Demographic and Disease-Based Subgroups Based on IRC Assessment (DREAMM-2 13-Month FU, ITT Population, 2.5 mg/kg Cohort)**



[1] A subject is considered as high risk if the subject has any of the following cytogenetics: t(4;14), t(14;16), and 17p13del.
[2] Defined as prior CTX regimen with Daratumumab as the only drug in the regimen.
[3] Defined as prior CTX regimen with Daratumumab and other drugs.
[4] Defined as refractory to: Bortezomib AND Carfilzomib AND Lenalidomide AND Pomalidomide AND Daratumumab.
The 95% Confidence Interval is based on Exact method.

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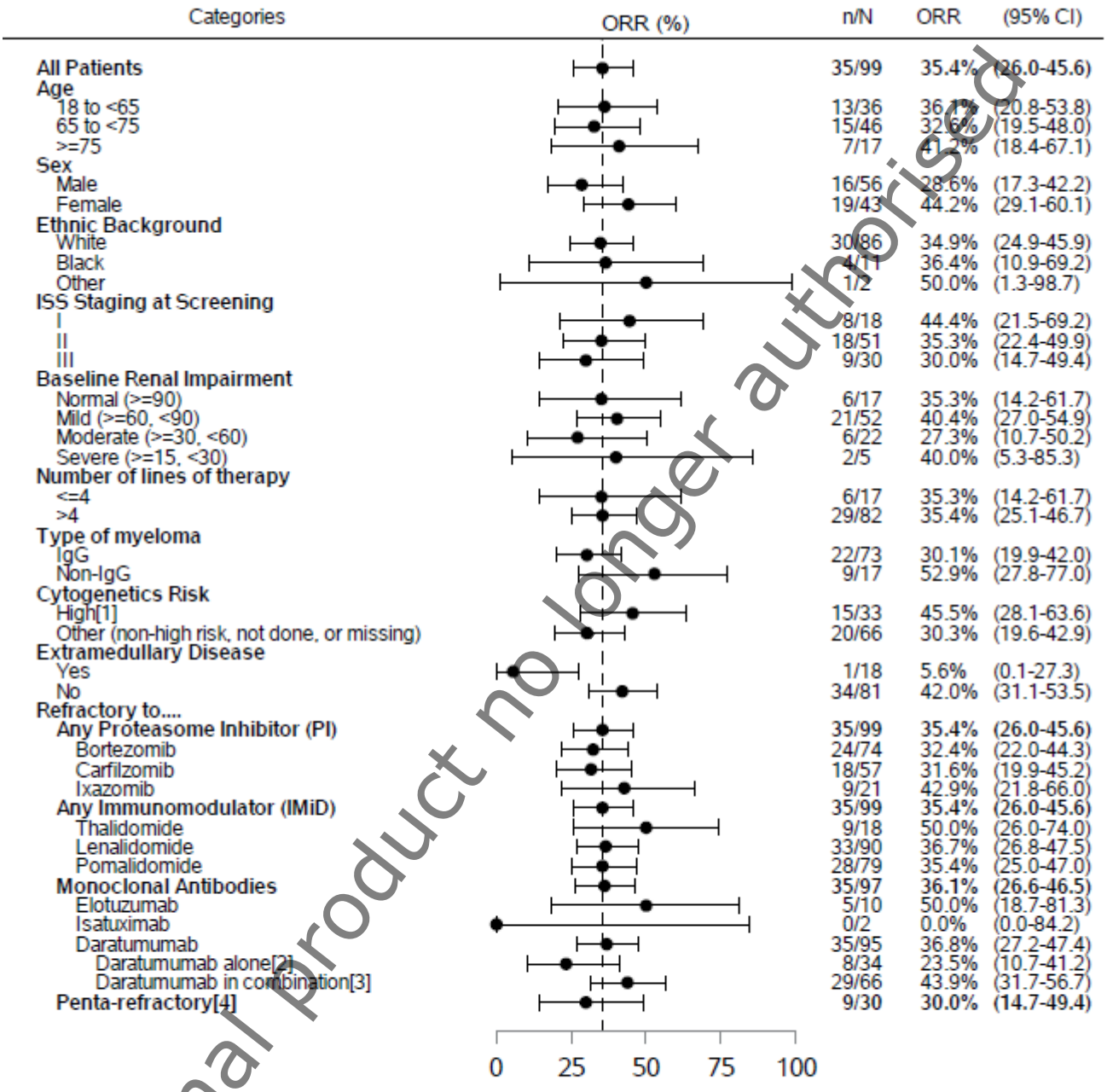
Figure 9 ORR in Demographic and Disease-Based Subgroups Based on IRC Assessment (DREAMM-2 13-Month FU, ITT Population, 3.4 mg/kg Cohort)



[1] A subject is considered as high risk if the subject has any of the following cytogenetics: t(4;14), t(14;16), and 17p13del.
[2] Defined as prior CTX regimen with Daratumumab as the only drug in the regimen.
[3] Defined as prior CTX regimen with Daratumumab and other drugs.
[4] Defined as refractory to: Bortezomib AND Carfilzomib AND Lenalidomide AND Pomalidomide AND Daratumumab.
The 95% Confidence Interval is based on Exact method.

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The DREAMM-2 study included an additional independent cohort 24 additional participants who received a lyophilized presentation of belantamab mafodotin at 3.4 mg/kg.

Based on available data, the ORR by IRC assessment was numerically higher in the Lyo cohort (48%) than in the frozen cohort (34%). A total of 24% of participants achieved VGPR or better; this was similar to the frozen cohort (20%).

Table 35 IRC-Assessed Best Response with Confirmation (DREAMM-2, 13-Month FU (cut-off date of 31 January 2020, Full Analysis Population)

	DREAMM-2	
	3.4 mg/kg (n=99)	3.4 mg/kg Lyo (n=25)
Best Response		
sCR	3 (3)	0
CR	0	0
Very Good Partial Response (VGPR)	17 (17)	6 (24)
Partial response (PR)	14 (14)	6 (24)
Minimal response (MR)	5 (5)	1 (4)
Stable disease (SD)	23 (23)	5 (20)
Progressive disease (PD)	26 (26)	6 (24)
Not evaluable (NE)	11 (11)	1 (4)
ORR		
sCR+CR+VGPR+PR	34 (34)	12 (48)
97.5% CI	(23.9, 46.0)	(25.5, 71.1)
CBR		
sCR+CR+VGPR+PR+MR	39 (39)	13 (52)
97.5% CI	(28.5, 51.1)	(28.9, 74.5)

The other efficacy parameters for the 3.4 mg/kg Lyo cohort were similar to the 3.4 mg/kg frozen liquid-cohort (data not shown).

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36 Summary of Efficacy for Study 205678 (DREAMM-2)

Title: A Phase II, open label, randomized, two-arm study to investigate the efficacy and safety of two doses of the antibody drug conjugate GSK2857916 in participants with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody (DREAMM-2)		
Study identifier	205678, EudraCT number 2017-004810-25	
Design	A multi-centre, randomised, Phase II study to evaluate the efficacy and safety of belantamab mafodotin at two dose levels: 2.5 mg/kg and 3.4 mg/kg Q3W (frozen presentation). An additional independent cohort of 25 participants received 3.4 mg/kg belantamab mafodotin as a lyophilised presentation. An ocular sub-study was conducted in 30 participants who were randomly assigned to either 2.5 mg/kg or 3.4 mg/kg to characterise the role of steroid eye drops in the prevention of corneal events.	
	Duration of treatment phase:	Until disease progression, death or unacceptable toxicity occurred.
	Duration of Screening/Baseline phase:	Up to 21 days. Older cytogenetics results were accepted if available.

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	Duration of Post-treatment Follow-up phase:		For participants who discontinued study treatment for a reason other than PD, PFS follow-up occurred every 21 days (±7 days). Disease evaluations continued until confirmed PD, death, start of a new anti-cancer treatment, withdrawal of consent, or end of the study, whichever occurred first. For participants who discontinued due to PD, follow-up occurred every 3 months (±14 days).
Hypothesis	Study DREAMM-2 was designed to provide evidence with respect to ORR to either support the null hypothesis: H_0: ORR ≤15% or reject H_0 in favour of the alternative hypothesis: H_1: ORR >15%.		
Treatments groups	2.5 mg/kg		2.5 mg/kg belantamab mafodotin (frozen), n (number randomised/ITT) = 97
	3.4 mg/kg		3.4 mg/kg belantamab mafodotin (frozen), n (number randomised/ITT) = 99
	3.4 mg/kg Lyo		3.4 mg/kg belantamab mafodotin (lyophilised), n (number randomised) = 25
Endpoints and definitions	Primary endpoint	Overall response rate (ORR)	The percentage of participants with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent CR), according to the 2016 IMWG Response Criteria by Independent Review Committee (IRC).
	Secondary Endpoints	ORR by investigator assessment Duration of response (DoR) Time to response (TTR) Progression-free survival (PFS) Time to progression (TTP) Overall survival (OS)	The percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and stringent CR), according to the 2016 IMWG Response Criteria by investigator assessment (IA). The time from first documented evidence of PR or better until the earliest date of documented PD per IMWG, or death due to PD. The time between the date of randomisation and the first documented evidence of response (PR or better). The time from randomisation until the earliest date of documented PD per IMWG, or death due to any cause. The time from randomisation until the earliest date of documented PD per IMWG, or death due to PD. The time from randomisation until death due to any cause.
Database lock	31 January 2020		

Results and Analysis

Analysis description	**Primary Analysis – Overall Response Rate (ORR) by Independent Review Committee (IRC)**			
Analysis population and time point description	Full Analysis Population, which included all randomised participants, whether or not treatment was administered.			
Descriptive statistics and estimate variability	Treatment group	**2.5 mg/kg**	**3.4 mg/kg**	**3.4 mg/kg Lyo**
	Number of subjects	97	99	25
	ORR by IRC, n (%)	31 (32)	35 (35)	13 (52)
	97.5% CI	(21.7, 43.6)	(24.8, 47.0)	(28.9, 74.5)
Notes	Not applicable (NA)			

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Analysis description	**Secondary Analysis – Overall Response Rate (ORR) by Investigator Assessment**			
Analysis population and time point description	Full Analysis Population			
Descriptive statistics and estimate variability	Treatment group	**2.5 mg/kg**	**3.4 mg/kg**	**3.4 mg/kg Lyo**
	Number of subjects	97	99	25
	ORR by IA, n (%)	32 (33)	32 (32)	13 (52)
	97.5% CI	(22.6, 44.7)	(22.1, 43.9)	(28.9, 74.5)
Analysis description	**Secondary Analysis – Duration of Response (DoR) by IRC**			
Analysis population and time point description	Full Analysis Population			
Descriptive statistics and estimate variability	Treatment group	**2.5 mg/kg**	**3.4 mg/kg**	**3.4 mg/kg Lyo**
	Number of subjects	31	35	13
	Median DoR (months)	11.0	6.2	9.0
	95% CI	(4.2, -)	(4.8, -)	(2.8, -)
Analysis description	**Secondary Analysis – Time to Response (TTR) by IRC**			
Analysis population and time point description	Full Analysis Population			
Descriptive statistics and estimate variability	Treatment group	**2.5 mg/kg**	**3.4 mg/kg**	**3.4 mg/kg Lyo**
	Number of subjects	31	35	13
	Median TTR (months)	1.5	1.4	0.9
	95% CI	(1.0, 2.1)	(0.9, 2.1)	(0.8, 2.3)
Analysis description	**Secondary Analysis – Progression Free Survival (PFS) by IRC**			
Analysis population and time point description	Full Analysis Population			
Descriptive statistics and estimate variability	Treatment group	**2.5 mg/kg**	**3.4 mg/kg**	**3.4 mg/kg Lyo**
	Number of subjects	97	99	25
	Median PFS (months)	2.8	3.9	5.7
	95% CI	(1.6, 3.6)	(2.0, 5.8)	(2.2, 9.7)
Analysis description	**Secondary Analysis – Time to Progression (TTP) by IRC**			
Analysis population and time point description	Full Analysis Population			
Descriptive statistics and estimate variability	Treatment group	**2.5 mg/kg**	**3.4 mg/kg**	**3.4 mg/kg Lyo**
	Number of subjects	97	99	25
	Median TTP (months)	2.9	4.9	5.7
	95% CI	(2.0, 3.6)	(2.3, 6.2)	(2.2, -)
Analysis description	**Secondary Analysis – Overall Survival (OS)**			
Analysis population and time point description	Full Analysis Population			
Descriptive statistics and estimate variability	Treatment group	**2.5 mg/kg**	**3.4 mg/kg**	**3.4 mg/kg Lyo**
	Number of subjects	97	99	25
	Median OS (months)	13.7	13.8	NR
	95% CI	(9.9, -)	(10.0, -)	(8.7, -)

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Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

Table 37 Number of elderly participants in DREAMM-1 and DREAMM-2

	Age 65-74 (Older Participants number /total number)	Age 75-84 (Older Participants number /total number)	Age 85+ (Older Participants number /total number)
DREAMM-1	22/73 (30%)	3/73 (4%)	0
DREAMM-2	94/221 (43%)	33/221 (15%)	3/221 (1%)
Total	116/294 (39%)	36/294 (12%)	3/294 (1%)

Supportive study

Study BMA117159 (DREAMM-1)

Belantamab mafodotin was initially evaluated in a first time in human study in participants with RRMM (DREAMM-1; BMA117159), who were refractory to a PI and an immunomodulatory agent. The objectives of DREAMM-1 were safety, tolerability, and clinical activity. Participants were treated on Q3W schedule as a 1-hour IV infusion.

Part 1 of DREAMM-1 was a dose escalation phase testing doses from 0.03 to 4.60 mg/kg (n=38). The 3.4 mg/kg dose was chosen as the RP2D due to receptor saturation, promising clinical activity at the 3.4 and 4.6 mg/kg doses, and lower tolerability of the 4.6 mg/kg dose.

In Part 2, participants (n=35) received the 3.4mg/kg dose for up to 16 cycles. The primary analysis was performed based on a data cut-off date of 31 August 2018, with 1 participant still ongoing.

In Part 1 (dose escalation) the ORR in the 2.5mg/kg subgroup (n=8) was 13% (95% CI: 0.3, 52.7) and in the 3.4-mg/kg subgroup (n=3) the ORR was 100% (95% CI: 29.2, 100.0). However, no responses were noted in the 4 participants in the 2.5-mg/kg subgroup who had also received prior daratumumab treatment in addition to a PI and an immunomodulatory agent.

In Part 2 (dose expansion, 3.4 mg/kg; n=35), the ORR was 60% (95% CI: 42.1, 76.1), with 54% of participants achieving a VGPR or better and median DoR was 14.3 months (95% CI: 10.6, -). In the subpopulation of participants who had received prior daratumumab (n=13), ORR was 38% with all responders achieving a VGPR or better and median DoR was 6.7 months (95% CI: 5.3, -) (see section 2.5.1. Dose response study).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The justification for the selected two doses (2.5 mg/kg or 3.4 mg/kg) of belantamab mafodotin was based on the results of the dose-finding study BMA117159 (DREAMM-1). The DLTs were investigated in the Part 1 of the study and no dose-limiting toxicities were observed at any dose level, including the

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maximum administered dose (4.6 mg/kg). Thus, the MTD was not established. The 2.5 mg/kg dose was acceptable by the CHMP to be the recommended dose.

The efficacy data of belantamab mafodotin was based mainly on a single phase 2 study 205678 (DREAMM-2). In principle, the study design was fit for its purpose, *i.e.*, to demonstrate efficacy in this heavily pre-treated MM patient population. MM patients relapsed or refractory to a proteasome inhibitor and immunomodulatory agent and in whom treatment with an anti-CD38 antibody had failed, have a dismal prognosis. The target population on the pivotal phase II study represents a MM patient population with multi-refractory disease and most the patients were previously treated with more than 5 previous lines of therapy. Currently there are limited options for these last line MM patients.

Due to over-enrolment, 196 RRMM patients were recruited in this study; 97 in the 2.5 mg/kg dose cohort and 99 in the 3.4 mg/kg dose cohort. In general, the chosen inclusion and exclusion criteria are appropriate. Patients with prior allogeneic stem cell transplant were excluded mainly due the difficulties to separate possible corneal (eye) side-effects of belantamab mafodotin and clinical manifestations of GVHD, including keratoconjunctivitis sicca.

Before the initiation of the study and in response to the feedback from regulatory agencies, the study was amended from an original single-arm design with 1 dose level (3.4 mg/kg) to an open-label, randomized, 2-arm study with 2 dose levels, including the 2.5 mg/kg Q3W dose (Amendment 1) and the addition of a lyophilised cohort. Due to over-enrolment in DREAMM-2,the overall sample size was increased from 65 subjects to ~100 subjects per arm. As a result, the minimum observed ORR required for claiming efficacy changed from 26% (i.e. 17 responders for a sample size of 65 per arm) to 24% (i.e. 24 responders for sample size of 100 per arm).

The phase 2 study was conducted without an active control arm which is a limitation. Because there is no standard treatment for these patients, the missing control arm may be considered acceptable. To use historical data as a justification for the proposed ORR has also well-known limitations. The ORR rate of 15% (statistical design) of the study (amendment 1) was selected based on the previously reported response rate of 15% in participants at fourth relapse based on historical control data and was also discussed extensively with the applicant in Protocol Assistance (EMEA/H/SA/3559/2/2018/PA/PR/III). The target ORR rate (≥24%) was not rejected, but in order to demonstrate a positive benefit/risk for belantamab mafodotin in the context of a CMA, it was expected that ORR rates markedly greater than 15% are observed from historical data. Furthermore, it was concluded that when using ORR as a primary endpoint, the treatment effect on ORR will have to be substantial to allow confidence in the clinical benefit. It was concluded that if the ORR proves to be according to expectations (33%) and if the secondary objectives and safety data of this study demonstrate an adequate risk/benefit profile, these analyses could provide a clinically meaningful outcome.

Efficacy data and additional analyses

The originally proposed wording of the indication "BLENREP is indicated as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent" allows treatment of patients after three prior treatments, relapsed or refractory to an immunomodulatory agent, PI and anti-CD38 antibody. Only 5 patients in the pivotal study fulfilled these minimum criteria, and the majority of the patients were heavily pre-treated, with two proteasome inhibitors and two immunomodulatory agents. In addition, most of the patients were refractory to bortezomib, carfilzomib, lenalidomide and pomalidomide and, by definition, all patients in the pivotal study were refractory to an immunomodulatory agent and a proteasome inhibitor and an

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anti-CD38 antibody. Although the patients included in this pivotal trial had minimum requirement of having failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and being refractory to an immunomodulatory agent (i.e., lenalidomide or pomalidomide), to a proteasome inhibitor (e.g., bortezomib or carfilzomib) and to an anti-CD38 mAb (triple-class refractory), the vast majority of the patients were heavily pretreated. To better reflect the patient population, both in terms of prior lines of treatment received, and refractoriness to prior therapies, the indication was revised as follows:

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

The study met its primary endpoint for ORR as assessed by IRC in both the 2.5 mg/kg Q3W frozen cohort and 3.4 mg/kg Q3W frozen cohort. The ORR observed in this study by IRC was 31% (97.5%CI: 20.8, 42.6) in the 2.5 mg/kg cohort and 34% (97.5%CI: 23.9, 46.0) in the 3.4 mg/kg cohort (comparable to the 30% ORR observed in the pomalidomide study, study MM-003 which compared the efficacy of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone in patients with refractory MM who had failed therapy with both bortezomib and lenalidomide, administered either alone or in combination).

In the updated results with 13-month follow-up, the dose of 2.5 mg/kg Q3W has demonstrated ORR of 32% with mDOR of 11 months. There was a further deepening of response, with 58% of responders achieving VGPR or better, including 2 sCRs and 5 CRs. When interpreting these results, it should be kept in mind that these MM patients were heavily pre-treated with limited therapeutic options available. Thus, the updated data with longer FU confirmed that the responses are durable.

With regard to OS, based on the 13-month FU the median OS estimate was 13.7 months in the 2.5 mg/kg cohort. When compared indirectly to the expected survival in this patient population, the probability of an OS ≥12 months of 57%is acknowledged, taking into consideration of the immaturity of the OS data.

In the updated PFS results with 13-month follow-up, the median PFS estimate in the 2.5 mg/kg was 2.8 months compared to 3.9 in the 3.4 mg/kg cohort. The median PFS point estimate seems to be better in the 3.4 mg/kg dose cohort. The results of a sensitivity analysis with cytogenetics stratification (Yes, No and Other) were in-line with the primary results.

MRD data was missing from 14 participants. However, among these, eight of these participants have relapsed and one died before MRD assessment. It would have been preferable to have MRD-data available from all participant with CR or VGPR. However, whether these participants would have reached MRD-data negativity or not, relapse seem to be unavoidable for these participants. In addition, seven out of 20 MRD-tested participants had achieved MRD negativity as of the 9-month follow-up.

The study included an additional independent cohort of 24 participants who received a lyophilized presentation of belantamab mafodotin at 3.4 mg/kg. So far, no patients have been treated with the proposed (SmPC) dose of 2.5 mg/kg with the commercial lyophilized formulation. Some differences in terms of patient characteristics were reported between patients treated with the 3.4 mg/kg frozen and the 3.4 mg/kg lyophilized presentations. Patients included in the lyophilized cohort were less pre-treated and a lower percentage of them had high cytogenetic risk compared with those treated with the frozen formulation. In addition, response rate to most recent prior anticancer therapy was higher in the lyophilized cohort (52% vs. 30%). These differences in important prognosis factors along with the

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small sample size of the lyophilized cohort may explain the higher ORR reported in these patients (48% by IRC; 97.5% CI: 25.5%,71.1%) as compared to patients receiving the frozen formulation.

The exposure was decreased by ~10% when 3.4 mg/kg lyophilised formulation was administered compared to 3.4 mg/kg frozen formulation, which could suggest a lower exposure for 2.5 mg/kg Lyophilised than the 2.5 mg/kg frozen formulation. However, no significant differences were observed for Cmax and other exposure metrics, showing that the effect is not systematic, and it may likely be influenced by an imbalance in the distribution of patients receiving each formulation (lyophilised and frozen) (see discussion on clinical pharmacology). The covariate analysis did not identify a formulation effect as a significant covariate relationship. According to model predictions and efficacy/safety data, those differences are considered of minor relevance. Besides, from a quality point of view, both formulations are considered comparable (see section 2.2 Quality aspects).

Additional efficacy data needed in the context of a conditional MA

Based on the observed efficacy, a clinical benefit for belantamab mafodotin can be considered established, but a confirmation from a phase III comparative study is needed in order to better quantify the magnitude of the effect.

In view of the established clinical benefit, and the fact that this application falls within scope and fulfils the remaining conditional marketing authorisation requirements, the CHMP agreed that the conditional marketing authorisation requested by the applicant could be granted.

DREAMM-3, a phase III study of single agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone in participants with relapsed/refractory multiple myeloma is ongoing (SOB, Annex II.E) and a considerable proportion of patients would be in later treatment lines in line with DREAMM-2. Single arm study settings also impair the causality assessment of several key unfavourable effects leading to remaining uncertainties. These could be addressed by the proposed randomised study with pomalidomide/low-dose dexamethasone as comparator since it would allow comparisons of both efficacy and safety, and the proposed number of patients (n=320) would allow a more comprehensive analysis of both favourable and unfavourable effects. DREAMM-3 will be conducted in 184 sites and 19 countries worldwide.

In addition, the CHMP considered that the MAH should submit the final results of the pivotal study DREAMM-2 study investigating the efficacy of belantamab mafodotin in patients with RRMM who have failed prior treatment with an anti-CD38 antibody which will also provide comprehensive data suitable to confirm the positive benefit-risk balance of BLENREP (SOB, Annex II.E).

2.5.4. Conclusions on the clinical efficacy

Data from the pivotal study DREAMM-2 showed a clinically significant response rate to belantamab mafodotin as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy. These results are further supported by durable responses. The achieved ORR is considered clinically meaningful in this heavily pre-treated MM patient population. However, efficacy results from direct comparison with available regimens are needed in order to better quantify the magnitude of the effect. In addition, the CHMP considered that the MAH should submit the final results of the pivotal study DREAMM-2 study which, together with the results from the comparative phase III DREAMM-3 study, will provide comprehensive data suitable to confirm the positive benefit-risk balance of BLENREP in the recommended indication.

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The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to confirm the efficacy and safety of BLENREP in relapsed/refractory multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-2 (205678) study investigating the efficacy of belantamab mafodotin in patients with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody. The final results of the study should be submitted by April 2021.
- In order to confirm the efficacy and safety of BLENREP in multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-3 (207495) study comparing the efficacy of belantamab mafodotin vs. pomalidomide plus low dose dexamethasone (pom/dex) in patients with relapsed/refractory multiple myeloma. The final report of the study should be submitted by July 2024.

2.6. Clinical safety

Patient exposure

The safety database is based on two clinical studies, first in human trial (FIHT) study DREAMM-1 and phase 2 study DREAMM-2.

Two hundred and ninety-one (291) patients have been exposed to belantamab mafodotin (single agent), and 103 patients have been treated with the proposed registration dose. Safety assessment relies on pivotal study DREAMM-2, as the expansion cohort in the FIHT study DREAMM-1 was treated with a dose higher than the proposed registration dose (3.4 mg/kg vs. 2.5 mg/kg), and the enrolled patient population is not completely in line with the proposed indication. Thus, the primary safety assessment (21 June 2019) is mainly based on 103 patients (DREAMM-1 and DREAMM-2) with a median time on treatment of 9.1 weeks, and a median follow-up time of 6.37 months. At the time of the 13-month safety update (31 January 2020), median time on treatment was 9.3 weeks and the median time on study was 12.35 months.

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Table 38 Exposure to Belantamab Mafodotin (DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95[a])	3.4 mg/kg (N=99)	2.5 mg/kg (N=95[a])	3.4 mg/kg (N=99)	2.5 mg/kg (N=95[a])	3.4 mg/kg (N=99)
Number of cycles						
Mean (SD)	3.5 (2.13)	3.9 (2.51)	3.9 (2.91)	4.4 (3.14)	4.4 (3.86)	4.9 (3.96)
Median (min,max)	3 (1,11)	3 (1,10)	3 (1,15)	3 (1,14)	3 (1,17)	3 (1,17)
Dose Intensity (mg/kg/3 weeks)						
Mean (SD)	2.07 (0.572)	2.64 (0.841)	2.02 (0.625)	2.62 (0.870)	2.01 (0.636)	2.60 (0.897)
Median (min,max)	2.47 (0.7,2.6)	2.95 (1.0,3.7)	2.39 (0.5,2.6)	2.95 (0.9,3.7)	2.39 (0.5,2.6)	2.95 (0.8,3.7)
Time on Study Treatment (weeks) [b]						
Mean (SD)	14.4 (10.75)	16.5 (12.23)	17.3 (15.40)	19.2 (16.41)	20.2 (20.72)	22.3 (21.84)
Median (min,max)	9.1 (2,40)	12 (2,48)	9.3 (2,52)	12 (2,59)	9.3 (2,75)	12.0 (2,75)

Source: DREAMM-2 CSR Table 1.0300, DREAMM-2 CSR Table 1.0260, DREAMM-2 90-DU Table 1.0300, DREAMM-2 90-DU Table 1.0260; DREAMM-2 13-Month FU Table 1.0300, DREAMM-2 13-Month FU Table 1.60260

a. Two participants in the 2.5 mg/kg cohort and 1 participant in the 3.4 mg/kg cohort were randomised but did not receive any dose of study treatment; these participants were excluded from the Safety Population.

b. The time on study treatment includes dose delays. Duration of exposure in days is calculated as minimum of (treatment stop date +20, death date) minus treatment start date +1.

A named patient compassionate use program has treated 174 patients as of 27 February 2020. Physicians were not obligated to report adverse events. but asked to report SAEs and AEs and SAEs. This has been reported as supportive information.

In the pooled (DREAMM-2 and DREAMM-1) 2.5 mg/kg cohort, 22 (21%) of the 103 patients were ongoing and receiving study treatment at data cut-off (21 June 2019). The most common reason for discontinuation was progressive disease (65 patients, 63%). Eight patients (8%) discontinued due to AEs. Overall, the discontinuation rates were very similar in 2.5 mg/kg pooled group and 3.4 mg/kg pooled groups, with the exception of lower proportion of patients discontinuing due to progressive disease in the 3.4 mg/kg pooled (Patients receiving 3.4 mg/kg in DREAMM-1 and DREAMM-2, N=137).

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Table 39 Treatment Status and Reasons for Discontinuation of Study Treatment (DREAMM-2 Safety Population)

	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Treatment Status						
Ongoing	22 (23)	25 (25)	17 (18)	18 (18)	10 (11)	13 (13)
Discontinued	73 (77)	74 (75)	78 (82)	81 (82)	85 (89)	86 (87)
Primary reason for treatment discontinuation [a]						
Progressive disease	59 (62)	56 (57)	63 (66)	60 (61)	69 (73)	65 (66)
Adverse event	7 (7) [c]	10 (10)	8 (8)	12 (12)	8 (8)	12 (12)
Lack of efficacy	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)
Lost to follow-up	1 (1)	0	1 (1)	0	1 (1)	0
Physician decision [d]	4 (4)	4 (4)	4 (4)	4 (4)	4 (4)	4 (4)
Withdrawal by participant [d]	1 (1)	3 (3)	1 (1)	4 (4)	2 (2)	4 (4)

Source: DREAMM-2 CSR Table 1.0020, DREAMM-2 90-DU Table 1.0020; DREAMM-2 13-month FU Table 1.0020

a. Participant 5901 in the 3.4 mg/kg cohort does not have information entered in the database for treatment discontinuation related to study treatment.

c. Participant 306 had a disease-related headache, but discontinued treatment for the primary reason of disease progression.

d. Decisions to discontinue study treatment were considered treatment-related for 3 participants in the 2.5 mg/kg cohort and for 3 participants in the 3.4 mg/kg cohort.

Table 40 Dose Reductions of Belantamab Mafodotin (DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Participants with Any Dose Reduction, n (%)	28 (29)	42 (42)	32 (34)	43 (43)
Total Number of Dose Reductions	28	56	32	61
Dose Reductions, n (%)				
0	56 (59)	42 (42)	52 (55)	41 (41)
1	28 (29)	28 (28)	32 (34)	25 (25)
2	0	14 (14)	0	18 (18)
3	0	0	0	0
Not Evaluable [a]	11 (12)	15 (15)	11 (12)	15 (15)
Reasons for Reduction, n (%)				
Adverse Event	28 (100)	55 (98)	32 (100)	59 (97)
Other	0	1 (2)	0	2 (3)
Participants with Dose Reduction by Planned Time, n/N (%)				
Cycle 1 Day 1	0/95	0/99	0/95	0/99
Cycle 2 Day 1	6/84 (7)	15/84 (18)	6/84 (7)	15/84 (18)
Cycle 3 Day 1	10/54 (19)	20/61 (33)	11/55 (20)	20/61 (33)
Cycle 4 Day 1	8/39 (21)	8/43 (19)	8/40 (20)	9/44 (20)
Cycle 5 Day 1	4/26 (15)	9/33 (27)	4/26 (15)	11/38 (29)
Cycle 6 Day 1	0/14	1/26 (4)	2/20 (10)	2/34 (6)
Cycle 7 Day 1	0/10	2/20 (10)	0/15	3/27 (11)
Cycle 8 Day 1	0/5	0/11	0/11	0/19
Cycle 9 Day 1	0 3	1/7 (14)	0/8	1/13 (8)
Cycle 10 Day 1	0/2	0/2	0/6	0/8
Cycle 11 Day 1	0/1	0	0/4	0/3
Cycle 12 Day 1			0/3	0/2
Cycle 13 Day 1			0/2	0/2
Cycle 14 Day 1			1/2 (50)	0/1
Cycle 15 Day 1			0/1	0

Source: DREAMM-2 CSR Table 1.0280, DREAMM-2 90-DU Table 1.0280

Note: Participants may be counted multiple times in the same "reason' row if the participant had multiple reductions for the same reason.

a. Not evaluable means the participant did not receive any study treatment in any succeeding time period after the first dose.

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Table 41 Dose Delays of Belantamab Mafodotin (DREAMM-2 ITT Population) (cut-off date of 21 June 2019 and 20 September 2019)

	Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		Updated Data (20Sep19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Participants with Any Dose Delay, n (%)	37 (39)	48 (48)	39 (41)	48 (48)
Total Number of Dose Delays	55	82	74	105
Dose Delays, n (%)				
0	47 (49)	36 (36)	45 (47)	36 (36)
1	21 (22)	27 (27)	18 (19)	24 (24)
2	14 (15)	12 (12)	11 (12)	8 (8)
>=3	2 (2)	9 (9)	10 (11)	16 (16)
Not Evaluable [a]	11 (12)	15 (15)	11 (12)	15 (15)
Delay Duration (days), n (%)				
1-21	20 (36)	38 (46)	27 (36)	49 (47)
22-42	10 (18)	18 (22)	11 (15)	22 (21)
>42	25 (45)	26 (32)	36 (49)	34 (32)
Reasons for Delay, n (%)				
Adverse Event	53 (96)	78 (95)	68 (92)	97 (92)
Scheduling Conflict	1 (2)	2 (2)	4 (5)	4 (4)
Other	1 (2)	2 (2)	2 (3)	4 (4)
Participants with Dose Delays by Planned Time, n/N (%)				
Cycle 2 Day 1	9/84 (11)	17/84 (20)	9/84 (11)	17/84 (20)
Cycle 3 Day 1	14/54 (26)	20/61 (33)	15/55 (27)	20/61 (33)
Cycle 4 Day 1	13/39 (33)	13/43 (30)	14/40 (35)	14/44 (32)
Cycle 5 Day 1	11/26 (42)	13/33 (39)	11/26 (42)	18/38 (47)
Cycle 6 Day 1	3/14 (21)	6/26 (23)	9/20 (45)	8/34 (24)
Cycle 7 Day 1	1/10 (10)	9/20 (45)	4/15 (27)	13/27 (48)
Cycle 8 Day 1	3/5 (60)	3/11 (27)	6/11 (55)	8/19 (42)
Cycle 9 Day 1	1/3 (33)	1/7 (14)	2/ 8 (25)	4/13 (31)
Cycle 10 Day 1	0/2	0/2	2/ 6 (33)	2/ 8 (25)
Cycle 11 Day 1	0/1	0	2/ 4 (50)	0/3
Cycle 12 Day 1			0/3	0/2
Cycle 13 Day 1			0/2	0/2
Cycle 14 Day 1			0/2	1/1 (100)
Cycle 15 Day 1			0/1	0

Source: Table 1.0290

a. Not evaluable means the participant did not receive any study treatment in any succeeding time period after the first dose.

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Adverse events

An overview of the AEs observed in the safety population is given in ***Table 42***

Table 42 Adverse Event Overview (DREAMM-2 Safety Population)

	Number (%) of Participants Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any AE	**93 (98)**	**99 (100)**	**93 (98)**	**99 (100)**	**93 (98)**	**99 (100)**
AEs related to study treatment	84 (88)	94 (95)	84 (88)	94 (95)	84 (88)	94 (95)
AEs leading to permanent discontinuation of study treatment	8 (8)	10 (10)	9 (9)	12 (12)	9 (9)	12 (12)
AEs leading to dose reduction	28 (29)	41 (41)	32 (34)	43 (43)	33 (35)	44 (44)
AEs leading to dose interruption/delay	51 (54)	61 (62)	51 (54)	61 (62)	51 (54)	61 (62)
AEs related to study treatment and leading to permanent discontinuation of study treatment	6 (6)	4 (4)	7 (7)	5 (5)	7 (7)	5 (5)
Grade 3 or 4 AEs	78 (82)	81 (82)	78 (82)	82 (83)	79 (83)	82 (83)
Grade 3 or 4 AEs related to study treatment	52 (55)	62 (63)	53 (56)	64 (65)	54 (57)	64 (65)
Any SAE	**38 (40)**	**47 (47)**	**38 (40)**	**47 (47)**	**40 (42)**	**47 (47)**
SAEs related to study treatment	10 (11)	19 (19)	11 (12)	20 (20)	11 (12)	20 (20)
Fatal SAEs	3 (3)	7 (7)	3 (3)	9 (9)	3 (3)	9 (9)
Fatal SAEs related to study treatment	1 (1)	1 (1)	1 (1)	2 (2)	1 (1)	2 (2)

Treatment-related AEs

In the 2.5 mg/kg pooled data, a treatment-related AE was reported for 91 (88%) participants.

Table 43 Treatment-Related AEs by PT Reported for ≥10% of Participants in Any Cohort (DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any Event	**84 (88)**	**94 (95)**	**84 (88)**	**94 (95)**
Keratopathy	65 (68)	70 (71)	67 (71)	70 (71)
Thrombocytopenia	12 (13)	31 (31)	15 (16)	33 (33)
Vision blurred	13 (14)	24 (24)	14 (15)	26 (26)
Nausea	12 (13)	19 (19)	12 (13)	19 (19)
Dry eye	11 (12)	18 (18)	11 (12)	19 (19)
Fatigue	7 (7)	14 (14)	7 (7)	14 (14)
AST increased	14 (15)	13 (13)	14 (15)	14 (14)
Pyrexia	10 (11)	13 (13)	10 (11)	13 (13)
Anaemia	5 (5)	12 (12)	5 (5)	12 (12)
Neutropenia	3 (3)	12 (12)	4 (4)	12 (12)
Vomiting	2 (2)	12 (12)	2 (2)	12 (12)
Infusion related reaction	13 (14)	10 (10)	13 (14)	10 (10)

Adverse reactions

Adverse reactions described in this section were reported from 95 patients who received BLENREP 2.5 mg/kg in study DREAMM-2. The most frequent adverse reactions (≥30%) were keratopathy (71%) and thrombocytopenia (38%). The most commonly reported serious adverse reactions were pneumonia

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(7%), pyrexia (7%) and IRRs (3%). Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received BLENREP with 3% related to ocular adverse reactions.

Table 44 Adverse reactions reported in patients treated with Belantamab mafodotin

System Organ Class	Adverse reactions[a]	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Pneumonia[b]	Very common	11	7
	Upper respiratory tract infection	Common	9	0
Blood and lymphatic system disorders	Thrombocytopenia[c]	Very common	38	22
	Anaemia		27	21
	Lymphopenia[d]		20	17
	Leukopenia[e]		17	6
	Neutropenia[f]		15	11
Eye disorders	Keratopathy[g]	Very common	71	31
	Blurred vision events[h]		25	4
	Dry eye events[i]		15	1
	Photophobia	Common	4	0
	Eye irritation		3	0
	Ulcerative keratitis	Uncommon	1	1
	Infective keratitis		1	1
Gastrointestinal disorders	Nausea	Very common	25	0
	Diarrhoea	Common	13	1
	Vomiting		7	2
General disorders and administration site conditions	Pyrexia	Very common	23	4
	Fatigue		16	2
Investigations	Increased aspartate aminotransferase	Very common	21	2
	Increased gamma glutamyltransferase		11	3
	Increased creatine phosphokinase	Common	5	2
Injury, poisoning and procedural complications	Infusion-related reactions[j]	Very common	21	3

[a] Adverse reactions coded using MedDRA and graded for severity based CTCAE v4.03.
[b] Includes pneumonia, and herpes simplex pneumonia
[c] Includes thrombocytopenia and decreased platelet count.
[d] Includes lymphopenia and decreased lymphocyte count.
[e] Includes leukopenia and decreased leukocyte count.
[f] Includes neutropenia and decreased neutrophil count.
[g] Based on eye examination, characterised as corneal epithelium changes with or without symptoms.
[h] Includes diplopia, vision blurred, visual acuity reduced and visual impairment.
[i] Includes dry eye, ocular discomfort, and eye pruritus.
[j] Includes events determined by investigators to be related to infusion. Infusion reactions may include, but are not limited to, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

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Adverse events of interest

- *Corneal adverse reactions*

Events in this category include 45 MedDRA AE PTs that the applicant considered to be related to keratopathy. This includes the "microcyst-like epithelial keratopathy (MEK)" term that investigators were instructed to use to report ocular examination findings, which was mapped to the MedDRA PT keratopathy.

Corneal adverse reactions were assessed in Study DREAMM-2 from the safety population (n = 218) which included patients treated with 2.5 mg/kg (n=95). Eye disorder events occurred in 74% patients and the most common adverse reactions were keratopathy or microcyst-like epithelial changes in corneal epithelium [identified on eye exam, with or without symptoms] (71%), blurred vision (25%), and dry eye (15%). Decreased vision (Snellen score Visual Acuity worse than 20/50) in the better eye was reported in 18% and severe vision loss (20/200 or worse) in the better seeing eye was reported in 1% of patients treated with belantamab mafodotin (SmPC, section 4.8).

The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity or keratopathy on eye examination) was 36 days (range: 19 to 143 days). The median time to resolution of these corneal findings was 91 days (range: 21 to 201 days). Corneal findings (keratopathy) led to dose delays in 47% of patients, and dose reductions in 27% of patients. Three percent of patients discontinued treatment due to ocular events (SmPC, section 4.8).

Table 45 Characteristics of keratopathy events (CTCAE) (DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Participants with Event, n (%)	67 (71)	74 (75)	67 (71)	74 (75)	67 (71)	74 (75)
Event Characteristics, n/N (%)						
Serious	0/95	0/99	0/95	0/99	0/95	0/99
Study treatment related	65/95 (68)	70/99 (71)	67/95 (71)	70/99 (71)	67/95 (71)	70/99 (71)
Number of events, n/N (%)						
One	26/95 (27)	29/99 (29)	24/95 (25)	29/99 (29)	23/95 (24)	29/99 (29)
Two	14/95 (15)	8/99 (8)	15/95 (16)	7/99 (7)	15/95 (16)	8/99 (8)
Three or more	27/95 (28)	37/99 (37)	28/95 (29)	38/99 (38)	29/95 (31)	37/99 (37)
Worst Outcome, n/N (%)						
Recovered/Resolved	24/95 (25)	20/99 (20)	30/95 (32)	24/99 (24)	31/95 (33)	29/99 (29)
Recovered/Resolved with Sequelae	4/95 (4)	2/99 (2)	6/95 (6)	5/99 (5)	8/95 (8)	6/99 (6)
Recovering/Resolving	5/95 (5)	12/99 (12)	3/95 (3)	12/99 (12)	3/95 (3)	10/99 (10)
Not Recovered/Not Resolved	34/95 (36)	40/99 (40)	28/95 (29)	33/99 (33)	25/95 (26)	29/99 (29)
Fatal	0/95	0/99	0/95	0/99	0/95	0/99
Maximum Grade, n/N (%)						
Grade 1	12/95 (13)	12/99 (12)	11/95 (12)	11/99 (11)	11/95 (12)	10/99 (10)
Grade 2	29/95 (31)	41/99 (41)	28/95 (29)	39/99 (39)	27/95 (28)	40/99 (40)
Grade 3	26/95 (27)	20/99 (20)	28/95 (29)	23/99 (23)	28/95 (29)	23/99 (23)
Grade 4	0/95	1/99 (1)	0/95	1/99 (1)	1/95 (1)	1/99 (1)
Grade 5	0/95	0/99	0/95	0/99	0/95	0/99
Action Taken [a], n/N (%)						
Study treatment withdrawn	2/95 (2) [b]	3/99 (3)	1/95 (1)	3/99 (3)	1/95 (1)	3/99 (3)
Dose reduced	22/95 (23)	27/99 (27)	25/95 (26)	28/99 (28)	26/95 (27)	30/99 (30)
Dose not changed	57/95 (60)	59/99 (60)	58/95 (61)	62/99 (63)	60/95 (63)	62/99 (63)
Dose interrupted/delayed	45/95 (47)	48/99 (48)	45/95 (47)	49/99 (49)	45/95 (47)	49/99 (49)
Dose reduced or interrupted/delayed	45/95 (47)	49/99 (49)	45/95 (47)	49/99 (49)	45/95 (47)	49/99 (49)

Source: DREAMM-2 CSR Table 3.0180, DREAMM-2 90-DU Table 3.0180; DREAMM-2 13-Month FU Table 3.0180
CTCAE: Common Terminology Criteria for Adverse Events.
a. Participants could have more than 1 Action Taken and be represented more than once.
b. One participant was withdrawn due to keratopathy, this has been corrected in the eCRF and is reflected in the updated data.

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Table 46 Keratopathy events (CTCAE) by PT (DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31 Jan 2020)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any event	**67 (71)**	**74 (75)**	**67 (71)**	**74 (75)**	**67 (71)**	**74 (75)**
Keratopathy	67 (71)	74 (75)	67 (71)	74 (75)	67 (71)	74 (75)
Keratitis	1 (1)	0	1 (1)	0	1 (1)	0
Corneal epithelium defect	0	1 (1)	0	1 (1)	0	0
Limbal stem cell deficiency	0	0	1 (1)	0	1 (1)	0
Ulcerative keratitis	0	0	1 (1)	0	1 (1)	0

Table 47 Characteristics of blurred vision events (CTCAE) (DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Participants with Event, n (%)	21 (22)	30 (30)	22 (23)	32 (32)	24 (25)	33 (33)
Number of Events	29	43	34	45	41	52
Event Characteristics, n/N (%)						
Serious	0/95	0/99	0/95	0/99	0/95	0/99
Study treatment related	17/95 (18)	29/99 (29)	18/95 (19)	31/99 (31)	20/95 (21)	31/99 (31)
Number of events, n/N (%)						
One	16/95 (17)	21/99 (21)	15/95 (16)	23/99 (23)	14/95 (15)	22/99 (22)
Two	3/95 (3)	6/99 (6)	4/95 (4)	6/99 (6)	6/95 (6)	6/99 (6)
Three or more	2/95 (2)	3/99 (3)	3/95 (3)	3/99 (3)	4/95 (4)	5/99 (5)
Worst Outcome, n/N (%)						
Recovered/Resolved	10/95 (11)	14/99 (14)	11/95 (12)	14/99 (14)	15/95 (16)	22/99 (22)
Recovered/Resolved with Sequelae	0/95	1/99 (1)	0/95	2/99 (2)	0/95	2/99 (2)
Recovering/Resolving	3/95 (3)	4/99 (4)	3/95 (3)	6/99 (6)	1/95 (1)	2/99 (2)
Not Recovered/Not Resolved	8/95 (8)	11/99 (11)	8/95 (8)	10/99 (10)	8/95 (8)	7/99 (7)
Fatal	0/95	0/99	0/95	0/99	0/95	0/99
Maximum Grade, n/N (%)						
Grade 1	12/95 (13)	15/99 (15)	12/95 (13)	16/99 (16)	11/95 (12)	14/99 (14)
Grade 2	5/95 (5)	13/99 (13)	6/95 (6)	13/99 (13)	9/95 (9)	15/99 (15)
Grade 3	4/95 (4)	2/99 (2)	4/95 (4)	3/99 (3)	4/95 (4)	4/99 (4)
Grade 4	0/95	0/99	0/95	0/99	0/95	0/99
Grade 5	0/95	0/99	0/95	0/99	0/95	0/99
Action Taken[a], n/N (%)						
Study treatment withdrawn	0/95	0/99	2/95 (2)	0/99	2/95 (2)	0/99
Dose reduced	2/95 (2)	3/99 (3)	2/95 (2)	3/99 (3)	2/95 (2)	3/99 (3)
Dose not changed	16/95 (17)	27/99 (27)	17/95 (18)	28/99 (28)	18/95 (19)	29/99 (29)
Dose interrupted/delayed	5/95 (5)	9/99 (9)	5/95 (5)	10/99 (10)	7/95 (7)	10/99 (10)
Dose reduced or interrupted/delayed	6/95 (6)	9/99 (9)	6/95 (6)	10/99 (10)	8/95 (8)	10/99 (10)

a. Participants could have more than 1 Action Taken and be represented more than once.

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Table 48 Blurred vision events (CTCAE) by PT (DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any Event	**21 (22)**	**30 (30)**	**22 (23)**	**32 (32)**	**24 (25)**	**33 (33)**
Vision blurred	17 (18)	25 (25)	18 (19)	27 (27)	21 (22)	27 (27)
Visual acuity reduced	3 (3)	4 (4)	5 (5)	4 (4)	5 (5)	5 (5)
Diplopia	2 (2)	4 (4)	2 (2)	4 (4)	2 (2)	4 (4)
Visual impairment	2 (2)	1 (1)	3 (3)	1 (1)	3 (3)	1 (1)

Table 49 Characteristics of dry eye events (CTCAE) (DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Participants with Event, n (%)	13 (14)	23 (23)	13 (14)	24 (24)	14 (15)	25 (25)
Number of Events	15	25	16	26	17	29
Event Characteristics, n/N (%)						
Serious	0/95	0/99	0/95	0/99	0/95	0/99
Study treatment related	13/95 (14)	23/99 (23)	13/95 (14)	24/99 (24)	14/95 (15)	24/99 (24)
Number of Events, n/N (%)						
One	12/95 (13)	21/99 (21)	12/95 (13)	22/99 (22)	13/95 (14)	22/99 (22)
Two	0/95	2/99 (2)	0/95	2/99 (2)	0/95	2/99 (2)
Three or more	1/95 (1)	0/99	1/95 (1)	0/99	1/95 (1)	1/99 (1)
Worst Outcome, n/N (%)						
Recovered/Resolved	8/95 (8)	3/99 (3)	9/95 (9)	5/99 (5)	11/95 (12)	8/99 (8)
Recovered/Resolved with Sequelae	0/95	3/99 (3)	0/95	3/99 (3)	0/95	3/99 (3)
Recovering/Resolving	0/95	2/99 (2)	0/95	2/99 (2)	0/95	1/99 (1)
Not Recovered/Not Resolved	5/95 (5)	15/99 (15)	4/95 (4)	14/99 (14)	3/95 (3)	13/99 (13)
Fatal	0/95	0/99	0/95	0/99	0/95	0/99
Maximum Grade, n/N (%)						
Grade 1	8/95 (8)	16/99 (16)	8/95 (8)	16/99 (16)	9/95 (9)	16/99 (16)
Grade 2	4/95 (4)	7/99 (7)	4/95 (4)	8/99 (8)	4/95 (4)	9/99 (9)
Grade 3	1/95 (1)	0/99	1/95 (1)	0/99	1/95 (1)	0/99
Grade 4	0/95	0/99	0/95	0/99	0/95	0/99
Grade 5	0/95	0/99	0/95	0/99	0/95	0/99
Action Taken[a], n/N (%)						
Study treatment withdrawn	0/95	0/99	0/95	0/99	0/95	0/99
Dose reduced	0/95	0/99	0/95	0/99	0/95	0/99
Dose not changed	10/95 (11)	20/99 (20)	10/95 (11)	21/99 (21)	11/95 (12)	22/99 (22)
Dose interrupted/delayed	3/95 (3)	3/99 (3)	3/95 (3)	3/99 (3)	3/95 (3)	3/99 (3)
Dose reduced or interrupted/delayed	3/95 (3)	3/99 (3)	3/95 (3)	3/99 (3)	3/95 (3)	3/99 (3)

a. Participants could have more than 1 Action Taken and be represented more than once.

Medicinal product no longer authorised

Table 50 Dry eye events (CTCAE) by PT (DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any Event	**13 (14)**	**23 (23)**	**13 (14)**	**24 (24)**	**14 (15)**	**25 (25)**
Dry eye	11 (12)	18 (18)	11 (12)	19 (19)	12 (13)	20 (20)
Eye pruritus	1 (1)	3 (3)	1 (1)	3 (3)	1 (1)	3 (3)
Foreign body sensation in eyes	0	3 (3)	0	3 (3)	0	3 (3)
Ocular discomfort	2 (2)	0	2 (2)	0	2 (2)	0

- *Infusion-related reactions*

In clinical studies, the incidence of infusion-related reactions (IRR) with belantamab mafodotin 2.5 mg/kg was 21%, and most (90%) occurred during the first infusion. Most IRRs were reported as Grade 1 (6%) and Grade 2 (12%) while 3% experienced Grade 3 IRRs. Serious IRRs were reported by 4% of patients and included symptoms of pyrexia and lethargy. Median time to onset and the median duration of the first occurrence of an IRR was 1 day. One patient (1%) discontinued treatment due to IRRs, experiencing Grade 3 IRRs at first and second infusion. No Grade 4 or 5 IRRs were reported (SmPC, section 4.8).

Although not protocol-mandated, pre-medications for IRR prophylaxis were administered to 33 (32%) participants in the 2.5 mg/kg pooled data, most commonly analgesics (26%), antihistamines (22%) and steroids (16%).

Table 51 Infusion-Related Reactions by PT, grade and cycle (DREAMM-1/DREAMM-2 Safety Population) Primary Analysis

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	<2.5 mg/kg (N=21)	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)	4.6 mg/kg (N=6)	All Treated (N=291)
Infusion-Related Reactions (Any Grade)						
Any event	**5 (24)**	**21 (20)**	**28 (20)**	**31 (19)**	**1 (17)**	**58 (20)**
Infusion-related reaction	0	17 (17)	15 (11)	16 (10)	0	33 (11)
Pyrexia	1 (5)	5 (5)	11 (8)	13 (8)	0	19 (7)
Chills	3 (14)	2 (2)	11 (8)	12 (7)	1 (17)	18 (6)
Nausea	1 (5)	2 (2)	5 (4)	5 (3)	0	8 (3)
Diarrhoea	0	2 (2)	2 (1)	2 (1)	0	4 (1)
Flushing	1 (5)	0	1 (<1)	1 (<1)	0	2 (<1)
Hypertension	0	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)
Vomiting	0	0	2 (1)	2 (1)	0	2 (<1)
Asthenia	0	1 (<1)	0	0	0	1 (<1)
Dyspnoea	0	0	1 (<1)	1 (<1)	0	1 (<1)
Fatigue	0	0	1 (<1)	1 (<1)	0	1 (<1)
Gait disturbance	1 (5)	0	0	0	0	1 (<1)
Headache	1 (5)	0	0	0	0	1 (<1)
Hypotension	0	0	1 (<1)	1 (<1)	0	1 (<1)
Lethargy	0	1 (<1)	0	0	0	1 (<1)
Presyncope	1 (5)	0	0	0	0	1 (<1)
Tachycardia	0	1 (<1)	0	0	0	1 (<1)
Infusion-Related Reactions (Grade 3/4)						
Any event	0	3 (3)	3 (2)	3 (2)	0	6 (2)
Proportions of Participants with IRRs by Cycle						
IRRs at Cycle 1	5 (24)	19 (18)	25 (18)	28 (17)	1 (17)	53 (18)
IRRs at Cycle 2 or later	0	7 (7)	5 (4)	5 (3)	0	12 (4)

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Table 52 Characteristics of infusion-related reactions (DREAMM-1/DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
Number of subjects with event, n (%)	21 (20)	28 (20)	31 (19)
Number of events	37	53	57
Event characteristics (% based on all subjects) [a], n/N (%)			
Serious	5/103 (5)	4/137 (3)	4/161 (2)
Study treatment-related	18/103 (17)	27/137 (20)	30/161 (19)
Number of occurrences (% based on all subjects), n/N (%)			
One	12/103 (12)	14/137 (10)	16/161 (10)
Two	4/103 (4)	6/137 (4)	7/161 (4)
Three or more	5/103 (5)	8/137 (6)	8/161 (5)
Outcome (% based on all subjects) [b], n/N (%)			
Recovered/resolved	19/103 (18)	24/137 (18)	27/161 (17)
Recovered/resolved with sequelae	1/103 (<1)	0/137	0/161
Recovering/resolving	1/103 (<1)	2/137 (1)	2/161 (1)
Not recovered/not resolved	0/103	2/137 (1)	2/161 (1)
Fatal	0/103	0/137	0/161
Maximum grade (% based on all subjects), n/N (%)			
Grade 1	6/103 (6)	13/137 (9)	14/161 (9)
Grade 2	12/103 (12)	12/137 (9)	14/161 (9)
Grade 3	3/103 (3)	3/137 (2)	3/161 (2)
Grade 4	0/103	0/137	0/161
Grade 5	0/103	0/137	0/161
Action taken (% based on all subjects) [a], n/N (%)			
Study treatment withdrawn	1/103 (<1)	0/137	0/161
Dose reduced	1/103 (<1)	2/137 (1)	2/161 (1)
Dose not changed	21/103 (20)	26/137 (19)	29/161 (18)
Dose interrupted/delayed	1/103 (<1)	0/137	0/161
Dose reduced or interrupted/delayed	2/103 (2)	2/137 (1)	2/161 (1)
Infusion interrupted but completed	0/103	1/137 (<1)	1/161 (<1)
Infusion stopped early and not completed	0/103	1/137 (<1)	1/161 (<1)

Source: Table 3.5100

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

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

As of the 13-month FU data cut-off for DREAMM-2, there were no additional IRR events reported in comparison to the 9-month FU.

- *Thrombocytopenia*

Thrombocytopenic events, (thrombocytopenia and platelet count decreased) occurred in 38% of patients treated with belantamab mafodotin 2.5 mg/kg. Grade 2 thrombocytopenic events occurred in 3% of patients, Grade 3 in 9%, and Grade 4 in 13%. Grade 3 bleeding events occurred in 2% of patients and no Grade 4 or 5 events were reported (SmPC, section 4.8).

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Table 53 Characteristics of thrombocytopenic events (DREAMM-2 Safety Population)

	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Participants with Event, n (%)	33 (35)	58 (59)	35 (37)	56 (57)	36 (38)	56 (57)
Number of Events	46	88	51	91	54	97
Event Characteristics, n/N (%)						
Serious	1/95 (1)	3/99 (3)	1/95 (1)	5/99 (5)	1/95 (1)	5/99 (5)
Study treatment related	19/95 (20)	38/99 (38)	21/95 (22)	38/99 (38)	22/95 (23)	38/99 (38)
Number of Events, n/N (%)						
One	22/95 (23)	42/99 (42)	23/95 (24)	40/99 (40)	23/95 (24)	39/99 (39)
Two	9/95 (9)	11/99 (11)	8/95 (8)	7/99 (7)	8/95 (8)	8/99 (8)
Three or more	2/95 (2)	5/99 (5)	4/95 (4)	9/99 (9)	5/95 (5)	9/99 (9)
Worst Outcome, n/N (%)						
Recovered/Resolved	9/95 (9)	16/99 (16)	10/95 (11)	16/99 (16)	10/95 (11)	17/99 (17)
Recovered/Resolved with Sequelae	0/95	0/99	0/95	0/99	0/95	0/99
Recovering/Resolving	3/95 (3)	3/99 (3)	2/95 (2)	4/99 (4)	1/95 (1)	3/99 (3)
Not Recovered/Not Resolved	21/95 (22)	38/99 (38)	23/95 (24)	34/99 (34)	25/95 (26)	34/99 (34)
Fatal	0/95	1/99 (1)	0/95	2/99 (2)	0/95	2/99 (2)
Maximum Grade, n/N (%)						
Grade 1	10/95 (11)	10/99 (10)	12/95 (13)	10/99 (10)	12/95 (13)	10/99 (10)
Grade 2	4/95 (4)	14/99 (14)	3/95 (3)	12/99 (12)	3/95 (3)	12/99 (12)
Grade 3	8/95 (8)	11/99 (11)	8/95 (8)	9/99 (9)	9/95 (9)	9/99 (9)
Grade 4	11/95 (12)	22/99 (22)	12/95 (13)	23/99 (23)	12/95 (13)	23/99 (23)
Grade 5	0/95	1/99 (1)	0/95	2/99 (2)	0/95	2/99 (2)
Action Taken [a], n/N (%)						
Study treatment discontinued	0/95	1/99 (1)	0/95	2/99 (2)	0/95	2/99 (2)
Dose reduced	5/95 (5)	13/99 (13)	6/95 (6)	13/99 (13)	6/95 (6)	13/99 (13)
Dose not changed	24/95 (25)	46/99 (46)	26/95 (27)	45/99 (45)	28/95 (29)	46/99 (46)
Dose delayed	0/95	6/99 (6)	2/95 (2)	6/99 (6)	2/95 (2)	6/99 (6)
Dose reduced or delayed	5/95 (5)	15/99 (15)	7/95 (7)	15/99 (15)	7/95 (7)	15/99 (15)

Source: DREAMM-2 CSR Table 3.0280, DREAMM-2 90-DU Table 3.0280; DREAMM-2 13-Month FU Table 3.0280

a. Participants could have more than 1 Action Taken and be represented more than once.

Table 54 Thrombocytopenic events by preferred term (DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any Event [a]	**33 (35)**	**58 (59)**	**35 (37)**	**56 (57)**	**36 (38)**	**56 (57)**
Thrombocytopenia	20 (21)	44 (44)	23 (24)	46 (46)	23 (24)	46 (46)
Platelet count decreased	15 (16)	14 (14)	14 (15)	11 (11)	15 (16)	11 (11)
Cerebral haemorrhage	0	1 (1)	0	2 (2)	0	2 (2)

a. Designated by the site as a thrombocytopenic AESI for Participant 6002; Platelets were 52 Gi/L at the event and were always >50 Gi/L during the study.

b. Note: The total number of participants who had a thrombocytopenic event decreased by two in the 3.4 mg/kg cohort in the updated data. This was due to the deletion of 3 events of platelet count decreased that were confirmed as not clinically significant by the investigator (therefore not considered an AE), and due to the addition of 1 new event of cerebral haemorrhage.

Original product no longer authorised

- *Infections*

Upper respiratory tract infections were commonly reported across the belantamab mafodotin clinical programme and were mostly mild to moderate (Grade 1 to 3), occurring in 9% in patients treated with belantamab mafodotin 2.5 mg/kg. There were no SAEs of upper respiratory tract infections reported. Pneumonia was the most frequent infection reported in 11% of patients treated with belantamab mafodotin 2.5 mg/kg. Pneumonia was also the most frequent SAE, reported in 7% of patients. Infections with a fatal outcome were primarily due to pneumonia (1%).

Serious adverse event/deaths/other significant events

- *Serious adverse events*

In the 2.5 mg/kg pooled data, an SAE was reported for 42 (41%) participants. A treatment-related SAE was reported for 12 (12%) participants. The most commonly reported treatment-related SAE PT was IRR, reported for 4 (4%) participants, followed by pyrexia and sepsis, each reported for 2 (2%) participants.

Table 55 SAEs by PT Reported for ≥2 participants in any cohort (DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any Event	**38 (40)**	**47 (47)**	**38 (40)**	**47 (47)**	**40 (42)**	**47 (47)**
Pneumonia	4 (4)	12 (12)	6 (6)	14 (14)	7 (7)	14 (14)
Pyrexia	6 (6)	5 (5)	6 (6)	5 (5)	7 (7)	5 (5)
Cerebral haemorrhage	0	2 (2)	0	3 (3)	0	3 (3)
Febrile neutropenia	0	3 (3)	0	3 (3)	0	3 (3)
Thrombocytopenia	1 (1)	2 (2)	1 (1)	3 (3)	1 (1)	3 (3)
Cellulitis	1 (1)	1 (1)	1 (1)	2 (2)	1 (1)	2 (2)
Epistaxis	1 (1)	2 (2)	1 (1)	2 (2)	1 (1)	2 (2)
Escherichia urinary tract infection	0	2 (2)	0	2 (2)	0	2 (2)
General physical health deterioration	0	2 (2)	0	2 (2)	0	2 (2)
Hyperviscosity syndrome	0	2 (2)	0	2 (2)	0	2 (2)
Influenza	0	2 (2)	0	2 (2)	0	2 (2)
Infusion related reaction	3 (3)	2 (2)	3 (3)	2 (2)	3 (3)	2 (2)
Osteolysis	0	2 (2)	0	2 (2)	0	2 (2)
Sepsis	2 (2)	2 (2)	2 (2)	2 (2)	2 (2)	2 (2)
Upper respiratory tract infection	0	2 (2)	0	2 (2)	0	2 (2)
Acute kidney injury	2 (2)	1 (1)	2 (2)	1 (1)	2 (2)	1 (1)
Pathological fracture	0	2 (2)	0	1 (1)	0	1 (1)
Pleural effusion	2 (2)	1 (1)	2 (2)	1 (1)	2 (2)	1 (1)
Gastrointestinal haemorrhage	1 (1)	1 (1)	1 (1)	1 (1)	2 (2)	1 (1)
Hypercalcaemia	4 (4)	0	4 (4)	0	4 (4)	0
Hypokalaemia	2 (2)	0	2 (2)	0	2 (2)	0
Lung infection [0]	3 (3)	2 (2)	0	0	0	0
Staphylococcal sepsis	2 (2)	0	2 (2)	0	2 (2)	0
Vascular device infection	2 (2)	0	2 (2)	0	2 (2)	0

Medicinal product no longer authorised

- *Deaths*

Table 56 Summary of deaths (DREAMM-2 Safety Population)

	Number (%) of Participants			
	Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Participant Status				
Dead	31 (33)	31 (31)	38 (40)	42 (42)
Alive at the last contact, follow-up ended	4 (4)	2 (2)	6 (6)	2 (2)
Alive at the last contact, follow-up ongoing	60 (63)	66 (67)	51 (54)	55 (56)
Primary Cause of Death				
Disease under study	25 (26)	23 (23)	33 (35)	32 (32)
SAE possibly related to study treatment	1 (1)	1 (1)	1 (1)	2 (2)
Other [a]	2 (2)	7 (7)	2 (2)	7 (7)
Unknown	3 (3)	0	3 (3)	1 (1)
Time to Death from Last Dose				
≤30 days	8 (8)	13 (13)	8 (8)	16 (16)
>30 days	23 (24)	18 (18)	30 (32)	26 (26)

Source: DREAMM-2 CSR Table 3.0450, DREAMM-2 90-DU Table 3.0450
SAE: serious adverse event.
a. A primary cause of death of 'other' means the death was unrelated to the disease under study and unrelated to study treatment.

Laboratory findings

Renal parameters

Renal failure is a common complication of MM. In preclinical studies, degeneration of the kidney and glomerulopathy associated with proteinuria were observed. In the 2.5 mg/kg group, 26% of patients had an increase from baseline in serum creatinine. One patient experienced a grade 4 increase and developed an acute kidney failure, not considered to be related to the study treatment. 18% of patients had a decrease from normal to low GFR. In approximately half of these patients, the decrease in eGFR was associated with disease progression. Four patients had a post-baseline albumin creatinine ratio of >2000 and required treatment interruption as per protocol. One of the patients discontinued the treatment permanently due to this AE. Proteinuria was reported in 4% of patients in 2.5 mg/kg group, 3/4 cases being grade 1 events.

Haematology assessments

Decreased cellularity of the bone marrow and adaptive effects of the hematopoietic system were observed in the preclinical studies. In the 2.5 mg/kg pooled data, the most frequent increases to any AE grade were in platelets decreased (63% of patients), lymphocytes (lymphocyte count decreased) (50%), leukocytes (white blood cell decreased) (36%), and haemoglobin (anaemia) (32%). Increases to grade 3 occurred in 17% of patients for haemoglobin (anaemia), and lymphocytes (lymphocyte count decreased), reported for 19% of patients. Platelets decreased was reported as a grade 4 event for 12 (12%) patients.

Medicinal product no longer authorised

Table 57 Worst Case Haematology Grade Changes from Baseline Grade (cut-off date of 31 January 2020)

Test Category	Number (%) of Participants	
	Belantamab Mafodotin Q3W	
	13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg Frozen (N=99)
Haemoglobin (Haemoglobin increased) (g/L), n	95	97
Any Grade Increase	2 (2)	0
Haemoglobin (Anaemia) (g/L), n	95	97
Any Grade Increase	33 (35)	44 (45)
Increase to Grade 3	19 (20)	30 (31)
Lymphocytes (Lymphocyte count increased) (10^9/L), n	95	97
Any Grade Increase	1 (1)	1 (1)
Lymphocytes (Lymphocyte count decreased) (10^9/L), n	95	97
Any Grade Increase	48 (51)	46 (47)
Increase to Grade 3	16 (17)	24 (25)
Increase to Grade 4	5 (5)	5 (5)
Neutrophils decreased (10^9/L), n	95	97
Any Grade Increase	30 (32)	47 (48)
Increase to Grade 3	4 (4)	10 (10)
Increase to Grade 4	6 (6)	3 (3)
Platelets decreased (10^9/L), n	95	97
Any Grade Increase	62 (65)	74 (76)
Increase to Grade 3	8 (8)	11 (11)
Increase to Grade 4	13 (14)	25 (26)
Leukocytes (Leukocytosis) (10^9/L), n	95	97
Any Grade Increase	0	0
Leukocytes (White blood cell decreased) (10^9/L), n	95	97
Any Grade Increase	37 (39)	44 (45)
Increase to Grade 3	5 (5)	8 (8)
Increase to Grade 4	3 (3)	3 (3)

Note: Subjects with missing baseline grade are assumed to have baseline of Grade 0. All increases are an increase in grade from baseline.

Liver-related assessments

In preclinical studies, hepatocellular necrosis and increased liver enzymes were observed. Increased alanine aminotransferase (22%), aspartate aminotransferase (58%), alkaline phosphatase (26%), bilirubin (5%) and gamma glutamyl transferase (26%) were observed, all showing some degree of dose proportionality (higher frequency of increased values in 3.4 mg/kg group). However, increases to grade 3/4 were infrequent, with the exception of gamma glutamyl transferase (increase to grade 3 in 6% of patients). ALT was increased more than 3 x Upper Limit of Normal (ULN) in only one patient in 2.5 mg/kg group (<1%). No patient in either DREAMM-1 or DREAMM-2 met the Hy's law criteria.

Medicinal product no longer authorised

Table 58 Hepatobiliary Laboratory Abnormalities (Primary Analysis)

Laboratory Criteria [a]	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
n	101	135	159
ALT≥3xULN - <5xULN	1 (<1)	4 (3)	4 (3)
ALT≥5xULN - <10xULN	0	0	0
ALT≥10xULN - <20xULN	0	0	0
n	100	135	158
BIL ≥2xULN [b]	1 (1)	0	0
n	100	135	158
ALT ≥3xULN and BIL ≥2xULN [b]	0	0	0
n	8	38	38
ALT ≥3xULN and INR >1.5 [c]	0	0	0
n	100	135	158
ALT ≥3xULN and BIL ≥2xULN [b] and (ALP <2xULN)	0	0	0
n	101	135	159
Hepatocellular injury [d]	0	2 (1)	2 (1)
n	100	135	158
Hepatocellular injury [d] and BIL ≥2xULN [b]	0	0	0
n	101	135	159
ALP ≥2xULN and Baseline ALP <2xULN or Baseline ALP missing	7 (7)	18 (13)	18 (11)
Time from First Dose to First ALT Elevation ≥3xULN (days)			
n	1 (<1)	4 (3)	4 (3)
Mean (SD)	287.0 (NA)	57.0 (98.15)	57.0 (98.15)
Median (range)	287.0 (287 to 287)	11.0 (2 to 204)	11.0 (2 to 204)

Source: Table 3.7400

ALP: alkaline phosphatase; ALT: alanine transaminase; BIL: bilirubin; INR: International Normalised Ratio; ULN: upper limit of normal.

Note: Table includes all non-missing post-baseline lab assessments.

a. Subjects may be counted in more than one category of 'Laboratory Criteria'.
b. If direct bilirubin is available, then direct bilirubin must also be ≥35% when total bilirubin is ≥2xULN, in order to satisfy the criteria. Bilirubin value is on or up to 28 days after ALT value.
c. INR value is on or up to 28 days after ALT value.
d. Hepatocellular injury is defined as ((ALT/ALT ULN)/(ALP/ALP ULN)) ≥5 and ALT ≥3xULN. ALT and ALP values must occur on the same day.

Safety in special populations

No significant differences were observed in safety profile based on baseline renal impairment status. However, majority of the patients were categorized to have a mild renal impairment (n=48) and only two patients had severe renal impairment in the 2.5 mg/kg group. In population pharmacokinetic analyses, baseline renal function was not found to be a significant factor accounting for interindividual variability.

No safety data has been presented based on hepatic insufficiency.

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Table 59 AEs by age groups and by MedDRA terms (9-month data cut)

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs	134 (99%)	116 (100%)	38 (100%)	2 (67%)
Serious AEs – Total	56 (41%)	53 (46%)	21 (58%)	0
Fatal	4 (3%)	7 (6%)	1 (3%)	0
Hospitalization/prolong existing hospitalization	54 (40%)	52 (45%)	18 (50%)	0
Life-threatening	7 (5%)	2 (2%)	0	0
Disability/incapacity	0	1 (<1%)	0	0
Other (medically significant)	5 (4%)	2 (2%)	3 (8%)	0
AE leading to drop-out	13 (10%)	14 (12%)	3 (8%)	0
Psychiatric disorders	12 (9%)	15 (13%)	6 (17%)	0
Nervous system disorders	46 (34%)	30 (26%)	8 (22%)	1 (33%)
Accidents and injuries	31 (23%)	31 (27%)	12 (33%)	0
Cardiac disorders	12 (9%)	14 (12%)	2 (6%)	0
Vascular disorders	19 (14%)	18 (16%)	8 (22%)	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	65 (48%)	61 (53%)	19 (53%)	2 (67%)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	16 (12%)	19 (16%)	10 (28%)	0
Other AE appearing more frequently in older patients:				
Keratopathy	70 (51%)	72 (62%)	24 (67%)	1(33%)
Infusion related reactions	13 (10%)	16 (14%)	5 (14%)	0
Aspartate aminotransferase (AST) increased	36 (26%)	21 (18%)	12 (33%)	0
Hypercalcaemia	18(13%)	17 (15%)	7 (19%)	0
Asthenia	6 (4%)	8 (7%)	4 (11%)	0
White blood cell count decreased	7 (5%)	7 (6%)	4 (11%)	0
Decreased lymphocyte count	14 (10%)	11 (9%)	6 (17%)	0
Increased GGT	15 (11%)	12 (10%)	6 (17%)	0
UTI	5 (4%)	7 (6%)	4 (11%)	2 (67%)
Muscular weakness	4 (3%)	3 (3%)	4 (11%)	0
Increased blood creatinine	7 (5%)	11 (9%)	8 (22%)	1 (33%)
Visual acuity decreased	1 (<1%)	7 (6%)	2 (6%)	0
Weight decreased	4 (3%)	2 (2%)	3 (8%)	1 (33%)

Immunological events

In silico modelling

Using an *in silico* approach, the potential immunogenicity risk for belantamab mafodotin was calculated using T-cell epitopes predicted with the TEpredict software. Belantamab mafodotin scored in same range as other therapeutic mAbs that have low incidence of clinical immunogenicity.

Immunogenicity assessment

Serum samples for immunogenicity assessment were collected on day 1 of cycles 1, 2, 3, 6, 9, 12 and 16, on day 15 of cycle 1 and at the end of study in study DREAMM-1, and on day 1 of cycles 1, 2, 3, 6, 9, 12, and on every 6 cycles thereafter until end of treatment in study DREAMM-2.

In study DREAMM-1, all patients tested negative for ADAs both at baseline and in all assessments after treatment. In study DREAMM-2, 5/211 patients tested positive for anti-belantamab mafodotin ADAs, with one patient testing positive for NAbs at baseline. Only one of these patients tested positive after treatment. A total of 2 patients tested positive for ADAs at a single time point after treatment with one patient testing positive for NAbs. Thus, 1/274 patients with post-baseline ADA results had treatment-emergent ADAs. All antibody titers were close to sensitivity limit of the assay.

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Safety related to drug-drug interactions and other interactions

No specific clinical studies assessing the effects of other drugs or extrinsic factors on belantamab mafodotin, total mAb, or cys-mcMMAF pharmacokinetics were submitted (see discussion on clinical safety).

Discontinuation due to adverse events

In 2.5 mg/kg group, 9% of patients discontinued treatment due to an AE. The most commonly reported AE that led to permanent discontinuation of study treatment was keratopathy, reported for 3 (3%) participants.

Table 60 Adverse Events Leading to Permanent Discontinuation of Study Treatment by PT (DREAMM-2 Safety Population)

Preferred Term	Number (%) of Participants					
	Belantamab Mafodotin Q3W					
	Primary Analysis (21Jun19)		9-Month FU (20Sep19)		13-Month FU (31Jan20)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any Event	8 (8)	10 (10)	9 (9)	12 (12)	9 (9)	12 (12)
Cerebral haemorrhage	0	2 (2)	0	3 (3)	0	3 (3)
Keratopathy	2 (2) [a]	3 (3)	1 (1)	3 (3)	1 (1)	3 (3)
Pneumonia	0	2 (2)	0	2 (2)	0	2 (2)
Acute myeloid leukaemia	0	1 (1)	0	1 (1)	0	1 (1)
Cardiac arrest	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)
Device related sepsis	0	0	0	1 (1)	0	1 (1)
Haemophagocytic lymphohistiocytosis	0	1 (1)	0	1 (1)	0	1 (1)
Viral infection	0	1 (1)	0	1 (1)	0	1 (1)
Headache	1 (1)	0	1 (1)	0	1 (1)	0
Herpes simplex pneumonia	1 (1)	0	1 (1)	0	1 (1)	0
Infusion related reaction	1 (1)	0	1 (1)	0	1 (1)	0
Sepsis	1 (1)	0	1 (1)	0	1 (1)	0
Urine albumin/creatinine ratio increased	1 (1)	0	1 (1)	0	1 (1)	0
Vision blurred	0	0	1 (1)	0	1 (1)	0
Visual acuity reduced	0	0	1 (1)	0	1 (1)	0

AE: adverse event; PT: preferred term.
a. One participant was reported in the primary analysis as having an AE of keratopathy that led to withdrawal, that was later confirmed as not having led to withdrawal and is reflected in the updated data.

No other reason for discontinuation was reported for more than one patient.

Post marketing experience

N/A

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2.6.1. Discussion on clinical safety

Single arm study settings impair the causality assessment of several key unfavourable effects. Adverse effects of disease under study, previous treatments and adverse events predicted based on mechanism of action and structure of belantamab mafodotin are overlapping, and only rough estimates for frequencies of these events can be made in this heterogeneous patient population. Dose-dependency of these adverse effects is not evident for rare AEs, and absence of dose-dependency may in some cases be due to small differences between exposure levels achieved between the two dose levels studied. This issue will be addressed in the randomized confirmatory study DREAMM-3 which will evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM (see Annex II and RMP).

The number of patients treated with belantamab mafodotin in studies DREAMM-1 and DREAMM-2 is limited. A total of 103 patients have been exposed to the proposed registration dose of 2.5 mg/kg as a single agent, majority of them in the pivotal study DREAMM-2. In the 13-month follow-up, the median number of treatment cycles was 3 (range 1-15), and median time on treatment 9.3 weeks. Treatment was discontinued due to disease progression in majority of cases and thus, loss of benefit, rather than tolerability, mainly determined the duration of exposure. The median time on study was 12.35 months, and therefore for majority of the patients, follow-up covering the expected time on treatment is available. Moreover, the most common toxicities (keratopathy and other ocular AEs, thrombocytopenia) have mainly been reported within this period, and no major differences were reported between the primary analysis (data cut-off 21 June 2019) and 13-month follow-up (data cut-off 31 January 2020) despite significantly longer follow-up time. The pivotal study is ongoing, and 10 patients (11%) in the 2.5 mg/kg cohort were receiving study treatment at the time of the latest data cut-off. The final study report from DREAMM-2 will provide further information on the AEs (see Annex II and RMP).

The frozen formulation of belantamab mafodotin has been used in majority of patients so far. The lyophilized formulation, intended for commercial use, has been tested in a separate cohort of 25 patients treated with 3.4 mg/kg dose in DREAMM-2. The incidence of SAEs was numerically higher in the lyophilised cohort compared with the frozen dose cohort (63% vs 47%). However, the difference does not seem to be driven by any particular adverse event. The various numerical differences observed in side-by side comparison of the two formulations are likely attributed to the small number of participants in the lyophilized cohort and different baseline disease characteristics. The final study report of DREAMM-2 will provide further information on the AEs (see Annex II and RMP).

Two different dose levels were compared in the pivotal study DREAMM-2. Dose dependency both in terms of frequency and severity or majority of the AEs were observed. Selection of the registration dose was largely based on better tolerability of the 2.5 mg/kg dose as compared to 3.4 mg/kg. Incidence of thrombocytopenia, particularly those associated with bleeding events, neutropenia, infections and increased incidence and severity of corneal events were considered to favour selection of the lower dose level of 2.5 mg/kg. Moreover, more deaths were reported in the 3.4 mg/kg group. Although these AEs are agreed to be serious, the number of each of these events in this small single-arm study is very low, and causality difficult to determine due to overlapping toxicities related to the disease under study and previous treatments. However, the small differences in individual AEs are consistent between the dose groups, and the overall safety profile of the lower dose level is more favourable.

Although there is more clinical experience with 3.4 mg/kg dosing (n=161) and the commercial formulation has only been tested with 3.4 mg/kg dosing, from safety perspective selection of the lower dose level of 2.5 mg/kg is supported. The safety differences observed in clinical studies may become more exaggerated in clinical use due to likely less vigorous patient follow-up and dose modifications in

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clinical practice. Due to small differences in median exposure between the dose levels, safety data from the higher dose level 3.4 mg/kg is considered relevant for assessment of the overall safety profile of belantamab mafodotin.

Numerous dose reductions and delays were applied; keratopathy events were the most common reason for dose modifications in both dose groups. Discontinuation of study treatment was rare, only 9% of patients in the pooled 2.5 mg/kg cohort permanently discontinued treatment due to an AE. The most common reason for discontinuation was corneal events. Cautious criteria for dose modifications likely prevented progression of adverse events to a point when discontinuation was necessary. The follow-up and dose modification criteria are considered adequate to ensure that dose modifications are guided in a similar fashion in clinical use (SmPC, section 4.2). Moreover, higher exposure resulting from different dose modification criteria is unlikely to pose unexpected safety concerns, as safety data from higher exposure level achieved in 3.4 mg/kg dose group (2.95 mg/kg/3 weeks) is available.

Adverse events were reported in nearly all the patients (98%), and 83% of patients reported a grade 3 or 4 AE. The most frequent adverse reactions (≥30%) (any grade) were keratopathy (71%) and thrombocytopenia (38%) (SmPC, section 4.8).

Common eye-related AEs included vision blurred (25%), dry eye (15%) and photophobia (4%). Other common adverse events in the 2.5 mg/kg pooled data were anaemia (27%) and nausea (25%). For AEs possibly related to disease under study or previous medications (thrombocytopenia, anaemia, neutropenia) assessment of causality is complicated. Worsening of these events during treatment can also be caused by disease progression. However, a clear dose dependency has been shown for these events indicating that study treatment contributes to these AEs.

Events like keratopathy were closely monitored during the study, and thus likely assigned as treatment related. For some AEs like pyrexia and infections, evaluation of causality seemed to vary between apparently similar cases. Overall, in this heavily pre-treated population, distinction between disease symptoms and AEs is, in general, very challenging in this open label, uncontrolled study.

Keratopathy (31%), thrombocytopenia (22%) and anaemia (21%) were the most common grade 3 or 4 AEs reported in 2.5 mg/kg pooled data.

Serious adverse events were reported in 42% of the patients in the pooled 2.5mg/kg cohort. The most commonly reported serious adverse reactions were pneumonia (7%), pyrexia (7%) and Infusion-related reactions (IRRs) (3%) (SmPC, section 4.8). There is no clear difference in number of individual SAEs between the dose levels.

In the 2.5 mg/kg group, 32 patients died during the study. The primary cause of death was disease under study for 25% of patients. In the 13-month follow-up data, 7 new deaths were reported, all considered to be due to disease under study. One patient had a fatal SAE (sepsis) that was considered to be related to the study treatment. Several of the fatal events reported during the clinical studies included adverse events of special interest for belantamab mafodotin. Due to lack of control/comparator group, last line disease setting and varying previous treatment regimens, the likelihood of specific disease-related complications is difficult to estimate. Additional follow up data provided did not suggest that the events were causally related, or particularly that belantamab mafodotin may have contributed to events.

Limited data are available on progression of asymptomatic keratopathy findings during treatment. Based on data from 28 patients who continued treatment despite corneal findings, the AEs did lead to symptoms and dose modifications later, but the outcome was not altered due to the delay.

Corneal adverse reactions have been reported with the use of BLENREP. The most commonly reported adverse reactions were keratopathy or microcyst-like epithelial changes in corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye. Patients with

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a history of dry eye were more prone to develop changes in the corneal epithelium. Changes in visual acuity may be associated with difficulty in driving or operating machinery (SmPC, section 4.4).

Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, should be performed at baseline, before the subsequent 3 treatment cycles and during treatment as clinically indicated. 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 (SmPC, section 4.4).

Patients experiencing keratopathy with or without changes in visual acuity may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings (SmPC, section 4.4).

Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. These should be managed promptly and as clinically indicated by an eye care professional. Treatment with BLENREP should be interrupted until the corneal ulcer has healed (SmPC, section 4.4).

Corneal adverse reactions may include findings upon eye examination and/or changes in visual acuity. The treating physician should review the patient's ophthalmic examination report before dosing and should determine the dose of BLENREP based on the highest category from the report in the most severely affected eye as both eyes may not be affected to the same degree.

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

- The corneal examination finding(s) and the decline in best corrected visual acuity (BCVA).
- If there is a decline in BCVA, the relationship of corneal examination findings to BLENREP should be determined.
- The highest category grading for these examination findings and BCVA should be reported to the treating physician (SmPC, section 4.2).

An ocular sub-study was performed to further characterize the keratopathy events, and to explore the possibility to use topical corticosteroid administration to prevent the eye-related adverse events. The sample size was small (17 patients in the 2.5 mg/kg group, and 13 patients in the 3.4 mg/kg group). Topical corticosteroid did not appear to prevent keratopathy or any other ocular symptoms. This is in contrast with published results (Eaton JS et al, 2015, Donaghy H. 2016, Matulonis UA et al, 2019) from other MMAF-conjugated ADCs. Corneal epithelial cells do not express BCMA, and as with other ADCs, the toxicity has been shown to be caused by macropinocytosis of the ADC into the cells and intracellular release of cys-mcMMAF. However, as there does not appear to be inflammatory component to the ocular toxicity, and it was confirmed that systemic corticosteroids were not a significant confounding factor in the sub-study, no additional studies are deemed necessary. As corticosteroids are themselves associated with potential adverse events, the available information does not support prophylactic use of topical corticosteroids to prevent belantamab mafodotin-induced keratopathy. Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye has been classified as an important identified risk in the RMP. The corneal events and visual changes can be managed in clinical practice through appropriate monitoring, as well as dose modifications, and additional risk minimisation measures have been implemented in order to mitigate the possible risks of keratopathy. The additional risk minimisation activity will help oncologists, eye care professionals and patients to understand the corneal risks associated with belantamab mafodotin, so that corneal examination findings, and/or visual changes can be promptly identified and managed according to the product labelling (see Annex II and RMP).

Thrombocytopenic events (thrombocytopenia and platelet count decreased) were frequently reported.

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Thrombocytopenia may lead to serious bleeding events, including gastrointestinal and intracranial bleeding. Complete blood counts should be obtained at baseline and monitored during treatment, as clinically indicated. Patients experiencing Grade 3 or 4 thrombocytopenia or those on concomitant anticoagulant treatments may require more frequent monitoring and should be managed with a dose delay or dose reduction. Supportive therapy (e.g. platelet transfusions) should be provided according to standard medical practice (SmPC, section 4.4).

Infusion-related reactions have been reported with belantamab mafodotin. Most IRRs were Grade 1-2 and resolved within the same day. If a grade 2 or higher infusion- related reaction occurs during administration, the infusion rate should be reduced or the infusion should be stopped, depending on the severity of the symptoms. It is recommended to institute appropriate medical treatment and restart infusion at a slower rate, if the patient's condition is stable. If Grade 2 or higher IRR occurs, premedication for subsequent infusions should be administered (SmPC, section 4.4). IRRs were more common in patients who received pre-medication (38%) as compared to the patients who did not (16%). However, this difference may be biased as the patients who were pre-treated were likely identified as high-risk patients.

Although not identified as AESIs, infections are considered to be relevant AEs for safety of belantamab mafodotin. Infections were the most frequent treatment-related SAEs. The frequency and severity, and particularly clinical consequences of neutropenia, appeared to be dose dependent. The targeted therapeutic effect of belantamab mafodotin is depletion of B cells, and thus increased risk of infections is plausible. In a patient population prone to infections, consequences of these effects may be more pronounced. Events within SOC infections and infestations were reported for 43% of patients in 2.5 mg/kg pooled data, and 56% of patients in 3.4 mg/kg group. In analysis of additional information on infection events, no clear pattern regarding types or timing of the infections, or patient sub-groups, apart from higher incidence in older patients. The PI has been updated to reflect the most recent AE data from the 13-month update. Increased risk of infections due to immunosuppression and/or neutropenia has been classified as an important potential risk in the RMP.

The immunogenicity potential of belantamab mafodotin appears to be low. Two out of the 274 exposed patients with post-baseline results tested positive for ADAs, and treatment-emergent ADAs were only observed in one patient. All antibody titers were low, near the sensitivity of the assays used. Very limited data is thus available on effect of ADAs, and due to lack of post-baseline PK data from the only NAb positive patient, the effect of NAbs could not be determined. The immunogenicity potential of belantamab mafodotin is considered to be low; however, additional data from on-going studies will be provided for a more comprehensive analysis of immunogenicity and its clinical role (see RMP).

BLENREP has a moderate influence on the ability to drive or use machines. Patients should be advised to use caution when driving or operating machines as BLENREP may affect their vision (SmPC, section 4.7).

There has been no experience of overdosage in clinical studies. There is no known specific antidote for belantamab mafodotin overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate supportive treatment should be instituted immediately (SmPC, section 4.9).

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded (SmPC, section 4.4).

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially "sodium-free" (SmPC, section 4.4).

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

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Additional safety data needed in the context of a conditional MA

The various numerical differences observed in side-by side comparison of the two formulations are likely attributed to the small number of participants in the lyophilized cohort and different baseline disease characteristics. Final study report of DREAMM-2 will provide further information on resolution of the AEs (see Annex II and RMP).

Single arm study setting impairs the causality assessment of several key unfavourable effects. Adverse effects of disease under study, previous treatments and adverse events predicted based on mechanism of action and structure of belantamab mafodotin are overlapping, and only rough estimates for frequencies of these events can be made in this heterogeneous patient population. This issue will be addressed in the randomized confirmatory study DREAMM-3 which will evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM (see Annex II and RMP).

2.6.2. Conclusions on the clinical safety

Overall, the toxicity profile is considered to be acceptable in the target patient population. Ocular toxicities and their clinical management are currently considered to be the most important safety concern. Haematological toxicities are also significant, both due to overlapping toxicity profile with previous treatments and disease under study, and due to possibly serious clinical consequences (infections and bleeds). However, the follow-up and dose modification recommendations are considered sufficient to manage the observed toxicity profile in clinical practice. Relevant safety information and recommendations are presented in the SmPC.

Additional studies are expected to provide further information regarding effects of belantamab mafodotin on keratopathy, nephrotoxicity and increased risk of infections (due to immunosuppression and/or neutropenia) and also in patients with severe renal impairment and hepatic impairment (see RMP).

The safety has been considered sufficiently characterised in the context of a conditional MA. Additional data from confirmatory studies will be provided in support of the overall safety profile of belantamab mafodotin.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- In order to confirm the efficacy and safety of BLENREP in relapsed/refractory multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-2 (205678) study investigating the efficacy of belantamab mafodotin in patients with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody. The final results of the study should be submitted by April 2021.

- In order to confirm the efficacy and safety of BLENREP in multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-3 (207495) study comparing the efficacy of belantamab mafodotin vs. pomalidomide plus low dose dexamethasone (pom/dex) in patients with relapsed/refractory multiple myeloma. The final report of the study should be submitted by July 2024.

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2.7. Risk Management Plan

Safety concerns

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

Pharmacovigilance plan

Table 61 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody (DREAMM-2) - Ongoing	Primary: To evaluate the clinical efficacy of 2 doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma Secondary: To further evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM To evaluate the safety of belantamab mafodotin in participants with RRMM To evaluate the pharmacokinetic profile of belantamab mafodotin To assess anti-drug antibodies (ADAs) against belantamab mafodotin Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin To evaluate disease and treatment related symptoms and impact on function and health-related quality-of life	Standard clinical and laboratory tests Collection of AEs and SAEs AEs of special interest Ocular findings on ophthalmic exam Further characterization of important identified and potential risks: • Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye • Nephrotoxicity • Increased risk of infections due to immunosuppression and/or neutropenia	Final study report Final study report submission	Jan 2021 Apr 2021
207495 (DREAMM-3): Phase III Study of Single Agent	Primary: To compare the efficacy with belantamab mafodotin vs pomalidomide plus	Incidence of AEs and changes in laboratory parameters	Projected Primary	Aug 2021

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Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma – Planned	low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma Key Secondary: To compare the overall survival with belantamab mafodotin vs pom/dex in participants with RRMM Secondary: To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the pharmacokinetic profile of belantamab mafodotin To assess anti-drug antibodies (ADAs) against belantamab mafodotin To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects To evaluate and compare changes in symptoms and health-related quality of life (HRQOL)of belantamab mafodotin to pom/dex To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better for belantamab mafodotin vs pom/dex	Ocular findings on ophthalmic exam Symptomatic adverse effects as measured by the PRO-CTCAE and OSDI Changes in safety assessments, including vital signs and ECGs Further characterization of important identified and potential risks: • Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye • Nephrotoxicity • Increased risk of infections due to immunosuppression and/or neutropenia	endpoint analysis Study report submission Overall survival and Final analysis	2Q 2022 Jul 2024
Category 3- Required additional pharmacovigilance activities				
209626: A Phase 1 open label study of GSK2857916 in relapsed/refractory multiple myeloma patients with renal impairment	Primary: To describe the effects of renal impairment on the pharmacokinetics of belantamab mafodotin in participants with RRMM and with severe renal impairment, ESRD (not on dialysis) or ESRD (on dialysis) compared to participants with normal renal function Secondary: To evaluate safety and tolerability using parameters, including adverse events, vital signs, ECGs, and clinical laboratory assessments in participants with RRMM who have normal or impaired renal functions	Safety of belantamab mafodotin in patients with severe renal impairment Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic parameters;dialysate PK parameters, as data permit Change from baseline in vital signs (blood pressure and heart rate), monitoring and incidence of adverse events, toxicity	Final study report	1Q2025

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

Risk minimisation measures

Table 62 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Identified Risks		
Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye	**Routine risk minimisation measures**: SmPC Sections: 4.2, 4.4, 4.8 PL Sections: 2, 4 Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4. Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: Healthcare professionals (haematologists/oncologists/eye care professionals) educational materials: • The Summary of Product Characteristics	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow-up questionnaire **Additional pharmacovigilance activities**: 205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody (DREAMM-2) - Ongoing 207495 (DREAMM-3): Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM-3)

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

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Safety in patients with severe renal impairment	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: 209626: A Phase 1 open label study of GSK2857916 in relapsed/refractory multiple myeloma patients with renal impairment
Safety in patients with hepatic impairment	**Routine risk minimisation measures**: Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: 209627: A Phase 1 open label study of GSK2857916 in patients with relapsed/refractory multiple myeloma and hepatic impairment

Conclusion

The CHMP and PRAC considered that the RMP version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that belantamab mafodotin has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers belantamab mafodotin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

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2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, BLENREP (belantamab mafodotin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

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

3.1.1. Disease or condition

Multiple myeloma is a rare and incurable disease of the plasma cells which typically affects adults who are more than 60 years of age (median age is at diagnosis is ~ 70 years). It is the second most common haematological malignancy (after non-Hodgkin's lymphoma [NHL], representing 1% of all cancers and 2% of all cancer deaths. Progress has been made over the last 15 years in the treatment of multiple myeloma, such that survival of patients with newly diagnosed multiple myeloma has increased from approximately 3 years from the years 1985 to 1998 (Kyle 2003) to 6 to 10 years (Moreau 2015).

3.1.2. Available therapies and unmet medical need

Current treatment of MM includes glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell transplantation (ASCT), PIs (such as bortezomib, carfilzomib and ixazomib), mAbs (such as daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat. There is a clear unmet medical need for new therapies because the treatment options are very limited, and their median OS is around 3-5 months.

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With the approval of daratumumab and its wide use in combinations in earlier lines of MM treatment, a new population of patients is created who have become refractory to all available agents (including daratumumab). This population can be referred to as triple-class refractory MM and it encompasses those patients with disease refractory to at least 1 PI, 1 immunomodulatory agent, and 1 anti-CD38 mAb (such as daratumumab).

Therefore, the discovery of therapies with new mechanisms of action to overcome drug resistance, also including patients pre-treated with daratumumab, remains as an unmet medical need.

3.1.3. Main clinical studies

The clinical package of belantamab mafodotin was primarily supported by data from a phase II, open-label, 2-arm, randomized, multicentre study to evaluate the efficacy and safety of belantamab mafodotin monotherapy at a dose of 2.5 mg/kg or 3.4 mg/kg IV, Q3W, in participants with RRMM who had 3 or more prior lines of treatment, were refractory to a proteasome inhibitor and an immunomodulatory agent, and for whom treatment with an anti-CD38 antibody had failed (study 205678 [DREAMM-2]).

3.2. Favourable effects

• The ORR per IRC based on IMWG criteria was 32% (97.5%CI: 21.7, 43.6) in the 2.5 mg/kg dose cohort (13 months follow up). There was a further deepening of response, with 58% of responders achieving VGPR or better, including 2 sCRs and 5 CRs.

- The mDOR was 11 months.

• The point estimate of median PFS for 2.5 mg/kg and 3.4 mg/kg was 2.8 months versus 3.9 months with the Hazard ratio (HR) estimate of 3.4 mg/kg versus 2.5 mg/kg being 0.92.

• The mOS was 13.7 months in the 2.5 mg/kg cohort.

• In addition, to gain clinical experience with the lyophilized presentation, 25 participants were enrolled in a separate cohort (the 3.4-mg/kg Lyophilized cohort). The ORR by IRC assessment for the Lyophilized cohort (n=25) was 52% (97.5% CI: [28.9, 74.5]).

3.3. Uncertainties and limitations about favourable effects

One limitation of the study is the single-arm design, since the phase 2 study was conducted without an active control arm. Although the observed durable response in highly pre-treated patients whose disease is refractory to three classes of agents is considered a clinically meaningful benefit there is a need to further quantify the efficacy of belantamab mafodotin in the approved indication in a comparative trial (Annex II.E).

3.4. Unfavourable effects

Adverse events were reported in 98% of patients, and 80% of the patients reported a grade 3 or 4 AE in the pooled 2.5 mg/kg cohort.

Adverse events in SOC eye disorders were reported in 71% of patients. The most commonly reported PT was keratopathy (66%), and 25% of patients reported a grade 3 or 4 keratopathy AE. Blurred

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vision was reported in 18% of patients, dry eye in 12%, and photophobia in 4% of patients. Patients also reported clinically significant deterioration of visual function both by NEI VFQ-25 and OSDI indices. The first incidence of a corneal event usually occurred within the first 4 treatment cycles. The 13-month safety update revealed that the median duration of a keratopathy, blurred vision and dry eye events were longer than reported in the primary analysis. Majority of the events resolved during the treatment period, and in 11% of patients the event resolved after treatment discontinuation. Eye-related AEs were the most common reason for dose reductions and delays. Three percent of patients permanently discontinued belantamab mafodotin treatment due to corneal AE. Eye disorders were closely monitored and actively managed during the clinical studies mainly by dose modifications, and majority of the events resolved, and dosing was resumed.

Thrombocytopenic events were more common in 3.4 mg/kg group: 58% of patients experienced a thrombocytopenic event, 34% of patients experienced a grade 3/4 event, and 5% of patients experienced a thrombocytopenic event and concomitant bleeding event. The probability of grade ≥3 thrombocytopenia was positively related to cys-mcMMAF maximum plasma concentration.

Twenty-six (25%) participants experienced an AE of anaemia, a Grade 3 event was reported for 19 (18%) participants and 1 (<1%) participant had an SAE of anaemia.

Infections were reported for 43% of patients in the 2.5 mg/kg pooled data. The most common SAE PTs were pneumonia, reported for 21 (7%) patients, followed by pyrexia (5% patients) and lung infection reported for 3% of patients. Two of the fatal SAEs in the 2.5 mg/kg group were infection-related (sepsis and lung infection).

3.5. Uncertainties and limitations about unfavourable effects

Single arm study setting impairs the causality assessment of several key unfavourable effects. Adverse effects of disease under study, previous treatments and adverse events predicted based on mechanism of action (MoA) and structure of belantamab mafodotin are overlapping, and only rough estimates for frequencies of these events can be made in this heterogeneous patient population. Dose-dependency of these adverse effects is not evident for rare AEs, and absence of dose-dependency may in some cases be due to small differences between exposure levels achieved between the two dose levels studied. This issue will be addressed in the randomized confirmatory study DREAMM-3 (see Annex II and RMP).

The number of patients treated with belantamab mafodotin in studies DREAMM-1 and DREAMM-2 is limited, and no patient has been treated with the commercial formulation on the applied dose level. At the time of data cut-off, 11% of the patients were still on study treatment. Final study report of DREAMM-2 will provide further information on the AEs (see Annex II and RMP).

Corneal events were the most significant factor in tolerability of belantamab mafodotin. The applicability of the proposed follow-up measures, and the toxicity profile observed in clinical practice remains to be tested in the post-marketing setting. Data from the on-going studies and confirmatory study DREAMM-3 will provide additional data on the current recommendations and prevention measures (see Annex II and RMP).

Cytopenia's have been carefully characterized by regular blood counts, but the causality of these events is particularly difficult to evaluate. Consistent dose-dependency supports treatment-related effects in thrombocyte, red blood cell and neutrophil counts. Ongoing clinical studies and study DREAMM-3 will provide additional data to evaluate the clinical significance of these events (see Annex II and RMP).

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3.6. Effects Table

Table 63 Effects Table for BLENREP, as monotherapy for the treatment of adult patients multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy''. (data cut-off 31 January 2020)

Effect	Short Description	Treatment	Result	Uncertainties/ Strength of evidence	Reference
Favourable Effects					
ORR (%)	Percentage of participants with a confirmed partial response (PR) or better (*i.e.*, PR, VGPR, CR and sCR, according to the 2016 IMWG Response Criteria by IRC.	2.5 mg/kg Q3W = 97	32%	No control arm other than another dose cohort Median follow up of 12.35 months	
DOR, (median, months)	Time from first documented evidence of PR or better until the earliest date of documented PD per IMWG, or death due to PD	2.5 mg/kg Q3W = 97	11 months	95% CI: 4.2, NR	
OS	The time from randomisation until death due to any cause	2.5mg/kg Q3W = 97	13.7 months	(9.9, -)	
Unfavourable Effects					
Keratopathy	- All grades - Grade 3-4	%	71 31		
Thrombocytopenia	- All grades - Grade 3-4	%	38 22		
Lymphopenia	- All grades - Grade 3-4	%	20 17		
Anaemia	- All grades - Grade 3-4	%	27 21		

Abbreviations: CI: confidence interval, CR: complete response, DOR: duration of response, IMWG: International Myeloma Working Group, IRC: independent review committee, NR: not reached, ORR: overall response rate, PD: progression of disease, PR: partial response, Q3W:every three weeks, sCR: stringent complete response, VGPR: very good partial response,

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3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The use of the belantamab mafodotin as a single-agent therapy provides a clinically meaningful anti-tumour activity. The ORR (32% in the 2.5 mg/kg cohort) is comparable or better with previous last line

therapies such as pomalidomide or daratumumab. This antitumor activity is durable as the mDoR was 11 months (95% CI: 4.2, NR). This benefit in this very last line of treatment is considered clinically relevant, providing a new alternative with a new MoA in the current therapeutic landscape of MM. Although the observed durable response is considered a clinical benefit, there is a need to further quantify the efficacy of BLENREP in the approved indication in a comparative trial (see Annex II).

Adverse effects of belantamab mafodotin were mostly reversible. Treatment is tolerated when adverse effects are closely monitored and actively managed, mainly by dose modifications. Overall, the safety profile of belantamab mafodotin monotherapy appears sufficiently characterised. Additional data from future studies are expected to be provided in support of the overall safety (see Annex II).

3.7.2. Balance of benefits and risks

Given the poor prognosis of patients heavily pre-treated, relapsed, who had received at least three prior therapies (median 7) and were refractory to at least one proteasome inhibitor (PI), at least one immunomodulatory agent , and an anti-CD38 mAb the treatment effect of belantamab mafodotin is considered clinically relevant and has been demonstrated in the single pivotal study that was submitted. Treatment is tolerated when adverse effects are closely monitored and actively managed, mainly by dose modifications.

Therefore, the benefit-risk balance for belantamab mafodotin in the proposed indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Justification for the wording of the indication

The originally proposed wording of the indication "BLENREP is indicated as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received three prior lines of therapy including an anti-CD38 antibody, a proteasome inhibitor, and an immunomodulatory agent" allows treatment of patients after three prior treatments, relapsed or refractory to an immunomodulatory agent, PI and anti-CD38 mAb. Only 5 patients in the pivotal study fulfilled these minimum criteria, and the majority of the patients were heavily pre-treated, with two proteasome inhibitors and two immunomodulatory agents. In addition, most of the patients were refractory to bortezomib, carfilzomib, lenalidomide and pomalidomide and, by definition, all patients in the pivotal study were refractory to an immunomodulatory agent and a proteasome inhibitor and an anti-CD38 antibody. Although the patients included in this pivotal trial had minimum requirement of having failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and being refractory to an immunomodulatory agent (i.e., lenalidomide or pomalidomide), to a proteasome inhibitor (e.g., bortezomib or carfilzomib) and to an anti-CD38 mAb (triple-class refractory), the vast majority of the patients were heavily pretreated. To better reflect the patient population, both in terms of prior lines of treatment received, and refractoriness to prior therapies, the indication was revised as follows:

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

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Conditional marketing authorisation

As comprehensive data on the product are not available, a CMA was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

1. The benefit-risk balance is positive, as discussed above.

2. It is likely that the applicant will be able to provide comprehensive data

Efficacy has been established on the basis of durable ORR. Although the durable response is considered a clinically meaningful benefit, there is a need to further quantify the efficacy of BLENREP in the approved indication in a comparative trial. DREAMM-3, a phase III study of single agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone in participants with relapsed/refractory multiple myeloma is planned and a considerable proportion of patients would be in later treatment lines in line with DREAMM-2. Single arm study setting also impairs the causality assessment of several key unfavourable effects leading to remaining uncertainties. These could be addressed by the proposed randomised study with pomalidomide/low-dose dexamethasone as comparator since it would allow comparisons of both efficacy and safety, and the proposed number of patients (n=320) would allow a more comprehensive analysis of both favourable and unfavourable effects. DREAMM-3 will be conducted in 184 sites and 19 countries worldwide. The Applicant has submitted applications for ethics committee and regulatory agency approval in all participating countries and has received 17 and 16 approvals respectively.

Based on the above, the CHMP considered that DREAMM-3 is likely to provide comprehensive data suitable to confirm the positive benefit-risk balance of BLENREP.

In addition, the CHMP considered that the MAH should submit the final results of the pivotal study DREAMM-2 study investigating the efficacy of belantamab mafodotin in patients with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody which will also provide comprehensive data suitable to confirm the positive benefit-risk balance of BLENREP. In addition, the final study report of DREAMM-2 will provide further information on resolution of the AEs.

3. Unmet medical needs will be fulfilled

Unmet medical needs will be addressed, as RRMM is a condition where there are a number of authorised treatment options but no curative treatments. Recently approved products for RRMM include lenalidomide, pomalidomide, bortezomib, carfilzomib, ixazomib, panobinostat, daratumumab, isatuximab, and elotuzumab.

For patients that have received at least 4 prior therapies and who are refractory to at least one immunomodulatory drug, one proteasome inhibitor, and one anti-CD-38 antibody, and whose disease has progressed on the last therapy, as detailed in the claimed indication for BLENREP, the treatment options become very limited.

Additional treatment options are needed in RRMM aiming to achieve control and remission of the disease for as long as possible given that almost all patients eventually relapse and become resistant to available treatments, where the remission duration generally decreases with each subsequent

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treatment regimen, and where the toxicity of different regimens is significant and quite different between products. In this context, medicinal products with a positive benefit-risk balance and new mechanism of action can provide a major therapeutic advantage to patients if they offer possible alternative or additional treatment options based on a different safety profile, or based on therapeutic efficacy when other products are not expected to be effective.

BLENREP has a mechanism of action that is different from that of authorised treatments and has shown to be associated with a 32% objective response rate and a median duration of response of 11 months in this group of highly pre-treated patients whose disease is refractory to three classes of agents. BLENREP has a distinct toxicity profile including significant toxicities like corneal toxicity and haematological toxicity. Adverse effects of belantamab mafodotin are mostly reversible. Treatment is tolerated when adverse effects are closely monitored and actively managed, mainly by dose modifications. Therefore, BLENREP can be considered a major therapeutic advantage in the proposed target population for whom there are very limited and often no other treatment options available, in particular when available options are unlikely to be efficacious, or when it is the preferred option in view of its efficacy and safety profiles.

In conclusion, BLENREP fulfils an unmet medical need as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy.

4. The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

In view of the limited treatments options for the highly pre-treated patients whose disease is refractory to three classes of agents and the new mechanism of action, the immediate availability of BLENREP on the market outweighs the risk inherent in the fact that additional data are still required.

Conclusions

The overall B/R of BLENREP is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that BLENREP is not similar to Darzalex, Farydak, Imnovid, Kyprolis, and Ninlaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of BLENREP is favourable in the following indication:

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

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

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

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

Prior to the launch of BLENREP (belantamab mafodotin) in each Member State the MAH must agree about 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.

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

- Educational materials for Healthcare professionals (HCPs) (includes haematologists/oncologists/eye care professionals):
    - Corneal adverse reaction guides
    - Eye care screening sheet
- Educational materials for the patient
    - Corneal adverse reaction guides
    - Patient and pharmacy eye drop wallet cards.
- Summary of the Product Characteristics (SmPC) and Package Leaflet (PL)

Key elements to be included

The healthcare professional's corneal adverse reaction guides

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

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

- Advise patients that corneal adverse reactions may occur during treatment.
- Patients with a history of dry eyes are more prone to develop changes in the corneal epithelium.

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

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

<u>Key messages to convey during patient counselling</u>:

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

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Healthcare professionals' training material

Anatomy and physiology of the eye:

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

Description of eye exams:

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

Eye care screening sheet:

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

Patient corneal adverse reaction guides

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

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

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

- If you experience changes with your vision whilst on belantamab mafodotin, contact your haematologist/oncologist. Symptoms include the following:

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- redness, dryness, itching, burning sensation, or sandy or gritty sensation in their eyes;
- sensitivity to light;
- blurred vision;
- pain in their eyes;
- excessive watering of their eyes.

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

Patient eye drop wallet card:

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

Pharmacy eye drop wallet card:

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to confirm the efficacy and safety of BLENREP in relapsed/refractory multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-2 (205678) study investigating the efficacy of belantamab mafodotin in patients with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody.	April 2021
In order to confirm the efficacy and safety of BLENREP in multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-3 (207495) study comparing the efficacy of belantamab mafodotin vs. pomalidomide plus low dose dexamethasone (pom/dex) in patients with relapsed/refractory multiple myeloma.	July 2024

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Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that belantamab mafodotin is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Medicinal product no longer authorised

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