22 May 2025
EMA/240108/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Blenrep

International non-proprietary name: belantamab mafodotin

Procedure No. EMEA/H/C/006511/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
ADCC	Antibody -dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
BCVA	Best-corrected visual acuity
BIL	Total bilirubin
BLQ	Below the limit of quantification
BMI	Body mass index
BOR	Best overall response
Bor/dex	Bortezomib/dexamethasone
BPd	Combination of belantamab mafodotin, pomalidomide, and dexamethasone
BRd	Combination of belantamab mafodotin, Revlimid (lenalidomide) and dexamethasone
BVd	Combination of belantamab mafodotin, bortezomib, and dexamethasone
CAR	Chimeric antigen receptor
CBR	Clinical benefit rate
CD38	Cluster of differentiation 38
C-EOI	Concentration at the end of infusion
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CR	Complete response
CRO	Contract research organization
CRR	Complete response rate
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Cys-mcMMAF	Cysteine maleimidocaproyl MMAF
DoR	Duration of response

DVd	Combination of daratumumab, bortezomib and dexamethasone
DSI	Drug substance intermediate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDR	Early discrepancy rate
EMD	Extramedullary disease
EORTC Q	LQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 item Core module
EORTC QLQ -MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma module
EORTC IL52	European Organisation for Research and Treatment of Cancer Item Library 52
EOT	End of treatment
EQ-5D-3L	EuroQol Group EQ 5D 3 Level version
FACT-GP5	Functional Assessment of Cancer Therapy – General Population
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GHS	Global Health Status
GSK	GlaxoSmithKline
GSK916	GSK916 refers to belantamab mafodotin
HCRU	Health care resource utilization
HDAC	Histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IA1	Interim analysis 1
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	Information fraction
Ig	Immunoglobulin
IgG1	Immunoglobulin G subclass 1
IMWG	International Myeloma Working Group
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous(ly)

IVIG	Intravenous immunoglobulin
IVRS	Interactive voice response system
KM	Kaplan Meier
KVA	Keratopathy Visual Acuity
LDH	Lactate dehydrogenase
LDR	Late discrepancy rate
MAA	Marketing authorization application
mAb	Monoclonal antibody
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified ITT
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
MMRM	Mixed model repeated measures
MoA	Mechanism of action
mPFS	Median progression free survival
MR	Minimal response
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
NE	Not evaluable
NGS	Next-generation sequencing
NK cell	Natural killer cell
NOAEL	No observed adverse effect level
NR	Not reached
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
Pd	Combination of pomalidomide and dexamethasone
PD	Progressive disease
PD2	Progressive disease after the first new line of anti-myeloma therapy started and before the second new line of anti-myeloma therapy started
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PFS2	Progression-free survival on subsequent line of therapy
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PhRMA	Pharmaceutical Research and Manufacturers Association
PI	Proteasome inhibitor
PK	Pharmacokinetics
PO	Oral(ly)

PPK	Population pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PRO-CTCAE	Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PT	Preferred term
PY	Person year
QoL	Quality of life
QSAR	Quantitative structure-activity relationships
QTL	Quality tolerance limit
QxW	Once every x weeks
RDI	Relative dose intensity
R-ISS	Revised-International Staging System
RMDoR	Restricted mean duration of response
RoW	Rest of the World
RPTEC	Renal proximal tubule epithelial cells
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sBCMA	soluble B-cell maturation antigen
SC	Subcutaneous(ly)
SCS	Summary of clinical safety
sCR	Stringent complete response
SD	Standard deviation
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
TTBR	Time to best response
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
Vd	Combination of bortezomib and dexamethasone
VGPR	Very good partial response
VGPR+	Very good partial response or better

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxosmithkline Trading Services Limited submitted on 28 June 2024 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 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2024.

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

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 13 June 2025. More information on the COMP's review can be found in the orphan designation withdrawal assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep-0

The applicant applied for the following indication:

Blenrep is indication in adults for the treatment of multiple myeloma:

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

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

1.2. Legal basis, dossier content

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 test(s) or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0347/2019 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Applicant's request for consideration

1.5.1. Accelerated assessment

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

1.6. Protocol assistance

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
31 January 2019	EMEA/H/SA/3559/2/FU/2/2018/PA/HTA/PR/III	Olli Tenhunen, Blanca García-Ochoa Martín and Daniel O'Connor

The Scientific advice pertained to the following clinical aspects:

- The adequacy of the proposed studies to support use of the product in MM who have received at least 1 prior line of anti-myeloma treatment
- The acceptability of the proposed comparator arms and PFS as a primary endpoint with further data from secondary endpoints including OS to support use of the product in second-line RRMM
- The suitability of the proposed strategy to determine the dose of belantamab mafodotin in these studies and of the safety monitoring plan, specifically the dose reduction/delay guidance
- The possibility to demonstrate significant benefit through a clinically meaningful and statistically significant improvement in efficacy over current treatments for patients who have had at least 1 prior line of anti-myeloma treatment

1.7. Steps taken for the assessment of the product

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

Rapporteur: Johanna Lähteenvuo Co-Rapporteur: Edward Laane

PRAC Rapporteur: Mari Thorn

The application was received by the EMA on	28 June 2024
The procedure started on	18 July 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 October 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	15 October 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 October 2024

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	31 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 April 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 April 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 May 2025
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	22 May 2025
The CHMP adopted a report on similarity of Blenrep with Talvey, Carvykti, Abecma, Farydak, Blenrep, Ninlaro and Kyprolis on (see Appendix on similarity)	22 May 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is pursuing a marketing authorisation (MA) for belantamab mafodotin in combination with bortezomib and dexamethasone or pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma (MM) who have received at least 1 prior therapy.

Patients with relapsed/refractory MM (RRMM) are defined as patients with relapsed, "primary refractory" or "relapsed-and-refractory" disease according to the International Myeloma Working Group (IMWG) classification:

- Relapsed Disease: Previously treated myeloma patients who, after a period of being off-therapy, require salvage therapy but do not meet criteria for "primary refractory" or "relapsed-and-refractory" categories, as outlined below.

- Refractory Disease: MM that is non-responsive while on therapy or progresses within 60 days of last therapy. Relapsed-and-refractory myeloma is defined as relapse of disease in patients who achieve minor response (MR) or better, and then either become non-responsive while on salvage therapy, or progress within 60 days of last therapy. Primary refractory myeloma refers to patients who have never achieved an MR with any therapy.

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). MM is the second most common haematological malignancy (after non-Hodgkin's lymphoma, NHL), representing 1% of all cancers and 2% of all cancer deaths. The incidence of MM in the European Union (EU) is 4.5 to 6.0/100,000/year and the mortality is 4.1/100,000/year. Furthermore, the number of new cases of MM in the EU is expected to increase to almost 46,000 by 2025 and the number of deaths attributed to MM in Europe is estimated to increase to over 27,000 by 2030. 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).

2.1.3. Biologic features, aetiology and pathogenesis

MM is characterised 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. The cause of a myeloma cell's failure to differentiate is unknown.

MM represents the far end of the spectrum of B cell–derived neoplasms. It is the neoplastic counterpart of terminally differentiated immunoglobulin-producing, long-lived plasma cells (PCs). Long-lived PCs are a subset of PCs characterized by long-term (months to years) survival within the bone marrow (BM) and thought to be key for immunologic memory. 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 chromosomes.

Tumour cells do not grow isolated from their surroundings, but they rather establish close ties with the microenvironment important for tumour survival and progression. Unlike solid malignancies, where the sites of primary disease and metastases are typically distinct, MM is characterised by widespread cancer involvement of multiple sites within the same microenvironment: the BM. The BM niche, therefore, acquires primary interest as a pathogenic factor 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. It was revised by the International Myeloma Working Group (IMWG) including cytogenetics by fluorescence in situ hybridization (FISH) and lactate dehydrogenase (LD, to the Revised International Staging System for Multiple Myeloma, R-ISS), which is now widely accepted. 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 damage, cytopenia, infections and bone weakening). Patients with relapsed disease can achieve responses to subsequent anti-myeloma regimens, the duration of response typically decreases with successive relapses until disease becomes resistant to all different options.

2.1.5. Management

Currently there are several different classes of approved agents for MM, including proteasome inhibitors (PIs), immunomodulatory agents, mAbs targeting a range of antigens, steroids, alkylators, and selective inhibitors of nuclear export, which can be combined in doublet, triplet, or even quadruplet regimens and used with or without high-dose chemotherapy rescued by autologous stem cell transplant (ASCT) (Moreau, 2021).

Different combination regimens have been studied in clinical trials in these settings (Mikhael, 2019; Dimopoulos, 2021; Moreau, 2021; NCCN, 2022). Despite this, there remains a need for expanding the therapeutic armamentarium with more treatment options, especially for the increasing number of patients who have received 1 or more prior line/s of therapy and are exposed or refractory to standard agents like PIs, lenalidomide, and anti-CD38 antibodies.

Further advanced targeted therapies like chimeric antigen receptor-T cell (CAR-T) and bispecific antibody-based therapies have also been added to the therapeutic armamentarium in recent years. CAR-T therapies are now approved as second- and third-line treatments. Several bispecifics are currently approved for patients who have received 4 or more lines of therapy.

Treatment of RRMM is complex, as it has to be individualised based on several patient-related (e.g., age, ECOG performance status, comorbidities, patient preference), treatment-related (e.g., prior exposure and refractoriness to specific therapies, depth and duration of response [DoR] to prior therapies, toxicity from prior therapies), and disease related factors (e.g., cytogenetic risk status, presence of extramedullary disease [EMD], relapse characteristics [biochemical vs. clinical]).

2.2. About the product

Belantamab mafodotin is an anti-B-cell maturation antigen (BCMA) immuno-conjugate with an afucosylated, humanized immunoglobulin G1 anti-BCMA mAb conjugated by a protease-resistant maleimidocaproyl (mc) linker to a microtubule disrupting agent, monomethyl auristatin F (MMAF). Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell, disrupting the microtubule network and leading to cell cycle arrest and apoptosis, in its function as an ADC. Additionally, the antibody is afucosylated, which increases binding to fragment crystallisable (Fc) γRIIIa receptors and enhances recruitment and activation of immune effector cells, which can kill tumour cells by antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP).

The initially claimed indication for belantamab mafodotin was for the treatment of multiple myeloma in adults who have received at least one prior therapy in combination with bortezomib and dexamethasone or pomalidomide and dexamethasone. It is supplied as powder presentations of 70 and 100 mg per vial which will be stored at 2 to 8°C. It is administered intravenously via infusion over approximately 30 minutes.

The recommended dose is either 2.5 mg/kg every 3 weeks (Q3W) in combination with bortezomib and dexamethasone (BVd) or 2.5 mg/kg administered once in Cycle 1 and 1.9 mg/kg administered once every 4 weeks (Q3W) Cycle 2 onwards in combination with pomalidomide and dexamethasone (BPd).

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the availability of numerous effective options available in the second line or later RRMM patient population. The CHMP therefore concluded that the addition of belantamab mafodotin as a new component to triplet therapies would not address an unmet medical need in the claimed indication.

On 25 August 2020, belantamab mafodotin (Blenrep) monotherapy was originally granted with a conditional marketing authorisation (CMA) for the treatment for adult patients with 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 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

As a specific obligation, the MAH conducted a phase 3, open-label, randomised study (DREAMM-3) to evaluate the efficacy and safety of single agent belantamab mafodotin compared to pomalidomide/dexamethasone (pom/dex) in patients with relapsed/refractory myeloma who had been previously treated with at least 2 prior lines of therapy. The study failed to confirm the positive benefit/risk of the monotherapy treatment, leading to non-renewal of the marketing authorization. On 23 February 2024, the European Commission (EC) issued a decision endorsing the negative CHMP opinion of the non-renewal of the Blenrep Conditional Marketing Authorisation.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 70 mg and 100 mg of belantamab mafodotin as active substance.

Other ingredients are: sodium citrate dihydrate, citric acid monohydrate (E330), trehalose dihydrate, disodium edetate, and polysorbate 80 (E433).

The product is available in type 1 glass vial, sealed with bromobutyl rubber stopper, and aluminium overseal with a plastic removeable cap.

Each vial is reconstituted with 1.4 mL (70 mg vial) and 2.0 mL (100 mg vial) of sterile water for injections (WFI) respectively to provide a reconstituted strength of 50 mg/mL.

2.4.2. Active substance

2.4.2.1. General information

The belantamab mafodotin active substance is manufactured from 2 active substance intermediates: SGD-1269 (maleimidocaproyl monomethylauristatin F or mc-MMAF, a cytotoxic small molecule) and belantamab (monoclonal antibody). As such, Module 3 of the Marketing authorisation application (MAA) is organized in 3 drug substance nodes so that full CMC information is presented for both active substance intermediates as well as for the belantamab mafodotin active substance. This structure is reflected in this report as well.

Active substance intermediate SGD-1269

General information on the active substance intermediate SGD-1269

Full information on the active substance intermediate SGD-1269 (presented in ***Figure 1***) was provided in the dossier. Other common names are maleimidocaproyl monomethylauristatin F and mc-MMAF. SGD-1269 is composed of monomethyl auristatin F and maleimide functional group linked by hexanoic 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.

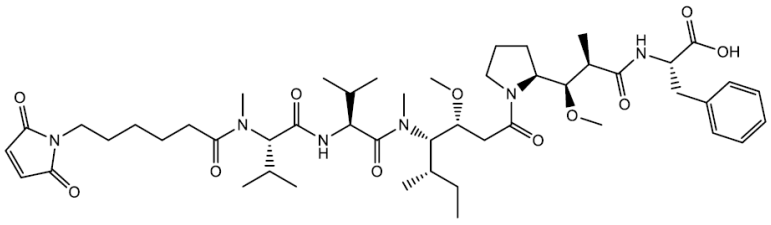


Figure 1. Structure of active substance intermediate SGD-1269

Manufacture and process controls of SGD-1269

The synthesis includes acceptable starting materials and isolated intermediates. The starting materials have been agreed with CHMP (Procedure No: EMEA/H/SA/3559/2/FU/1/2018/PA/PR/II). All starting materials have defined chemical properties and structures and are incorporated as significant structural fragments into the structure of the active substance in line with ICH Q11. Starting material structures have been characterised by nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Starting materials undergo chemical transformations and chromatographic purifications. The synthetic routes of the starting materials were given and typical impurities were determined using validated analytical methods. Appropriate specifications were set for the starting materials including identity, content, impurities and stereochemical purity and are sufficient for controlling the starting materials. Names and addresses of all suppliers were included and batch data was provided from each supplier complied with the specifications.

The manufacturing process of SGD-1269 is a six-stage convergent synthesis, described in sufficient detail, including quantities/ranges of all reagents and materials, reaction conditions and solvents for the current production scale. Critical and non-critical process parameters (with their ranges), process controls and yields for each stage are also defined. No alternative processes, reworking or reprocessing are proposed.

All SGD-1269 intermediates are controlled by specifications that include tests for identification, content and total impurities. Structure elucidation by ^{1}H NMR, MS and IR and batch data are presented and validated analytical methods are briefly described. The chirality of the intermediates is controlled by the starting materials in the route of synthesis. Impurities in the intermediates are sufficiently discussed.

The overall control strategy is based on specifications of the starting materials, intermediates, control of impurities, critical and non-critical process parameters and design space for all reaction stages. 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 development followed Quality by Design principles outlined in ICH Q8, Q9, Q10 and Q11 using a risk management approach.

Design space is claimed to cover all stages (1-6) of the commercial manufacturing process. Multivariate robustness studies by design of experiments (DoE) methodology demonstrate that the combination of parameter ranges result in intermediates and SGD-1269 that meet the required specifications. Scaling effect has been studied from laboratory to commercial scale and risk of scaling was considered low in stages 1-4 as there are no critical process parameters (CPPs) in these stages. For the stages 5-6, where the CPP's are linked to CQA's of SGD-1269 scaling effect was studied more in detail and risk of scaling up is low. Design space is considered acceptable.

Characterisation SGD-1269

The structure of SGD-1269 was characterized by ^{1}H and ^{13}C NMR, MS of the protonated molecule and fragment ions and IR. The methods used are appropriate for structure elucidation of SGD-1269.

SGD-1269 exists as an amorphous solid.

The final active substance belantamab mafodotin is intended for the treatment of patients with advanced cancer as defined in the scope of ICH S9, therefore ICH M7 is not applicable for SGD-1269 intermediate product.

The origin and fate of each observed and potential related impurity was discussed thoroughly and examined by stretching studies of the manufacturing process and spiking experiments 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 based on (Q)SAR assessments and/or literature-database search. No risk has been identified for the presence of nitrosamines in SGD-1269.

Specification, analytical procedures, reference standards, batch analysis, and container closure SGD-1269

The specification of SGD-1269 contains the relevant parameters to control the quality of the active substance intermediate. The absence of tests for elemental impurities, benzene, bacterial endotoxins and microbiological limits, stereochemical purity and residue of ignition are sufficiently justified.

Omission of microbiological test is justified as SGD-1269 is a product of chemical synthesis and during manufacturing it is exposed to organic solvents, chromatographic purifications, reactive species, and harsh conditions that are unfavorable for microbial growth. The intermediate is stored in the dry state, at -20 °C, which will further minimise microbial proliferation.

SGD-1269 has nine stereogenic centers, and various stereoisomers could arise as impurities due to epimerization. Stereochemistry is controlled by enantiomeric purity of starting materials and several individual stereoisomers are controlled in the specification either as specified or unspecified impurities. Diastereomers and stereoisomers resulting from epimerisation are discussed sufficiently and it is considered that the test for optical rotation or stereochemical purity control is not necessary in the specification.

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

The proposed specification limit for assay has been justified. The specification limits for SGD-7350 and trifluoroacetic acid (TFA) are acceptable. Dichloromethane level is above the ICH limit of 600 ppm. This can be accepted since the level will be significantly lower after conjugation with the antibody.

Since SGD-1269 is not an active substance, ICH Q3A does not apply for the impurities limits. Therefore, proposed wide impurities limits can be considered acceptable for SGD-1269 and the tightening based on the actual data is not requested.

The applicant has provided a short risk assessment summary on nitrosamine impurities in SGD-1269 material, which is accepted for the active substance intermediate stage. SGD-1269 manufacturing Process 2 does not contain amines or amine sources in combination with nitrosating agents, which would lead to formation of nitrosamine impurities and no risk has been identified for the presence of nitrosamines in SGD-1269.

Analytical methods to control SGD-1269 have been validated for their intended use.

Results from five production-scale batches, manufactured according to the proposed Process 2, have been provided. Supporting results from other 22 batches, manufactured for use in GLP non-clinical and clinical studies, validation and stability, are also presented.

The primary reference standard is used for qualification of the working standard. Information of the impurity reference materials is sufficient including purity. The impurity structures have been characterised using NMR spectroscopy and mass spectrometry.

The proposed container closure provides protection from light and moisture.

Stability SGD-1269

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.

Active substance intermediate belantamab

General information on the active substance intermediate belantamab

Belantamab (presented in ***Figure 2***) is a recombinant afucosylated humanized IgG1κ monoclonal antibody 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.

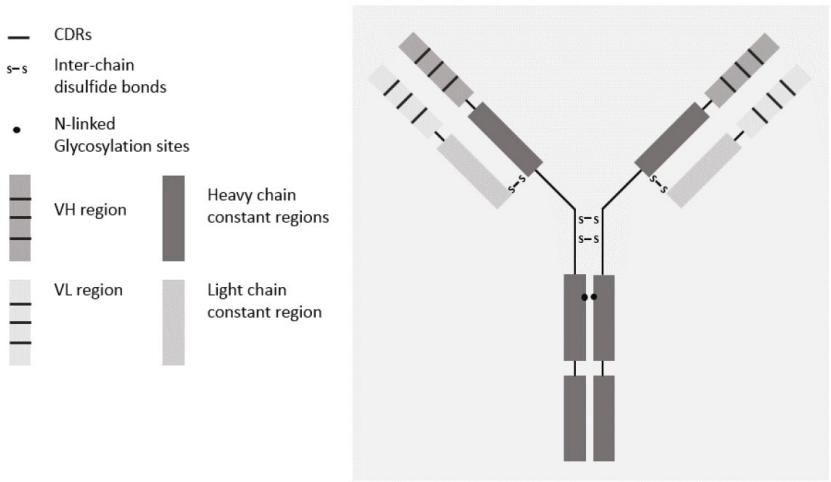


Figure 2. Schematic representation of belantamab antibody

Manufacture, process controls and characterisation of the active substance intermediate belantamab

The following facilities are responsible for the manufacture, testing and release of Belantamab. Sufficient information on EU-GMP compliance has been provided for all sites.

Description of manufacturing process and process controls

The manufacturing process is a standard monoclonal antibody production process that consists of 4 sequential up-stream process (USP) and 7 sequential down-stream process (DSP) steps.

The manufacturing process starts with thawing of a single working cell bank (WCB) vial followed by serial cell culture expansion in shake flasks. Cultures can be maintained through multiple passages of maintenance cycles in shake flasks. This seed maintenance step allows multiple belantamab batches to be generated from a single WCB vial. Cell culture expansion is continued in bioreactors. When sufficient viable cell concentration is achieved, the N-1 seed bioreactor culture is used to inoculate the production bioreactor. The total culture duration from master cell bank (MCB) thaw to the end of the production bioreactor culture is monitored to ensure that the validated limit of *in vitro* cell age (IVCA) is not exceeded. Antifoam is used to control foaming as needed. During review, information on the maximum concentration of antifoam used and the conditions for its use were clarified. The material from the production bioreactor is harvested and cells and cell debris are removed.

The downstream process for belantamab antibody consists of seven consecutive steps; protein A chromatography, low pH virus inactivation, anion exchange chromatography, virus filtration, ultrafiltration/diafiltration and final filtration, followed by filling, and freezing, storage and shipping steps. The descriptions of the process steps are sufficiently detailed.

Protocols and master batch records are in place defining the acceptance criteria for reprocessing operations.

Hold times for in-process intermediates are based on biochemical and microbiological stability validation data.

Information is given on process parameters and in-process tests for each manufacturing step. It is mentioned that exceeding the acceptable limits for these parameters and attributes will result in an investigation to identify root cause, assess impact on the specific batch, and develop and apply appropriate corrective and preventive actions (CAPA). For safety-related controls (mycoplasma *and in vitro* virus testing), confirmed failure to meet the acceptance criteria will lead to batch rejection.

Belantamab antibody batch size is described as the mass of the monoclonal antibody (mAb) produced from a bioreactor. The batch numbering system for belantamab has been described in sufficient detail.

Overall, the manufacturing process for belantamab antibody has been clearly defined and the purpose of each manufacturing step has been discussed in sufficient detail. The overall manufacturing process has been outlined in high-level flow diagrams and separate tables with process parameters and applied in-process controls (IPC) are provided for each manufacturing step.

Control of materials

Materials used in the manufacture of belantamab antibody have been listed together with information on the quality and control of these materials. No materials of human or animal origin are used in the manufacture of belantamab. Several materials are of compendial grade. Specifications are provided for all the non-compendial materials used in the manufacturing process. The non-compendial raw materials are tested by the applicant per local specification and they are required and verified to meet the specifications reported by the vendor on the certificate of analysis (CoA). This is considered acceptable. The applicant has presented a list of critical filters detailing the brand name, type, pore size/virus retention capacity and information about their quality control.

Buffer solutions are prepared according to specific standard operating procedures and are released for use according to in-process tests per approved specifications. The composition of cell culture media and buffer solutions are provided. The applicant has also confirmed that an agreement is in place with the supplier to notify the marketing authorisation holder (MAH) in case of changes to the cell culture medium.

Sufficient information on the history of the establishment of the gene expression system and generation of the production cell line from host cell line (CHO) is provided. The production cell line has been adapted to GSK proprietary chemically defined medium. However, in case all pre-defined acceptance criteria are met, the test cell bank will be considered qualified and acceptable for belantamab commercial manufacture. The applicant's approach is considered acceptable.

The presented two-tiered cell bank system consists of master cell bank (MCB) and working cell bank (WCB). The cell banks were established and characterised in compliance with ICH Q5A, ICH Q5B, and ICH Q5D guidelines. Satisfactory results were observed in all the tests. The stability of the MCB will be assessed through either data from thaws to support manufacturing of a new WCB or through a specific stability assessment. Stability of the WCB will be assessed by leveraging manufacturing data. In the case that manufacturing has been suspended for extended periods of time, specific stability checks on the WCB will occur. In addition, information on the future continuation of the cell bank system in line with ICHQ5D guideline has been presented.

Genetic stability of the cells was determined for EPCB cells at the limit of In Vitro Cell Age (IVCA). The limit of IVCA was established, based on a study conducted at commercial scale using belantamab Process 4. Cells at the limit of IVCA were characterised according to ICH Q5A and ICH Q5D guidelines. The genetic stability study was designed considering ICH guideline Q5B.

It is considered that cell banks have been sufficiently characterised to be free of microbial and viral contaminants and the stability of the cell line has been confirmed for EPCB at IVCA in line with current guidance.

Control of critical steps

Listed summaries of critical process parameters (CPPs), their acceptable ranges, and the quality attributes directly impacted by control of the parameter have been provided together with an overview of the microbial control strategy which includes in-process bioburden and endotoxin testing. In-process bioburden and endotoxin test results are required for batch release.

Sufficient information has also been given for the media and buffer control strategy. Media preparations used in the cell culture process are controlled via control of pre-filtration hold times and sterile filtration steps.

Section 3.2.S.2.4 of the dossier does not include information on in-process controls and process parameters (except for critical process parameters described above). Since IPCs and non-critical process parameters have been described in detail in section 3.2.S.2.2, it is considered acceptable not to duplicate that information in section 3.2.S.2.4.

The presented process controls for belantamab manufacturing are considered appropriate.

Process validation and/or evaluation

The validation of the belantamab manufacturing process was performed at the commercial scale using 4 consecutive batches. Acceptance criteria defined in the PPQ protocol were based on the cumulative process knowledge gained during development stage, at-scale production experience, proven acceptable ranges (PARs) established during process characterisation studies where results were available, and the belantamab release specifications. Each of the four PPQ batches was derived from its

own independent thaw of a single vial of the WCB and each production cell culture harvest was processed independently to produce a batch of belantamab. To qualify the different bioreactors of the same size to be used interchangeably in commercial manufacturing, each bioreactor of the same size was used at least once during the PPQ campaign. For each PPQ batch, parameters were evaluated against pre-determined acceptance criteria as defined in the PPQ protocol.

All four consecutive PPQ batches were successfully processed through cell culture, harvest, and purification stages. In-process attributes and parameters met all established acceptance criteria.

In conclusion, the conducted PPQ studies demonstrate that the belantamab manufacturing process 4 can consistently produce belantamab that meets specifications.

Impurity removal of process- and host- related residuals was studied at production scale for four consecutive PPQ batches. The test results for all process residuals and impurities met the PPQ protocol attribute limits and the current commercial belantamab specification. The clearance of tested residuals and impurities was demonstrated to be consistent and controlled throughout the purification process.

Resin and membrane studies were carried out to validate the lifetime, cleaning and storage of chromatography resins and UFDF membranes. Resin lifetime studies were carried out at small scale and are being verified at commercial scale. All the currently available data have met the pre-specified acceptance criteria. UFDF membrane performance and cleaning validation studies are being executed concurrently at commercial scale. This is considered acceptable. The applicant has also submitted the protocols for at-scale verification of chromatography resin and UFDF lifetime in accordance with EMA Guideline of process validation (EMA/CHMP/BWP/187338/2014).

The column cleaning effectiveness was assessed by evaluating protein-carry over during small-scale studies and is being verified at commercial scale for Process 4. Results support the efficiency of column cleaning process. The applicant intends to perform one additional at-scale mock run at the end of the resin lifetime. This approach is deemed acceptable.

The applicant has presented data to support the adequacy of UFDF membrane cleaning procedures and storage conditions. At scale data is provided and available data demonstrates the microbial purity (bioburden and endotoxins) and absence of protein-carry over.

Six hold points for manufacturing process intermediate pools have been identified in the belantamab manufacturing process. Microbial hold studies and biochemical stability studies were performed to determine the maximum acceptable hold times. Microbial hold times were established by holding the process intermediate in the intermediate hold vessels throughout the PPQ and post-PPQ campaigns. Biochemical intermediate hold times were mainly leveraged from small-scale studies conducted by the facility for Process 3. However, a separate study was performed to confirm the biochemical stability for the Anion Exchange and Virus Filtration Pools in single use hold bags. The maximum allowed hold times during manufacturing were set based on the shortest established maximum hold time of either the biochemical stability or microbial control study for each in process pool.

It was also demonstrated that microbial levels and chemical/functional stability (pH, conductivity, and/or osmolality and for media the ability to support cell growth) were within acceptable ranges at the specified hold times for media, solutions, and buffers.

The effect of reprocessing of each step was assessed at laboratory scale using Process 3 material, and the results demonstrated no significant impact on product quality. All data met the protocol acceptance criteria. An assessment was performed and it was determined that reprocessing studies performed for Process 3 are applicable and can be leveraged for Process 4. The Applicant has confirmed that as part of the commercial validation of the proposed reprocessing steps, the reprocessed batch will be placed on stability.

Shipping validation studies for belantamab have been completed and are presented in sufficient detail. The temperature retention capabilities of the temperature-controlled shipping container at or below the temperature limit of -35 °C has been qualified.

Taken together, the presented process validation studies are considered to be appropriately addressed and in line with current guidance. To provide continual assurance that the process remains in a state of control during commercial manufacture, process parameters and product quality attributes will be monitored, evaluated for trending, and reviewed for potential process improvement.

Manufacturing process development

Belantamab manufactured using Process 1 was used for clinical studies. Subsequently modifications were made based on process development work to improve robustness of the belantamab manufacturing process (Process 2). Process 2 was run at the same manufacturing scale as Process 1 and it was used to supply clinical studies and to generate Primary Reference Standard. Further modifications to the process were made in anticipation of belantamab commercialisation and to accommodate the site and scale changes associated with transferring the process from the clinical manufacturing site to the commercial manufacturing site (Process 3). Process 3 was used to supply clinical studies and to generate Working Reference Standard. Finally, to increase commercial manufacturing capacity, Process 3 was transferred with changes made to fit site and scale (Process 4). The modifications introduced to the manufacturing processes during the development have been adequately described and sufficient details and rationale for each step has been provided.

The applicant has conducted an extensive comparability assessment to evaluate the comparability of belantamab manufactured using the different manufacturing processes (Non-Clinical Process, Process 1, 2, 3, and 4) used during developmental phases. The assessment included the following elements: process comparability assessment, including a risk assessment for the potential impact of process changes on belantamab safety and efficacy, analytical comparability assessment, including extensive biophysical and biochemical analysis to demonstrate that there have been no changes to the quality, efficacy, and safety of belantamab, and stability comparability assessment, including a statistical analysis of the belantamab mafodotin active substance stability profiles to demonstrate that there have been no changes to the stability characteristics of belantamab mafodotin.

Comparison of in-process product quality and manufacturing attributes demonstrated, in general, consistent process performance between processes 1, 2, 3 and 4. The chosen quality attributes for each step are considered adequate. Some differences were observed for some process performance indicators and attributes for individual process stages; however these have been appropriately discussed. The analytical comparability assessments were performed based on extended biophysical and biochemical characterisation studies, forced degradation study, stability data assessment and belantamab testing results per specifications in effect at lot release. Forced degradation studies and the stability comparability studies further demonstrated that the process changes did not impact the stability characteristics of belantamab manufactured by different manufacturing processes.

The results of the comparability studies demonstrate that belantamab manufactured using process 1, process 2, process 3, and process 4 can be considered comparable and no concerns regarding comparability of the processes are raised.

The control strategy for belantamab manufacture includes control of raw materials and excipients, procedural controls, process parameter controls, process monitoring, in-process and release testing, product characterisation and comparability, and continued process and shelf-life stability monitoring. The belantamab process control strategy was developed using a risk-based approach applied with product, process, and facility knowledge. CQAs for belantamab were defined based on relationships of product attributes and characteristics with drug safety and efficacy, structure-function studies, as well

as knowledge gained from clinical and pre-clinical studies. Small-scale models were developed and qualified where appropriate and were used to execute the process characterization studies. Sufficient information on the scale-down models (SDM) parameters and their qualification has been provided. The data from the small-scale studies, from process characterisation and development, were analysed to define Proven Acceptable Ranges (PARs). The cumulative process knowledge gained from process development, process characterisation studies where results were available, and clinical production experience at commercial scale, were leveraged to determine acceptance criteria prior to executing the PPQ. The data from PPQ was further assessed in preparation for finalisation of the commercial control strategy. The process parameter criticality assessment was also re-evaluated, including the refined CQAs and the complete process characterisation study data, which led to the finalisation of CPPs. The output from the criticality-based classification of process parameters and PPQ data assessment were used to refine the commercial control strategy for the manufacture of belantamab. The commercial control strategy serves as the basis for the continued process verification approach. Overall, a thorough description of the systematic approach taken to develop the control strategy for belantamab has been provided. The process characterisation studies have been appropriately addressed and the rationale for control strategy for belantamab is clearly presented and acceptable.

A risk assessment considering the principles of ICH Q9 has been performed to assess all contact materials of the belantamab manufacturing process for all potential sources of leachables. It is also considered that as the manufacturing of belantamab is upstream of the belantamab mafodotin active substance ultra-filtration step, which provides an effective purge point for any potential leachables from the belantamab manufacturing process, the risk of patient exposure to leachables from belantamab manufacturing process is low.

Characterisation

Characterisation was performed using a variety of biochemical, biophysical and biological assays to determine the identity, purity and biological activity of belantamab. Extended testing was performed on the primary reference standard batch 172405900, which was manufactured from a process 2 clinical belantamab batch. Comparability between the commercial process 4 and the manufacturing processes used during developmental stages has been confirmed.

Peptide mapping LC-MS/MS confirmed that the HC and LC amino acid sequences were consistent with the sequences predicted by cDNA, and post-translational modifications were identified. Disulfide and trisulfide mapping LC-MS/MS confirmed the presence and location of the expected disulfide bonds and a low level of trisulfide bond formation. Intact and reduced mass analysis confirmed that the molecular mass of the intact antibody, HC, and LC match the theoretical masses for each species. Free sulfhydryl analysis confirmed low levels of free sulfhydryls are present within belantamab, which is aligned with the disulfide mapping LC-MS/MS results and expected of IgG1 molecules containing stable disulfide bonds. The main secondary structure component of the antibody is intra-molecular β-sheet, which is the expected secondary structure characteristic of IgG1 molecules. Near-UV CD results showed spectral maxima that represented contributions from aromatic residues, and the overall spectral characteristics expected of an IgG1 molecule.

The presented characterisation confirms the expected primary, secondary, and tertiary structures, glycosylation profile, charge isoform profile, and biological activity of belantamab. As antibody dependent cellular phagocytosis (ADCP) is indicated to be a part of belantamab mechanism of action by immune effector cell recruitment through FcγR interactions, information on ADCP and binding of belantamab to other Fc receptors other than FcγRIIIa and FcRn was also provided.

A process-related impurities risk assessment was performed to evaluate the raw materials used in the upstream and downstream processes. As a result, a risk-based testing strategy for demonstrating clearance of process-related impurities was developed. It was determined that testing for certain impurities was not needed since the maximum expected level was below the permitted daily exposure and the clearance of some was assumed based on a scientific understanding of the mechanisms for its clearance in the belantamab process. The levels of residual DNA, residual HCP, Protein A, other process-related impurities were evaluated using a variety of analytical methods. The results indicate that the belantamab purification process is robust and provides efficient and consistent clearance of process-related impurities to low levels. Monitoring is proposed only for residual HCP as part of release testing of belantamab. No monitoring is proposed for the other process-related impurities, which is supported by the presented data and acceptable.

As product-related impurities, the applicant has considered charge variants, aggregates, and fragments. Purity profiles were generated using cIEF for charge variants, CGE for fragments, and SEC for fragments and aggregates. Individual peaks of interest from these profiles were further characterised by biochemical and biophysical methods. Overall, product-related impurities are appropriately addressed.

Specification, analytical procedures, reference standards, batch analysis, and container closure Belantamab

Specification and justification of specification

The proposed belantamab specification (table 3) includes physico-chemical tests (appearance (colour and clarity), pH, and osmolality), an identity test (SPR), tests for purity, impurities and variants (SEC, cIEF, glycoform profile, HCP), tests for potency and protein content (SPR and protein concentration), and microbiological tests (bacterial endotoxin and bioburden). The testing panel for the release of belantamab intermediate is considered acceptable. Potency testing relies on antigen binding and FcγRIIIa binding by SPR. This is considered acceptable. The proposed test for bacterial endotoxins is BET (Ph.Eur. 2.6.14). The test parameters proposed to be included in the belantamab specification are considered relevant and in line with current guidance. An appropriate justification is also provided for excluding analytical methods (reduced capillary gel electrophoresis (R-CGE), non-reduced capillary gel electrophoresis, capillary isoelectric focusing (cIEF) % basic, protein A and host cell DNA) that were included in the clinical release and stability specification but were removed from the commercial specification.

The analytical tests proposed to be included in the belantamab specification have been discussed separately and justification is provided for the proposed acceptance criteria for each analytical test. Data was available from 94 belantamab batches for a statistical analysis (three standard deviation approach) at the time of specification setting. The proposed specification acceptance criteria is identical for release and stability.

The proposed specification for belantamab is considered to be in line with current guidance and sufficiently stringent to ensure the quality of belantamab for belantamab mafodotin active substance and finished product manufacturing.

Analytical procedures

Belantamab is tested using a combination of compendial (colour, clarity, pH, osmolality, bacterial endotoxins, and bioburden) and non-compendial methods (Antigen Binding and FcγRIIIa Binding by

Surface Plasmon Resonance, Size Exclusion Chromatography, Capillary Isoelectric Focusing, Glycoform Profile, Protein Concentration, and Host Cell Protein ELISA).

Overall, brief method descriptions that include critical method details, operational parameters and system and sample acceptance criteria as well as data reporting details, have been provided for all methods.

Compendial methods used for the release and stability analysis of belantamab have been verified to be suitable for their intended purpose according to compendial requirements and the results are presented for bioburden and endotoxin. The results meet the requirements set in the Ph. Eur.

In general, the validation for all non-compendial analytical procedures follows ICHQ2 (R1). All predetermined validation acceptance criteria were met, and all methods were considered validated for their intended use. Validation summaries with sufficient data are provided, with additional information on analytical method changes during development (HCP assay) and method transfers.

Batch analyses

Batch data was provided for 41 belantamab batches (including 5 process 3 and 4 process 4 PPQ batches). The results for the PPQ and commercial batches are presented against the proposed commercial specification.

Reference standards

A two-tiered reference material system comprising a primary reference standard (PRS) and a working reference standard (WRS) has been established and implemented for the manufacture of commercial supply. During the development of belantamab, altogether four reference standards (interim RS, RS, PRS and WRS) have been established. Relevant information on all historical reference standards including release and characterisation test results has been provided. Reference standard lot 172405900 is the PRS, against which future WRS will be qualified. This RS was chosen because it is representative of the clinical material used in the clinical studies. Reference standard lot FG9K-AA-R was qualified against the PRS lot 172405900 and is used as the WRS. The stability of the WRS will be monitored. The protocol and acceptance criteria for the stability testing of WRS and qualification of future WRS has been provided.

It is considered that the reference standards used throughout the product development have been adequately described. Available stability results for both PRS and WRS have been provided and considered acceptable.

Container Closure system

The same container closure system is used for both belantamab and belantamab mafodotin active substance. The container closure has been appropriately described in the active substance section and a risk assessment for leachables has been performed in line with ICH Q9.

Stability of belantamab

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.

Active substance belantamab mafodotin

2.4.2.2. General Information

Belantamab mafodotin is an antibody-drug conjugate that includes an IgG1 monoclonal antibody that contains sixteen (16) disulfide bonds, including four (4) interchain. Belantamab is partially reduced and conjugated with SGD-1269 at the interchain cysteine residues, resulting in belantamab mafodotin, which has a target drug-antibody ratio (DAR) of four (4). A schematic of the theoretical drug loaded species of belantamab mafodotin is shown in ***Figure 3***.

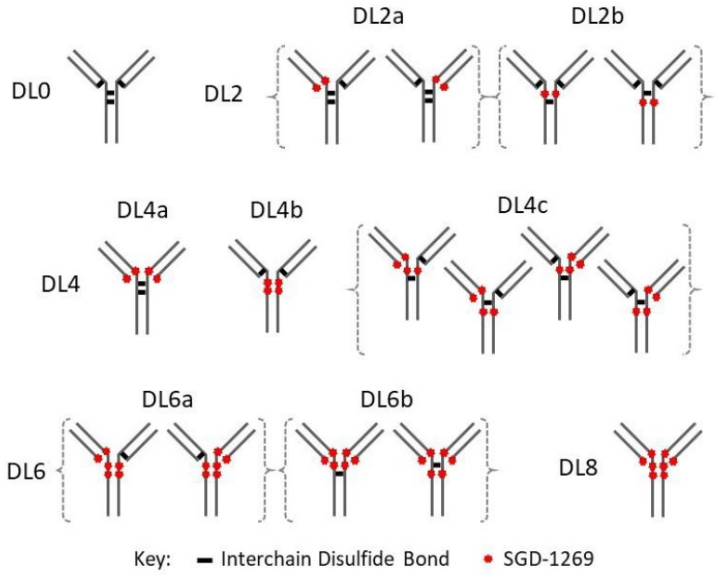


Figure 3. Schematic representation of drug-loaded species of belantamab mafodotin

2.4.2.3. Manufacture, process controls and characterisation

The manufacture of belantamab mafodotin active substance is performed in accordance with current Good Manufacturing Practice at GlaxoSmithKline Parma Italy.

Description of manufacturing process and process controls

The manufacturing process starts with thawing of belantamab and solution preparation (Stage 1). The process allows for one re-freeze and re-thaw of belantamab. Multiple containers of one or more belantamab and SGD-1269 batches can be pooled for active substance manufacturing. The pooling strategy for belantamab and SGD-1269 batches for active substance manufacturing has been discussed. Prior to the conjugation reaction, belantamab is partially reduced. Belantamab mafodotin is stored at ≤ -35 °C in flexible bags. No shipping is currently needed as the active substance and the finished product are manufactured in the same facility

The acceptable hold times for in-process pools are indicated based on process validation studies.

Each batch of belantamab mafodotin is assigned a unique lot number upon manufacture. A description of the batch numbering system has been provided.

The manufacturing process for belantamab mafodotin has been clearly defined and the purpose of each manufacturing step has been discussed in sufficient detail. The manufacturing process has been outlined in high-level flow-diagrams and separate tables with process parameters and applied in-process controls are provided for each manufacturing step.

Control of materials

Raw materials used in the manufacture of the active substance have been listed together with information on the quality and control of these materials. Most materials are of compendial grade (USP/NF, Ph. Eur.). No animal or human derived materials are used in the manufacturing of the active substance. Belantamab and SGD-1269 are released for active substance manufacturing as per the specifications presented in respective CTD Sections S.4.1 of the dossier. In addition to the release testing provided in the supplier CoA, identity testing is performed after receipt by the active substance manufacturer.

Sufficient information on the type, material and molecular weight cut-off of the UFDF membrane filter has been provided.

The provided information on raw materials used for active substance manufacturing is considered sufficient.

Control of critical steps and intermediates

Risk assessments have been performed on each stage of the active substance manufacturing process to identify process parameters that impact either the safety or efficacy of the product. Listed summary of the identified CPPs and IPCs, associated CQAs, and acceptable ranges or acceptance criteria with rationale are provided. The presented process controls for active substance manufacturing are considered appropriate.

An overview of the microbial control strategy for belantamab mafodotin is also presented. To ensure that the active substance meets acceptable standards for microbial-related quality attributes, including bioburden and endotoxin, the following controls were established in the manufacturing process: Control of materials, control and validation of facility, utilities, and equipment, control of equipment and facility cleaning and sterilization/sanitization processes, microbial control of the manufacturing process, in-process monitoring of bioburden and endotoxin levels, and validation of process holds between manufacturing steps.

Process validation and/or evaluation

The applicant has followed a three-stage approach to validation of the commercial active substance manufacturing process: stage 1 - process design; based on the cumulative process knowledge, a control strategy with acceptable ranges for parameters and attributes was established for PPQ. Small-scale development studies for process characterisation are discussed in CTD section S.2.6 of the dossier and found acceptable. Stage 2- process performance qualification; three consecutive PPQ batches were manufactured at the commercial scale. Stage 3 - continued process verification (CPV).

The validation of the active substance manufacturing process was performed at GSK Parma at the commercial scale using 3 consecutive batches manufactured under approved protocols with pre-defined acceptance criteria. In conclusion, the conducted PPQ studies demonstrate that the active substance manufacturing process can be operated routinely and consistently within the acceptable ranges of its process parameters, resulting with active substance that meets the pre-defined acceptance criteria for quality, purity and safety.

The active substance and the finished product are manufactured in the same facility in GSK Parma, therefore no shipping validation has been performed. The Applicant indicates that shipping conditions will be validated in case of shipping active substance outside the GSK Parma site.

To provide continual assurance that the active substance process remains in a state of control during commercial manufacture, CPPs and CQAs will be monitored, evaluated for trending, and reviewed for potential process improvement. A risk management approach will be applied throughout the product lifecycle to maintain process control and to meet product quality requirements.

The presented process validation studies are appropriately addressed and in line with current guidance.

Manufacturing process development

The modifications introduced to the active substance manufacturing processes during development have been adequately described and sufficient details and rationale for each development step has been provided.

The applicant has conducted comparability assessments for active substance process 1, process 2 (using belantamab from process 2 and process 3 as inputs), and process 3, to demonstrate that the active substance manufacturing process changes throughout the product's history have no negative impact on the quality, efficacy, and safety of belantamab mafodotin. These comparability assessments were performed based on extended biophysical and biochemical characterisation studies, active substance testing results per specifications in effect at batch release, forced degradation studies, and stability data assessment. As the SGD-1269 synthesis and manufacturing process has not changed significantly during the developmental phases it was not included in the comparability assessments, which is acceptable.

The comparability assessment between process 2 and 3 included a review of the batch release data from the process 3 PPQ batches against the active substance release specification (all general identity, purity, potency, and impurity assays). Additional comparison of release data from purity and potency tests against narrower comparability acceptance criteria statistically derived from process 2 active substance batch data, extended characterisation by testing three Process 3 PPQ active substance batches side-by-side with three process 2 active substance batches and assessing the results against comparability acceptance criteria to assess the primary, secondary and tertiary structure, purity, and biological activity of the materials, forced degradation studies to compare the degradation products and directional degradation trends between three process 2 and three process 3 active substance batches, and comparison of stability trends for process 3 active substance batches against the trends generated for process 2 under real-time recommended, accelerated, and stressed storage conditions. All comparability acceptance criteria were met.

The comparability assessment between process 1 and 2 included side-by-side testing of active substance process 1 batch with belantamab process 1, active substance process 2 batch with belantamab process 1 and active substance process 2 batches with belantamab process 2, forced degradation study with active substance process 1 with belantamab process 1, active substance process 2 batch with belantamab process 2 and active substance process 2 batch with belantamab process 3, comparability analysis of active substance process 1 and process 2, accelerated and stressed stability data, and comparison of batch analysis data of all active substance process 1 and process 2 batches manufactured to date. All comparability acceptance criteria were met. There were some expected differences observed in process 1 batch.

In addition, side-by-side testing of active substance process 2 batches with belantamab process 2 and active substance process 2 batches with belantamab process 3 was performed to confirm their biochemical and biophysical comparability and to demonstrate the comparability of belantamab mafodotin process 2 using belantamab process 2 and process 3. All comparability acceptance criteria

were met with one exception. The difference in total enthalpy of unfolding in DSC did not meet acceptance criteria; however, the review of the experiment and retesting of the active substance batches, it was determined that the results were due to assay variability and not lack of product comparability.

The presented data support the comparability of active substance process 1, process 2, and process 3 and it can be concluded that the quality of belantamab mafodotin has remained consistent throughout development.

The overall control strategy for belantamab mafodotin manufacture includes control of raw materials, procedural controls, process parameter controls, process monitoring, in-process testing, and release testing. The active substance process control strategy was developed using a risk-based approach based on product, process, and facility knowledge. CQAs for the active substance were defined based on the relationship among product quality attributes and the impact on biological activity, pharmacokinetics, immunogenicity, and safety.

Scale-down models (SDMs) were developed and qualified for manufacturing steps 1-4. Sufficient details of the SDMs with comparison to active substance process 2 have been provided. The considerations and results related to process 2 at manufacturing scale are also applicable to process 3 at manufacturing scale, confirmed by process 3 engineering batch performance, process 3 PPQ batch performance comparability, and stability reports.

Process knowledge gained from small-scale process development studies, clinical campaign runs, and manufacturing experience were used to develop risk assessments and identify the parameters and attributes to be evaluated during process characterisation studies. Process characterisation studies were performed to confirm the relationship of process parameters with, and their impact on, process performance and critical quality attributes. The studies included both multivariate and univariate studies for manufacturing steps 1-4 to develop proven acceptable ranges (PARs). The results from these studies were further used to determine criticality of process parameters based on risk assessments. Some of the parameters included in the PAR studies were subsequently classified as not being critical process parameters.

Three consecutive active substance batches were executed during the PPQ campaign including cumulative hold times to provide evidence that the commercial manufacturing process control strategy performed as expected. PPQ batch performance was evaluated, and the control strategy was updated. The process parameter criticality assessment was also updated to include the revised CQAs, PPQ data, and process characterisation study data, which led to the identification of CPPs. Following the parameter criticality assessment, a Process Failure Mode and Effect Analysis (Process FMEA) was performed combining the parameter severity rankings, the ability to control the parameters and to detect possible failures. The output from this process FMEA was used to refine the commercial control strategy.

The Applicant has performed a risk assessment applying the principles outlined in ICH Q9 to assess all contact materials of the active substance manufacturing process for potential sources of leachables. The risk assessment and subsequent experimental studies confirmed that the active substance manufacturing process poses a low risk of patient exposure to leachables. In addition, the results for the long term leachables studies on finished product showed that no leachables were detected at levels that would represent a risk to patients.

Overall, the process characterisation studies have been appropriately addressed and the rationale for control strategy is clearly presented.

Container closure system

A very high-level but sufficient description of the container closure system has been provided. The container closure system used for the active substance is a sterilized, single-use, flexible bag. A schematic diagram of the container as well as specifications were provided in the dossier. It is indicated that sterilisation of the bags is performed by irradiation according to ISO 11137. The applicant accepts the container based on supplier certificate, identity and sterilisation check. The Applicant has confirmed that the container closure system irradiation is performed according to the recommendations outlined in Ph. Eur. general chapter 5.1.1. The irradiation dose ranges from 25-45 kGy, which is considered acceptable.

In line with ICH Q9 a risk assessment has been performed to assess all contact materials of the active substance container closure system for all potential sources of leachables. The risk-based strategy and subsequent experimental studies are presented in P.2.4. Pharmaceutical Development Container Closure System section of the dossier. The risk assessment and experimental studies confirmed that the potential risk of patient exposure to leachables arising from the container closure system is low. The applicant has performed extractable studies to investigate the levels of potential leachables in single-use flexible bags. The study results indicate that leaching from single-use flexible bag surface is below 20 mcg/day reporting threshold and represents negligible risk to patient. The choice of the model solvents has been appropriately justified.

Compatibility of the active substance with the container closure system materials was demonstrated through stability studies. These stability studies include long-term recommended and accelerated storage conditions for the active substance using representative small-scale flexible bags and provide a worst-case ratio of container surface area to product volume.

As secondary packaging, the single-use flexible bags are encased in a rigid outer shell. The shell has no product contact and provides protection to the container closure system from physical damage during shipment. Sufficient information on the secondary packaging including materials has been provided.

Characterisation

Information on the structural, biochemical, and biological characteristics of belantamab mafodotin was obtained through characterisation tests on the primary reference standard (PRS) batch (manufactured from a process 2 clinical batch). The characterisation included both release testing as well as extended characterisation. Primary structure was determined by peptide mapping LC-MS/MS (MS) analysis, disulfide mapping LC-MS/MS, intact and reduced mass MS analysis, and free sulfhydryl analysis. The HC and LC sequences were consistent and identified post-translational modifications. The presence and location of the expected disulfide bonds was confirmed. Intact and reduced mass analysis confirmed that the molecular mass of the intact antibody, HC, and LC match the theoretical masses for each species. FTIR was used to characterise the secondary structure of belantamab mafodotin. The main secondary structure component of the antibody is intra-molecular β-sheet. The tertiary structure was characterised by near-UV CD and DSC. Purity was characterised using SEC, SV-AUC, reduced CGE, and non-reduced CGE. Belantamab mafodotin exists in primarily monomeric form with low levels of dimer present. HIC was used to confirm the drug load distribution and DAR. Charge variants were analysed by cIEF. SPR, cell growth inhibition and ADCC were used to characterise biological activity.

The results from extensive testing using a variety of biochemical, biophysical, and biological characterisation tests confirmed the expected structure and function of belantamab mafodotin.

A process-related impurities risk assessment was performed to evaluate the raw materials used in the conjugation process, identify process-related impurities that would pose patient safety risks, and determine the acceptable level or permitted daily exposure (PDE) for those impurities for patients.

These impurities arise from materials used during the active substance manufacturing process. There is no safety risk in belantamab mafodotin because the maximum expected levels are below the PDE.

As product-related impurities, the applicant has considered charge variants, aggregates, fragments, and drug load variants. These product-related impurities and substances have been extensively characterised to determine their identity and their impact to safety and efficacy. Analytical methods for monitoring the variants directly or indirectly at release and/or stability are in place.

The characterisation of potential impurities in belantamab mafodotin has been appropriately addressed and is considered comprehensive.

2.4.2.4. Specification

Active substance specifications include tests for appearance: (colour and clarity), an identity test (Antigen Binding SPR), tests for purity (SEC, CGE, HIC, cIEF), tests for potency (antigen and FcRII binding by SPR and DAR by HIC), quantity (protein concentration), general tests (pH and osmolality), impurities (HPLC for residual free drug linker), and microbiological purity tests (bacterial endotoxin and bioburden).

The test parameters proposed to be included in the active substance specification are considered relevant and in line with current guidance. The proposed test for bacterial endotoxins is BET (Ph.Eur. 2.6.14). An appropriate justification is also provided for excluding analytical methods (drug load distribution and drug antibody ratio by HIC, LMW by SEC, NR-CGE, residual free drug linker by RPHPLC and cell growth inhibition bioassay) that were included in the clinical release and stability specification but were removed from the commercial specification.

The analytical tests proposed to be included in the active substance specification have been discussed separately and justification is provided for the proposed acceptance criteria for each analytical test. The release and stability specification acceptance criteria were set based on statistical analysis and structure-function relationship data. Data was available from 61 active substance batches for a statistical analysis (three standard deviation approach) at the time of specification setting

The proposed specification acceptance criteria is identical for release and stability.

Overall, the proposed specification for the active substance is considered to be in line with current guidance and sufficiently stringent to ensure the quality of the active substance.

Analytical procedures

The active substance is tested using a combination of compendial (colour, clarity, pH, osmolality, bacterial endotoxins, and bioburden) and non-compendial methods (antigen binding and FcγRIIIa binding by surface plasmon resonance, size exclusion chromatography, reduced and non-reduced capillary gel electrophoresis, drug load distribution and drug antibody ratio (DAR) by hydrophobic interaction chromatography (HIC), capillary isoelectric focusing, protein concentration, and residual free drug linker.

Overall, brief method descriptions that include critical method details, operational parameters and system and sample acceptance criteria as well as data reporting details, have been provided for all methods.

Compendial methods used for the release and stability analysis of the active substance have been verified to be suitable for their intended purpose according to compendial requirements and the results are presented for bioburden and endotoxin. The results meet the requirements set in the Ph. Eur.

The validation for all non-compendial analytical procedures follows ICH Q2. Validation summaries with sufficient data are provided. All predetermined validation acceptance criteria were met, and all methods were considered validated for their intended use. The stability indicating properties of SPR, non-reducing and reducing CGE, SEC, and HIC have been confirmed through forced degradation studies. No concerns are raised and the validation of the analytical methods for the active substance are considered acceptable.

Batch analysis

Data is presented for twenty-nine (29) active substance batches including PPQ batches. All the batch analysis results were evaluated against specifications in place at the time of testing. The results for the PPQ batches batches are presented against the proposed commercial specification. The tables also include the results from tests that are not part of the proposed commercial specification.

Reference materials

A two-tiered reference material system that includes a primary reference standard (PRS) and a working reference standard (WRS) has been established for commercial manufacturing.

According to the applicant, all reference standard batches manufactured to date have been subjected to stability studies. A stability protocol with analytical tests and testing schedules has been presented. The stability of the PRS and WRS will be monitored annually up to 180 months (15 years). The available stability results for both PRS and WRS were provided.

The protocol and acceptance criteria for the qualification of future WRS has been provided.

2.4.2.5. 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.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and Pharmaceutical development

Belantamab mafodotin for injection, 70 mg (also referred to as belantamab mafodotin for injection, 70 mg/vial) and 100 mg (also referred to as belantamab mafodotin for injection, 100 mg/vial) are both a powder for concentrate for solution for infusion. Both are supplied as a sterile, preservative-free, white to yellow lyophilised powder in a single-dose vial, manufactured from a bulk finished product solution containing 50 mg/mL belantamab mafodotin, sodium citrate/citric acid, trehalose, disodium edetate, polysorbate 80 at pH 6.2. The excipients comply with Ph. Eur.

Belantamab mafodotin for injection, 70 mg and 100 mg are filled and lyophilised in DIN/ISO 6R Type 1 untreated clear glass vials, sealed with 20 mm single vent, fluorinated-polymer coated, gray bromobutyl

rubber stoppers, and aluminium overseals with blue removeable plastic caps (70mg) or orange removeable plastic caps (100 mg).

Belantamab mafodotin for injection, 70 mg is reconstituted with 1.4 mL of sterile water for injections (WFI). Belantamab mafodotin for injection, 100 mg is reconstituted with 2.0 mL of WFI. The lyophilised 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 for injection, 70 mg and 100 mg is not supplied by GSK. Belantamab mafodotin for injection, 70 mg and 100 mg are intended for administration by intravenous infusion.

Pharmaceutical development

The main objective of the formulation development was to achieve long-term stability of critical quality attributes and to develop 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 solution for infusion is proposed for commercialisation and therefore it is emphasised that the liquid presentation is not assessed or approved within this submission. Comparability of the liquid and powder finished product manufacturing processes has been adequately demonstrated.

The formulation for the finished product was developed in a series of studies. Knowledge from the early-phase development of both finished product presentations was used to optimise and select the current formulation. Initial formulation development studies used belantamab as a surrogate for belantamab mafodotin and formulations selected using belantamab were subsequently verified to be suitable with belantamab mafodotin. The suitability of sodium citrate/citric acid, trehalose, disodium edetate (EDTA), polysorbate 80 (PS80), pH 6.2 formulation for the lyophilised finished product was confirmed based on powder characterisation and 3 months of stressed stability data. Following the confirmation of powder stability, the strength of the finished product was selected for dosing at 3.4 mg/kg and potential reduction to 2.5 or 1.92 mg/kg. The 100 mg/vial and 70 mg/vial strengths address two safety considerations within the clinical/hospital environment: to minimise the number of vials required for administration and to minimise the amount of residual drug in a single-dose vial after dose preparation. The vial size and fill volume were adjusted relative to the lyophilised prototypes. Overall, the formulation development of belantamab mafodotin finished product has been adequately described.

Lyophilisiation Lyo E is the intended commercial process (using active substance process 3) for 100 mg and 70 mg finished product manufacture at commercial site. It has not been used in clinical studies and is intended for commercial use only. A clear description of differences of lyophilisation processes Lyo E, Lyo A, B and C; Lyo 1 and 2 have been provided upon request. Comparability between processes has been adequately demonstrated.

Manufacturing process development of belantamab mafodotin finished product 100 mg applies also to finished product 70 mg. The belantamab mafodotin finished product 100 mg has been developed to reproducibly meet specifications for the finished product CQAs of appearance, visible particles, sub-visible particles, pH, osmolality, product-related variants, quantity, weight variation, biological activity, microbiological safety, residual moisture, and reconstitution time.

The formulation and manufacturing process were developed to minimise 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. Once the manufacturing process had been defined, a systematic risk assessment of the process parameters and material attributes was undertaken. Risk assessments performed during development

of each unit operation were used to consider the potential impact of the process variables on finished product CQAs. The results of the risk assessments were used to identify process parameters, attributes and IPCs that had potential to influence finished product quality, for further investigation.

Process characterisation 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, characterisation studies, the production-scale process capability, and finished product quality data obtained from the engineering batch and clinical manufacturing.

Given the presence of polysorbate 80 excipient in the finished product formulation, a risk assessment was provided during the assessment to address the potential risk of phthalate extraction when using polyvinyl chloride (PVC) with diethylphtalate (DEHP) delivery devices (bags and sets of administration) for preparation and administration of the finished product (i.v). The studies concluded that the DEHP exposure associated with belantamab mafodotin administration remain significantly below established safety limits, and risk of to the patients due to phthalate leaching is considered minimal.

The container closure for both strengths is composed of a clear glass vial, a single vent stopper, and an aluminium overseal with a removable plastic cap that is not in contact with the product. Representative drawings, information on the dimensions of each component, and specifications for the components are presented in the dossier. The glass vial and rubber stoppers comply with Ph. Eur requirements. Extractables and leachables studies are presented and discussed in dossier section P.2.4 Pharmaceutical Development Container Closure System. Depyrogenation of the vials and steam sterilisation of the stoppers prior to filling are presented and discussed in dossier section P.3.3. Description of Manufacturing Process and Process Controls and found acceptable. Overall, the container closure systems are appropriately described, the provided information is considered sufficient, and no concerns are raised.

The applicant has performed compatibility studies for the reconstituted and for the diluted finished product at refrigerated and room temperature conditions (in-use stability). Finished product 100 mg batches used in in-use compatibility studies has been detailed in the dossier. The ability of the of PS80 to stabilise the antibody after dilution in IV bag protecting the finished product from degradation against various stresses during IV administration and storage including IV bag agitation stress has been demonstrated.

According to SmPC the use of in-line filter for diluted finished product solution IV administration in clinic is not mandatory. Therefore, the prevention of the potentially immunogenic subvisible particles in-use is crucial. The results for subvisible particles analyses after dilution and storage of the finished product in expected in-use conditions including IV bag agitation stress study was provided upon request, and are considered generally adequate.

A series of comparability assessments to evaluate the impact of manufacturing process changes throughout finished product development has been conducted. 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.

2.4.3.2. Manufacture of the product and process controls

The sites involved in the manufacture, packaging, testing, and release of the finished product are. The proof of GMP for all sites is considered acceptable.

A step-by-step description and a flow chart of the finished product manufacturing process including CPPs and IPCs were provided. The process starts with thawing of the active substance and involves preparation of diluent solution, pooling active substance and compounding of the bulk finished product, sterile filtration, filling and partial stoppering, and lyophilisation 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.

Description of a batch numbering system for the finished product was provided and found acceptable.

Control of critical steps and intermediates

CPPs and in-process tests (IPTs) with their associated acceptance criteria or limit (IPCs) or acceptable ranges (CPPs) have been presented in tables for all relevant manufacturing steps in section P.3.4 of the dossier. The overall control strategy is presented in section P.2.3 of the dossier. Controlled process parameters, and input material parameters with associated target values/ranges/limits for each operation step are provided in section P.2. of the dossier Manufacturing process development. These were found acceptable.

Rationale and justification for the classification of process controls applied in finished product manufacture was provided. Risk assessment tools were used to identify potential CPPs and process intermediate CQAs which might influence finished product CQAs. Experimental studies were conducted to understand the relationships between the potential CPPs, potential process intermediate CQAs and the finished product CQAs and understand any interactions. Controls were then defined for the manufacturing process parameters, process intermediate CQAs, critical in-process controls (IPCs) and specifications. Overall, the presented process controls seem appropriate and the proposed control strategy for the finished product manufacturing process can be agreed on.

There are no intermediate products in the manufacture of the finished product for injection, 70 mg and 100 mg.

Process validation and/or evaluation

Five 100 mg and three 70 mg consecutive commercial scale PPQ batches were produced for the studies. Additionally, one confirmatory batch of 100 mg finished product manufactured with active substance process 3 was produced. The finished product manufacturing process was validated at the proposed commercial manufacturing site through controlled process parameters and performance parameters with predetermined acceptance criteria. The data gathered demonstrated the finished product, 70 mg and 100 mg manufacturing process can be considered robust and consistently yields the finished product that meets pre-determined quality attributes.

Additionally, the applicant has performed successful validation of sterilisation processes, media fills, and shipping validation of the final finished product. The details and conditions used for sterilisation of sterile filtration system are specified in sufficient detail and found acceptable.

Monitoring, trending, and review of the product and process data will be applied to continued process verification (CPV) to provide continuous assurance that the process remains well-controlled and ensure product quality is maintained. Continued process verification is covered by EU GMP.

2.4.3.3. Product specification

The proposed finished product release and shelf-life specifications have been provided. The proposed specifications include general tests for appearance (colour and uniformity, color of reconstituted drug product, clarity of reconstituted drug, visible particulates), identity (antigen binding by SPR), purity (SEC, R-CGE, and cIEF), potency (antigen binding by SPR, FcγRIIIa binding by SPR, and cell growth inhibition assay), quantity (protein concentration by UV/Vis), contaminants (bacterial endotoxin, sterility, and container closure integrity), and general tests (pH, sub-visible particulate matter, residual moisture, reconstitution time, uniformity of dosage units, and osmolality). Overall, the test parameters proposed to be included in the specification are considered relevant and in line with current guidance. According to agency's request an appropriate control for PS80 has been implemented for finished product release. The provided stability data together with the supportive developmental stability data demonstrate that the PS80 content of the finished product remains consistent throughout the finished product shelf-life, thus, the omission from finished product shelf-life specification is considered justified.

The acceptance limits for individual parameters were generated using evaluation of clinical experience, statistical analysis, and structure-function relationship data. At the time of setting the specification acceptance criteria 42 belantamab mafodotin finished product batches were available. The stability of the finished product at recommended storage conditions for the lyophilised process batches was also assessed for trends. Overall, no meaningful trends that were outside of assay variability were observed; therefore, the applicant used a three-standard deviation approach to guide setting the release and shelf-life acceptance criteria. Considering the clinical experience and sufficient amount of finished product batches used for the evaluation of specification limits, the proposed specification are considered acceptable.

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

Batch analyses

Data is presented for 33 finished product batches.

Characterisation of impurities

There are no new degradants (related substances) or impurities in the finished product different from those discussed for the active substance. For further discussion on impurities please refer to active substance section Characterisation of this report. A risk analysis considering potential elemental impurities in the finished product has been conducted in line with ICH Q3D. The risk analysis was further completed by testing three finished product (100 mg, considered also representative of 70 mg finished product) batches for elemental impurities. Detected elemental levels are below limit of quantification and the set 30% PDE threshold limit which is below the PDE limit set by ICH Q3D. The requirements in ICH Q3D are considered fulfilled and it is agreed that the risk for elemental impurities in belantamab mafodotin DP can be considered low.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active

substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Reference materials

The same product-specific reference standard is used for release and stability testing of the active substance and the finished product.

2.4.3.4. Stability of the product

The applicant has provided data on stability studies performed with both 70 mg and 100 mg finished product strengths at the long-term storage condition (5 ± 3 °C upright and inverted), at the accelerated storage condition (25 °C ± 2 °C / 60 ± 5% RH), and at the stressed storage conditions (-20 °C and 40 ± 2 °C / 75 ± 5% RH). For stability studies the samples were stored in clear glass vials (DIN/ISO 6R Type 1 untreated clear glass vials, sealed with 20 mm single vent, fluorinated polymer coated, bromobutyl rubber stoppers and aluminium overseals with removeable caps) both in upright and inverted positions.

The proposed shelf-life specification differs from finished product release specifications for SEC (%monomer and % HMW) and residual moisture. In addition, for stability studies Container closure integrity (CCI) is tested instead of sterility. Specification for CCI was presented here and the specification for all other tested quality attributes is presented in dossier section P.5.1.

Real-time data at the long-term condition (5 ± 3°C) is currently available for 60 months for four 100 mg batches (including one clinical batch), 60 months for three 100 mg PPQ batches, 24 months for 1 100mg engineering batch, 48 months for three PPQ batches, 18 months for three 100 mg batches, 18 months for one 70 mg batch, and for 12 months for three 70 mg batches. Differences in manufacturing supply chains used in stability data have been clarified. Small statistically significant trends were identified in Reconstitution time, SEC, cIEF, Reduced CGE, FcγRIIIa receptor binding by SPR, protein concentration, Appearance Clarity, and residual moisture. Despite the small trends observed at 5°C, all results were within the defined acceptance criteria. Based on real-time stability data in addition to comparability, it is expected that all batches will remain within the commercial acceptance criteria for at least 60 months. Trends will continue to be monitored as more data becomes available. Data for the 70 mg strength is only available for 9 months for one batch and for 6 months for 3 batches, however, the available data were comparable to the 100 mg strength for all attributes.

The proposed shelf-life for both finished product strengths (70 mg and 100 mg) is based on the comparability data presented in dossier section P.2.3 for the 100 mg and 70 mg strengths and the stability data presented for the 100 mg strength. It was clarified that the proposed shelf life for the finished product 70 mg and finished product 100 mg is 48 months.

In-use microbiological study and in-use stability study for reconstituted and diluted finished product was presented and discussed. Both studies 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 (2 ºC to 8 ºC) 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". The applicant has provided compatibility data using 0.2 µm PES filter demonstrating that the product remains stable after filtration. Filtrating of the diluted solution is optional, however if it is chosen to be used, 0.2 µm PES in-line filter is recommended.

Based on available stability data, the shelf-life of 4 years when stored in a refrigerator (2 ºC – 8 ºC) as stated in the SmPC is acceptable.

2.4.3.5. Adventitious agents

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

The manufacturing process of the finished product does not contain any material of human or animal origin, and the transmitting spongiform encephalopathy (TSE) risk is regarded negligible. Therefore, the risk of adventitious agents entering the finished product is considered low. The risk of microbial and mycoplasma contamination has been adequately addressed. 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 finished product batches requires testing of unprocessed bulk for the presence of adventitious viruses.

The viral clearance validation (VCV) studies were performed in accordance with requirements in ICH Q5A(R1) to demonstrate the capacity of belantamab active substance intermediate process 3 to remove and/or inactivate viruses. It was determined that process 3 sourced material is representative of the commercial process 4. The process steps validated for virus clearance are run in a similar way and the sample matrix is similar. Therefore, the small-scale VCV studies using process 3 sourced material can be leveraged for process 4. This approach is considered acceptable.

The manufacturing process for belantamab active substance intermediate 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. At least two orthogonal steps are demonstrated to achieve a LRF of over 4 log and therefore the overall cumulative reduction is considered safe and acceptable.

2.4.4. Discussion on chemical, and pharmaceutical aspects

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 was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to provision of active substance stability data. This point is put forward and agreed as Recommendation for future quality development.

2.4.5. 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.

2.4.6. Recommendation 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 a point for investigation

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical program was designed in accordance with the guidance provided in ICH S9, ICH S6(R1) and ICH S7A, with consideration for the particular characteristics of a conjugated therapeutic antibody. The adequate justification for the absence of studies was provided. All definitive toxicology studies supporting the development of belantamab mafodotin were conducted in full compliance with 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.

Studies were carried out by the IV route of administration, the proposed therapeutic route in human, in cynomolgus monkeys, rats and rabbits. Cynomolgus monkey was selected as being the only pharmacologically relevant species for predicting the safety of belantamab mafodotin in humans, rat to further characterise the overall toxicity of belantamab mafodotin and rabbit to further explore ocular toxicity. The safety pharmacology evaluations (cardiovascular and/or respiratory) were incorporated into the GLP repeat dose toxicology studies in rats and monkeys.

Most nonclinical pharmacologic, pharmacokinetic (PK) and toxicologic studies were conducted using belantamab mafodotin. Selected evaluations were conducted with cys-mcMMAF (the active cytotoxic moiety) and GSK2857914, the parent, unconjugated afucosylated anti-BCMA antibody, to further characterise the overall nonclinical profile of belantamab mafodotin.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro studies

BCMA binding and internalisation, Fc-R binding

Reports 2013N175824, 2013N177426, 2013N176113, 2011N125952, 2011N125948.

Belantamab mafodotin is an antibody-drug conjugate (ADC) targeted to BCMA, which is widely expressed on malignant plasma cells in multiple myeloma, in B cells at later stages of differentiation, on germinal center B cells in tonsil, blood plasma blasts and long-lived plasma cells. Belantamab mafodotin has an average drug (MMAF)-antibody ratio of 4.

Belantamab mafodotin exerts it mode of action (MoA) after releasing the toxic payload MMAF disrupting the microtubule network and leading to cell cycle arrest and apoptosis after internalization, following the targeted binding to BCMA. Some internalization of the ADC also occurs via nonspecific pinocytosis. Other MoAs include triggering the effector functions ADCC and ADCP, and induction of immunogenic cell death of MM cells expressing BCMA. Belantamab mafodotin has afucosylated mAb moiety which increases the binding to FcγRIIIa and enhances recruitment and activation of immune effector cells.

Belantamab mafodotin binds with high and comparable nanomolar affinity to human and cynomolgus monkey rBCMA (Kd 1.1 - 1.6 nM at 25°C and 3.1 nM at 37°C), but do not cross-react with 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.

Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell via proteolysis resulting in cell killing through disruption of microtubules and enhancing the activation of immune effector cells.

Unconjugated parent anti-BCMA Mab (GSK2857914) neutralised binding of BCMA ligands BAFF and APRIL to BCMA in a cell-free plate assay with IC_{50} 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.

ADC-mediated cytotoxicity

Reports 2013N176113, 2013N176111, 2011N125948, 2013N176111, 2017N312863, 2014N219883.

G2/M arrest and apoptosis was induced by belantamab mafodotin in a concentration and time dependent manner in MM cell lines. Belantamab mafodotin (0.01 to 10 µg/mL) had cytotoxicity potency against MM cells with IC_{50} 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 cell surface BCMA receptors. The growth inhibitory activity was achieved even in the presence of physiologically relevant concentrations of soluble BCMA or the BCMA ligand APRIL.

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

ADCC/ ADCP activity

Reports 2011N125945, 2013N176111, 2013N183018.

Antibody afucosylation increases binding affinity to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells, which can kill tumour cells by ADCC and ADCP.

Belantamab mafodotin (and unconjugated afucosylated GSK2857914) had ADCC activity with an IC_{50} 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 the donor and cell line variability was noted, with the EC_{50} 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). EC_{50} values were estimated to be approximately 100 ng/mL. Belantamab mafodotin was active against the plasmablasts with the mean EC_{50} value was 98 ng/mL.

Induction of immunogenic cell death (ICD)

Reports 2019N397960, 2019N400866.

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

Reports 2015N249192, 2016N304715.

Belantamab mafodotin had minimal immunomodulatory effects on human PBMC-derived CD4+ and CD8+ T cell activation and no significant effect on IFN-γ 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

Reports 2013N178354, 2013N176111, 2018N392007, 2019N415573.

The apoptotic and ADC-mediated cytotoxicity 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

Reports 2013N175478, 2013N167720, 2017N317971, 2019N395917, 2013N175478, 2013N167720, 2019N395916, 2013N176111, 2019N396819, 2018N359715.

In xenograft mice bearing NCI-H929 human MM cell tumours, a complete tumour regression that was maintained for 60 days, was achieved with 4 mg/kg 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. Anti-tumour activity *i.e*. decreased necrosis, increased infiltration of leucocytes into the tumour, decreased markers for cell proliferation and apoptosis was confirmed in the histology.

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

Reports 2013N157994, 2013N163514.

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+). Belantamab mafodotin treatment resulted in drop in the level of free soluble BMCA (sBCMA) and increase in complexed sBCMA, which started to decrease at 4 days until undetectable levels.

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 varied between the animals but trended to increase towards the end of the study. IL-6 levels showed a small peak 6 hours post dosing in all animals. 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

Reports 2019N395340, 2017N345016, 2018N380821, 2017N348146, 2019N398617, 2017N348146, 2018N384601, 2018N393779, 2019N398490, 2023N528894, 2023N528895.

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

2.5.2.2. Secondary pharmacodynamic studies

Reports 2011N125952, 2013N175851, 2014N224675, 2013N176111, 2013N176110.

GSK2857914 neutralized BAFF and APRIL ligand binding to BCMA and inhibited BAFF- and APRIL -induced NFκB signalling. GSK2857914 completely neutralized APRIL induced NF-κB cell signalling in the absence of soluble BCMA.

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 signalling 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.

Belantamab mafodotin did not affect the viability of PBMCs, NK cells, CD14+ monocytes, or BMSCs. Belantamab mafodotin had no adverse effects no function of CD4+ or CD8+ T cells (proliferation, activation, and cytokine production). Low level of cell killing activity was observed on plasmacytoid DC from healthy donors and myeloma subjects expressing low levels of BCMA.

Belantamab mafodotin can also be taken up non-specifically such as by pinocytosis into the cells (without expression of BCMA). Nonspecific uptake may result the payload toxicities.

2.5.2.3. Safety pharmacology programme

Reports 2013N174857, 2013N158643, 2013N158643, 2018N374327, 2018N375127, 2013N177530, 2012N150466, 2013N174857, 2023N536587, 2013N177527, 2013N177530

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.

Belantamab mafodotin (and GSK2857914 mAb)

In the 13-week repeat dose toxicity study with belantamab mafodotin in the cynomolgus monkey ECG recordings were performed using a non-invasive telemetry system. 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.

Overall, there were no clinically relevant safety pharmacology findings related to belantamab mafodotin on cardiovascular, respiratory and central nervous systems in the repeated dose toxicology studies in cynomolgus monkeys and rats, including treatment-related effects in the serum cardiac troponin I levels.

The unconjugated anti-BCMA mAb had no effects on cardiovascular function in cynomolgus monkeys. 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. All ECGs were within normal limits.

Cys-mcMMAF

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. Therefore, cys-mcMMAF has no clinically relevant inhibitory effect on hERG channel.

There was no effect on qualitative or quantitative ECG parameters or respiratory rate following IV administration of cys-mcMMAF in cynomolgus monkeys. 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.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not submitted.

2.5.3. Pharmacokinetics

Absorption

Single-dose PK

In the single-dose PK studies in mouse, rat and monkey after IV and IP (mouse only) administration, belantamab mafodotin (ADC), GSK2857914 and cys-mcMMAF were characterised. Slow plasma clearance and low steady-state volume of distribution suggest that belantamab mafodotin was mainly confined to the systemic circulation. In mouse, serum t½ of ADC and total mAb was approximately 9 days, while for GSK2857914 t½ was longer, 13 days. In rats, serum t½ of ADC in rats was approximately 11 days. No difference between GSK2857914 and belantamab mafodotin in their PK was reported. For cys-mcMMAF, systemic exposure (AUC_{last} and C_{max}) increased slightly greater than in proportional to the dose after a single IV bolus of cys-mcMMAF. In monkeys, serum $t_{1/2}$ of belantamab mafodotin was 4 days. Similarity of the PK of ADC and total mAb suggests stability of MMAF. There was no significant difference between GSK2857914 and belantamab mafodotin in PK. For cys-mcMMAF, the decrease in terminal $t_{1/2}$ was proportional to increased dose.

Single-dose TK

The single-dose TK data showed similar absorption characteristics recorded during the single-dose PK studies. In rats, plasma concentrations of ADC and total mAb were similar at each respective dose level, suggesting that belantamab mafodotin remained largely intact in the plasma. In monkeys, exposure for ADC and total mAb increased dose-proportionally. No sex difference in the systemic exposure was observed between female and male monkeys.

Repeat-dose TK

Rat: Dose-proportional increase in the systemic exposure was reported with belantamab mafodotin. No sex differences were reported. The AUC of ADC and mAb were similar, generally higher for total mAb than ADC. However, in C_{max} this difference was not observed. Absorption was rapid and T_{max} ranged from 0.25 hours to 48 hours in the 3-week study and was 0.25 hours in the 13-week study. $t_{½}$ was 11 days for both ADC and total mAb in the 3-week study. For cys-mcMMAF, some accumulation was evident; systemic exposure in week 10 was 2.3-fold compared to Week 4.

Rabbit: In the 4-week IV study, systemic exposure of belantamab mafodotin was approximately 15-20% lower than total mAb. In the 7-week IV rabbit study, ADC, mAb and cys-mcMMAF levels were analysed from tears and plasma. No differences between analytes were observed in plasma exposure levels (AUC_{0-t} and C_{max}).

Monkey: T_{max} of ADC and total mAb varied widely in 3-week study. In some animals T_{max} was 3, 6 or 24 hours after dosing during Weeks 1 and 3, although mostly at 0.25 hour. In the 13-week study T_{max} was generally observed at 0.25 hours for ADC and total mAb. In these monkey studies, no markable differences in the systemic exposure was recorded to ADC and total Ab, with total mAb consistently being slightly higher than ADC. No sex differences were reported.

In the 5-day IV monkey study with cys-mcMMAF, low concentrations of cys-mcMMAF were found in 13 of 95 plasma samples from control male monkeys and in 15 of 95 plasma samples from control female monkeys. This indicates cross-contamination of plasma samples.

In the 4-week and 13-week IV studies with GSK2857914 in monkeys, dose-proportional increase in systemic exposure was recorded. In the 13-week study, a steady-state on plasma concentrations were reached on Week 4. In this study, more than half of the animals developed ADA, thus decreasing exposure levels on corresponding animals.

Distribution

In vitro distribution studies

Binding of cys-mcMMAF to mouse, rat, monkey and human plasma proteins is low.

Several *in vitro* studies were performed to investigate the uptake of belantamab mafodotin and GSK2857914 into the human cells. The data show that belantamab mafodotin was located within lysosomes and that internalisation of belantamab mafodotin and GSK2857914 into cells were mediated by multiple endocytic pathways.

Conflicting results were obtained from P-glycoprotein (P-gp) transport of cys-mcMMAF experiments. However, the applicant proposes a conservative presumptive conclusion that cys-mcMMAF is a P-gp substrate.

The data show that cys-mcMMAF is not a substrate of MRP4 and MRP5, but was a substrate of MRP1, MRP2 and MRP3 and a borderline substrate of BSEP *in vitro*. Cys-mcMMAF did not show an *in vitro* inhibition potential of P-gp, BCRP, BSEP, MRP1, MRP2, MRP3, MRP4 and MRP5. It was also demonstrated *in vitro* that cys-mcMMAF is not a substrate of OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K, but is a substrate of OATP1B1 and OATP1B3 or does not act as an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K.

In vivo distribution studies in rats

Belantamab mafodotin (ADC and total mAb) was shown to distribute to connective tissue in eyes, eye lids, extra-orbital lacrimal and harderian glands, liver, kidney and muscle of the eyelids. The concentration of belantamab mafodotin was 3- and 2-fold higher in the liver and kidney, respectively, than in the eye. Belantamab mafodotin was localised in the connective tissue and muscle of eye lids, but not in the cornea. The distribution correlated with GSK2857914. Cys-mcMMAF was detected only in the bone marrow but not in cornea, whole eye or eye lids in the rat.

In vivo distribution studies in rabbits

In the rabbit ocular toxicity study, belantamab mafodotin (ADC and total mAb) and cys-mcMMAF were detected in tear samples. Cross-contamination for total mAb and cys-mcMMAF was observed in some of the control samples. Following the repeated IV dosing, belantamab mafodotin and cys-mcMMAF were detected in tear samples, belantamab mafodotin in higher frequency.

Metabolism

In vitro

Belantamab mafodotin is largely stable *in vitro* in rat, monkey and human serum at 37°C with approximately 3% of MMAF released as free cys-mcMMAF.

Belantamab mafodotin was catabolised in the cells. Cys-mcMMAF metabolism was low and was primarily characterized by non-enzymatic transformations, and to a minor degree by oxidative and conjugative metabolisms. There were some differences in the metabolite profiles between the mouse, rat, monkey and human. This is, however, not a concern as the metabolites accounted for less than 5% of the total radioactivity. No markable oxidative or conjugative metabolites nor the unique human metabolites that would not have been characterised in the toxicity studies conducted in rats and cynomolgus monkeys, were identified.

Cys-mcMMAF was shown not to be an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5, or not to be an inducer of CYP1A2, 2B6 or 3A4/5.

In vivo metabolism study in rats

The major drug-related component identified in the rat urine was the unchanged liner form of cys-mcMMA (SGD-1362) accounting for 9.3% of the total radioactivity. In faeces, the cyclized isomer of cys-mcMMAF (SGD-1462) constituted the major component being 13.8% of the total radioactivity. Overall, these results suggest a minor metabolism of cys-mcMMAF following IV administration.

Excretion

The excretion study in rats suggests that cys-mcMMAF is predominantly excreted via the hepato-biliary/faecal pathway (83%) and to a lesser amount via renal clearance (13%).

No information is available on excretion to milk.

Pharmacokinetic drug interactions

The data obtained from *in vitro* metabolism and distribution studies show that cys-mcMMAF is unlikely to affect PK of co-administered drugs as it was not an inhibitor or inducer of any of the studied CYP enzymes and no inhibition of studied transporters was recorded.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single dose toxicity studies were conducted in rats and monkeys with belantamab mafodotin or the cytotoxic moiety cys-mcMMAF (**Table 1**).

Table 1. Single dose toxicity studies

Study details **Species** **Duration** **Route** **GLP status** **(Study ID)**	**No: Sex/ Group**	**Dose (mg/kg/day)** **Test item**	**Exposure**		**Major findings**
			Cmax **M/F**	**AUC** **M/F**	
Rat 8 or 22 Days + 14 D recovery IV No GLP (2012N134122)	4M/4F	10 30 100 **ADC**	µg/ml 242 / 249 626 / 695 2160 / 2150	µg.ml/h 19300 / 19100 48300 / 49900 88800/ 117000	100 mg/kg approx. lethal dose. Inflammation in lung, heart, spleen, lymph nodes, kidney, injection site. Atrophy/necrosis in gonads, eyes, bone marrow, liver, skin. Presences of ADAs.
Monkey 8 or 22 Days + 14 D recovery IV No GLP (2012N133495)	1M/1F	2 10 30 **ADC**	mg/ml 0.0750 / 0.0891 0.388 / 0.210 1.49 / 0.742	mg.ml/h 4.15 / 3.55 15.0 /10.5 60.7 / 53.4	Kidney injury, haemorrhage in heart, skin and stomach cholestasis, skeletal muscle injury.
Rat 14 D recovery IV No GLP (2013N177526)	3F	2.5 10 17.5 25 **Cys-McMMAF**	ng/ml 104900 123500 164500 284000	N/A	HNSTD ≥ 25 Reduced reticulocytes.
Monkey 14 D recovery IV GLP (2013N177529)	1M/1F	1 3 6 10 **Cys-mcMMAF**	ng/ml 10500 / 10900, 26700 / 25400, 142000 / 58800 971000 / 38400	ng.ml/h 1300 / 1450 6980 / 7090 12500 / 9200 38200 / 10400	HNSTD ≥ 10 Discoloration of the injection site. Reduced red cell mass Increased AST, bilirubin.

2.5.4.2. Repeat dose toxicity

Repeat dose toxicity studies were conducted to investigate the effects of repeated administration of belantamab mafodotin, cys-mcMMAF and GSK2857914 in rats and monkeys (**Table 2**).

Table 2. Repeat dose toxicity studies (all GLP-compliant)

Study ID	**Species/Sex/ Number/Group**	**Dose (mg/kg)** **Route**	**Duration**	**NOAEL (mg/kg)**	**Major findings**
Belantamab mafodotin					

2013N174857	Rat 10M/10F (main study) 6M/6F (TK)	3, 10, 30 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	Rat 12M/12F (main study) 6M/6F (TK)	3, 10, 30 IV	13 weeks	<3	Lung damage at all doses. Adverse findings in testes/epididymides, teeth, kidney. Non-adverse changes in eye, male mammary gland, spleen, liver.
2013N158643	Monkey 3M/3F (main study)	1, 3, 10 IV	3 weeks	1	Systemic inflammatory response: spleen, bone marrow, thymus. Increased CRP, WBC. Reduced albumin, red cell mass, platelets. Glomerulopathy, nephron degeneration. Lowered IgM, IgG, NK cells- Elevated AST, GLDH, GGT, ALT, bilirubin, cholesterol, triglyceride.
2018N375127	Monkey 3M/3F (main study) 2M/2F (recovery)	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 the liver and lymph nodes. Systemic inflammation. Seminiferous tubule degeneration.
Cys-mcMMAF					
2013N177527	Rat 12M/12F	1, 5, 10 mg/kg IV bolus injection	5 days	10	Corneal opacity. Increased lung weight, alveolar histiocytosis, inflammation. Elevated AST, ALT, neutrophils.
2013N177530	Monkey 3M/3F	0.5, 2, 5 mg/kg IV bolus injection	5 days	5	Elevated monocytes lymphocytes.
MAB (GSK2857914)					
2012N150466	Monkey 3M/3F	10, 30, 100 mg/kg/week IV	4 weeks	>100	Skin reddening, scrabs, epidermal degeneration and necrosis, hyperplasia and inflammation. Microscopic changes in spleen, liver, kidney, bone marrow. Increases in inflammatory cytokines and CRP. Systemic inflammation.
2023N536587	Monkey 4M/4F	2, 10, 40 mg/kg/week SC 40 mg/kg/week IV	13 weeks	10 SC 40 IV	Injection site reactions (macrophage vacuolation, perivascular monocyte infiltration). Systemic inflammation, increases in monocytes, fibrinogen, CRP and/or decreased albumin. ADA

The toxicology findings with belantamab mafodotin were primarily related to the safety of the cytotoxic drug conjugate, cys-mcMMAF, and included findings in the kidneys, testes, ovaries, incisor ameloblast/odontoblast layers (rat), liver, bone marrow, spleen and eye (rat). The histopathological changes observed in the testes and lung, were not reversible in rats. Overall, the principal adverse findings in the rat and monkey, at exposures similar to that 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).

2.5.4.3. Genotoxicity

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 (**Table 3**). Cys-mcMMAF did not lead to chromosomal aberrations *in vivo* in rat micronuclei bone marrow assay, likely related to the poor uptake of unconjugated cys-mcMMAF into the cells.

Table 3. Genotoxicity studies

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results positive/negative/equivocal
Gene mutations in bacteria (Ames) cys-mcMMAF Report 2019N406489 GLP	Salmonella strains TA98, TA100, TA1535, TA1537 and E. coli strain WP2 uvrA	+/- S9 50 -5000 µg/plate	Negative
Gene mutations in mammalian cells cys-mcMMAF Report 2019N406496 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 Report 2019N416146 non-GLP	Human peripheral lymphocytes	- S9 (24h) 577 µg/mL	Positive
Chromosomal aberrations in vivo cys-mcMMAF Report 2019N406497 GLP	Rat, micronuclei in bone marrow 5 males/group	2.5 – 25 mg/kg IV	Negative

2.5.4.4. Carcinogenicity

No carcinogenicity studies with belantamab mafodotin were submitted.

2.5.4.5. Reproductive and developmental toxicity

No reproduction toxicity studies with belantamab mafodotin were submitted. Effects on male and female reproductive organs was observed in repeat-dose toxicity studies in rats and monkeys at doses of ≥10 mg/kg.

2.5.4.6. Toxicokinetic (TK) data

TK of belantamab mafodotin (and GSK2857914, cys-mcMMAF) following weekly or every 3 weeks repeated intravenous administration was assessed in rats and monkeys (**Table 4**). 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 unconjugated mAb respectively). Safety exposure margins based on animal exposures (sex-averaged) are summarised in **Table 5**.

Table 4. Overview of toxicokinetics data following weekly or every 3 weeks intravenous administration of belantamab mafodotin, unconjugated mAb and cys-mcMMAF

Study ID/ species	Dose (mg/kg)	tudy duration	Animal AUC (µg·h/ml) (*ng/mL) ♂	♀	Cmax (µg/ml) (*ng/mL) ♂+♀ average
Belantamab mafodotin					
2013N174857/Rat	**3** 10 30	3 Wk	5960 2600 51300	6240 17500 45900	103 303 764
GSK2857914					
2013N174857/Rat	3 10 30	3 Wk	7170 30500 60000	7150 21000 54000	105 300 771
cys-mcMMAF					
2013N174857/Rat	3 10 30	3 Wk	0.252 1.13 2.90	2.63 1.360 2.670	3.9* 16.6* 53.4*
Belantamab mafodotin					
2018N374327/Rat	3 10 30	13 Wk	12700 45500 106000	8350 29100 74100	131 451 1250
GSK2857914					
2018N374327/Rat	3 10 30	13 Wk	15100 50900 125000	10400 34000 89400	133 406 1160
cys-mcMMAF					
2018N374327/Rat	3 10 30	13 Wk	NA 0.05 0.413	NA 0.0819 0.370	NA 1.71* 6.81*
Belantamab mafodotin					
2013N158643/Monkey	**1** 3 10	3 Wk	1180 3590 20500	1290 3922 22500	27.5 63.3 292
GSK2857914					
2013N158643/Monkey	1 3 10	3 Wk	1500 4402 24200	1540 4844 27400	27.3 68.2 306
cys-mcMMAF					
2013N158643/Monkey	1 3 10	3 Wk	0.0122 0.0856 0.416	0.0121 0.0615 0.285	0.499* 1.97* 5.4*
Belantamab mafodotin					
2018N375127/Monkey	**1** 3 10	13 Wk	1280 (1050) 6750 21600	1030 6870 21400	27.3 93.9 311
GSK2857914					
2018N375127/Monkey	1 3 10	13 Wk	1700 (1140) 8140 3200	1370 7930 28600	29.0 103 368
cys-mcMMAF					
2018N375127/Monkey	1 3 10	13 Wk	NA 25.1* NA	NA 25.5* NA	0.125* 0.415* NA

Table 5. Safety exposure margins based on animal exposures (sex-averaged)

	NOAEL (mg/kg)	**Test item**	**End study data**		**Animal: Human xxx Exposure Multiple**	
			Animal AUC (µg.h/ml)	**Cmax (µg/ml)**	**AUC**	**Cmax**
2013N174857/ Rat	3	Belantamab mafodotin	6100	103	1.0	2.0

		mAb	7160	105	0.6	1.8
		cys-mcMMAF	0.258	0.0039	3.1	4.9
2018N374327 / Rat	< 3*	Belantamab mafodotin	10500	131	1.7	2.5
		mAb	12700	133	1.0	2.3
		cys-mcMMAF	NC	NC	NA	NA
2013N158643/ Monkey	1	Belantamab mafodotin	1240	27.5	0.2	0.5
		mAb	1520	27.3	0.1	0.5
		cys-mcMMAF	0.0121	0.0005	0.1	0.6
2018N375127 / Monkey	1	Belantamab mafodotin	1130	27.3	0.2	0.5
		mAb	1500	29.0	0.1	0.5
		cys-mcMMAF	NA	0.000125	NA	0.2

2.5.4.7. Tolerance

No separate local tolerance studies have been conducted with belantamab mafodotin. IV injection sites were inspected in the toxicology studies.

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. 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 and four doses administered 3 weeks apart in the rat, up to 30 mg/kg, did not result in treatment-related changes at the injection site.

2.5.4.8. Other toxicity studies

Mechanistic ocular toxicity

In vitro

Reports 2019N410329, 2019N410330, 2019N409936, 2021N483916, 2022N507716, 2022N506460, 2022N508021, 2022N502360, 2023N528252, 2021N478152.

The potential for belantamab mafodotin to cause cytotoxicity and the mechanism of uptake that plays a role in human corneal epithelial cells was assessed in three primary human corneal epithelial cell (HCEC) lines and a primary human renal proximal tubule cells (RPTEC). All cell lines were confirmed by qPCR to have negligible or no expression of BCMA. The role of macropinocytosis in belantamab mafodotin-mediated cytotoxicity were conducted using EIPA to inhibit the pathway of non-specific uptake. Cytotoxicity was assessed with Caspase 3/7 apoptosis markers and cell viability. The uptake of belantamab mafodotin by mechanisms unrelated to BCMA expression, such as macropinocytosis, was demonstrated by bioimaging.

Belantamab mafodotin increased apoptosis concentration-dependently *in vitro* in HCEC and RPTEC. The inhibition of micropinocytosis with EIPA and pre/co-treatment with excess of immunoglobulins reduced the belantamab mafodotin-mediated apoptosis. Nystatin (inhibitor of caveolin-mediated uptake) reduced the cytotoxicity of belantamab mafodotin in HCEC. None of the compounds tested inhibiting the uptake pathways (macropinocytosis by wortmannin, imipramine, phenoxybenzamine), nystatin or clathrin-mediated uptake by chlorpromazine), had a significant effect on belantamab mafodotin-mediated toxicity in RPTEC. H1 receptors are expressed on the surface membrane of corneal epithelial

cells. The inhibition of H1 receptors had no effect on belantamab mafodotin cellular uptake or apoptosis in HCEC cells.

Gene expression patterns of 33 limbal stem cell-like markers of HCEC (from 3 donors) was evaluated after belantamab mafodotin or unconjugated mAb exposure. Transcriptomics analysis (affymetrix) did not identify differences between small proliferative and large squamous HCEC cell populations.

Cys-mcMMAF in the cornea originated from the plasma or tear compartments were considered limited, and not representing the primary mechanism for corneal toxicity.

In vivo rabbit tolerability and ocular toxicity

Reports 2018N385412, 2021N465838.

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).

2 weekly administrations up to 30 mg/kg/week was well tolerated. After four doses of 30 mg/kg/week, corneal epithelial single cell necrosis (minimal or mild) in all 3 rabbits and increased mitoses (minimal) in the corneal epithelium in 2/3 rabbits given 15 mg/kg/week for four weeks was observed. 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.

Tissue cross-reactivity

Reports 2013N169796, 2013N176627.

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 was observed in human and cynomolgus goblet cells in the colon. Specific positive staining was observed with belantamab mafodotin in several tissues generally associated with individual or focal groups of cells, blood vessel walls/perivascular tissue and connective tissue.

Immunotoxicity

Belantamab mafodotin induced release of cytokines from the effector cells (PBMN) when bound to target molecule BCMA on myeloma cells. Increases were noted in IFN-γ, TNF-α, and IL-8 release, but not in IL-6. Immunomodulatory effects are proposed as one mechanism of action of belantamab mafodotin, and it was demonstrated that on the absence of BCMA binding, belantamab mafodotin had a minimal effect on CD4 and CD8 T -cell activation or cytokine release.

Studies on impurities

Product- and process-related impurities have been justified in Module 3, and no additional studies are considered necessary. There are no impurities of known or potential mutagenic concern (as determined by Ames testing and/or Derek and/or Leadscope) that are considered likely to be present in final DS at a level that would not be considered acceptable.

2.5.5. Ecotoxicity/environmental risk assessment

Environmental risk assessment for IgG1 monoclonal antibody (belantamab)

The expected metabolic pathway of the mAb portion of belantamab mafodotin, an anti-B cell maturation antigen BCMA, is degradation to small peptides and individual amino acids by proteolytic enzymes. As stated in Guidance on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2), there is no need to perform environmental assessment for amino acids, peptides or proteins. Thus, no further assessment of the mAb portion has been undertaken.

Environmental risk assessment for Cys-mcMMAF

Screening for persistence, bioaccumulation and toxicity (PBT)

A microtubule disrupting agent monomethyl auristatin F (MMAF) is a synthetic analogue of the natural product peptide dolastatin 10 and is comprised of naturally occurring amino acid building blocks. MMAF consists of five amino acids, namely dolaproine, dolaisoleuine, valine, monomethyl valine and phenylalanine.

Instead of determining an experimental log Kow value for MMAF, the applicant extracted data from the scientific literature. Log K_{ow} of 0.70 was calculated from the structure of MMAF using QikProp 3.0 prediction program and compared to another tubulin inhibitor monomethyl auristatin E (MMAE) (Burns et al. 2017). The authors state that MMAF has a higher aqueous solubility and lower lipid permeability than MMAE due to the charged C-terminal phenylalanine group (Log Po/w = 0.7 vs 2.2) and therefore, as partitioning is intimately associated with solubility/ lipophilicity, it is very likely that the partitioning is lower for MMAF than for MMAE. A distribution coefficient (log D_{ow} at pH 7.4) for the active cytotoxic drug cys-mcMMAF was measured using an exploratory assay [Report 2020N437461]. The resulting Log D_{ow} (partitioning between phosphate buffered saline, pH 7 and octanol) was -1.25. Overall, the range in Log Dow values across pH 4 to 7 was (0.10 to -1.25).

Phase I Risk Assessment

$PEC_{surfacewater}$ of belantamab mafodotin is below the action limit of 0.01 µg/L and no further Phase II Tier A assessment is required.

Table 6. Summary of main study results

Substance (INN/Invented Name): Belantamab mafodotin			
CAS-number (if available): n/a			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Exploratory assay, Chemaxon QSAR prediction and published articles (Burns et al. Mol Pharm 2017 p 415-42; Pliska et al. J. Chromatogr 1981 p 79-92)	Log K_{ow} expected be <4.5	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default/ refined	0.875 (using default F_{pen})	µg/L	> 0.01 threshold Y (default) N (refined)

	0.0025 (using refined F_{pen})		
Other concerns (e.g. chemical class)			N

2.5.6. Discussion on non-clinical aspects

Pharmacology

A comprehensive set of *in vitro* and *in vivo* studies have been conducted in order to elucidate the activity and mechanism of action of belantamab mafodotin (and of the unconjugated mAb). 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 supporting its use in the proposed indication (MM). The *in vivo* anti-tumour activity of belantamab mafodotin was demonstrated in mouse xenograft, orthotopic and immune competent syngeneic models and the pharmacologic activity in cynomolgus monkey.

Belantamab mafodotin functionality was shown over a wide 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 shredded 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 also taken up into cells by a nonspecific mechanism (pinocytosis), unrelated to BCMA receptor expression on the cell membrane.

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.

Overall, the pharmacology of belantamab mafodotin is adequately characterised.

Pharmacokinetics

A comprehensive number of *in vitro* and *in vivo* PK/TK studies were performed with belantamab mafodotin, including the analyses of the antibody and payload. The analytical methods were adequately validated for accurate detection of analytes in different matrixes.

The PK/TK data was collected from single dosing in mouse, rat and monkey after IV and IP (mouse only) administration. The TK data was collected from rat and monkey toxicity studies after IV dosing. In the analysis, belantamab mafodotin, GSK2857914 and cys-mcMMAF were characterised.

In general, rapid absorption was recorded. No differences between analytes were observed in plasma exposure levels. Exposure for ADC and total mAb increased dose-proportionally, and no sex difference

in the systemic exposure (AUC_{0-t} and C_{max}) was observed. Slow plasma clearance and low steady-state volume of distribution suggest that belantamab mafodotin was mainly confined to the systemic circulation. Similarity of the PK of ADC and total mAb suggests stability of MMAF. There were no PK differences between belantamab mafodotin and GSK2857914. Serum $t_{½}$ of ADC was 11 days in rats, a slightly lower in mice, and 4 days in monkeys. In monkeys, ADA development was reported in some animals.

ADC, total mAb and GSK2857914 were shown to distribute to connective tissue in eyes, eye lids, extra-orbital lacrimal and harderian glands, liver, kidney and muscle of the eyelids. The concentration of belantamab mafodotin was 3- and 2-fold higher in the liver and kidney than in the eye. The signal in the eye was shown to be localised in the connective tissue and muscle of eye lids, but not in the cornea. Cys-mcMMAF was detected only in the bone marrow but not in cornea, whole eye or eye lids of the rat.

The metabolism of cys-mcMMAF was shown to be low and primarily characterized by non-enzymatic transformations and to a minor degree by oxidative and conjugative metabolism. There were some differences in the metabolite profiles between the mouse, rat, monkey and human. This is not a concern as the metabolites accounted for less than 5% of the total radioactivity. Furthermore, unique human metabolites that would not have been characterised in the toxicity studies in rats and cynomolgus monkeys were not identified.

Cys-mcMMAF is predominantly excreted via the hepato-biliary/faecal pathway (83%) and to a lesser amount via renal clearance (13%).

Cys-mcMMAF is unlikely to affect PK of co-administered drugs as it was not an inhibitor or inducer of any of the studied CYP enzymes and no inhibition of studied transporters was recorded.

Toxicology

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.

Studies were performed by the IV route of administration for periods of up to 13 weeks in rat (≤30 mg/kg) and monkey (≤10 mg/kg). The doses for sc administration were 2 and 10 mg/kg. The toxicology findings 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, alterations in the bone marrow, spleen and eye (rat) were considered likely to be related to MMAF.

Decreases in immunoglobulins were seen in monkeys at all doses. Increased risk of infections due to immunosuppression and/or neutropenia was noted.

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

Although ADA formation was evident in monkey studies, the exposures were generally maintained and were approximately at the same level in mid-dose animals as the recommended human dose of 2.5 mg/kg. 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 clinical settings, 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. Finding did not correlate with any microscopic alterations, and did not represent a retinal degeneration or adversely affect the surrounding layers. The eye alterations are followed in patients, and the risk mitigation of possible ocular changes and related potential visual impairment is discussed in the clinical safety section of this report.

No carcinogenicity or definitive genotoxicity studies have been conducted with belantamab mafodotin. Belantamab mafodotin was genotoxic in human lymphocytes, consistent with the pharmacological effect of cys-mcMMAF-mediated disruption of microtubules causing aneuploidy. The absence of carcinogenicity studies is accepted. Belantamab mafodotin do not bind to the rat target, thus the 2-year rat studies would not bring in additional information to that what is already known.

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

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. 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). Based on the mechanism of action of the cytotoxic component MMAF, belantamab mafodotin can cause embryo-foetal harm. IgG is known to cross the placenta and therefore, belantamab mafodotin has the potential to be transmitted from the mother to the developing foetus. The risk mitigation measures for pregnancy/duration of contraception for female and male subjects are implemented in section 4.6 of the SmPC.

It is not known whether belantamab mafodotin is excreted into human milk but IgGs are found in small amount in human milk. Based on the mechanism of action, belantamab mafodotin may cause serious adverse reactions in breast-fed children, and a warning is included in section 4.6 of the SmPC, advising women to discontinue breast-feeding prior to initiating treatment and for 3 months after the last dose.

ERA

Belantamab as a mAb is a natural substance and is not expected to pose a risk to the environment. For the cytotoxic drug cys-mcMMAF, instead of determining an experimental log K_{ow} value, the applicant has extracted data from the scientific literature. Evidence was provided that MMAF has a higher

aqueous solubility and lower lipid permeability than the payload analogue MMAE due to the charged C-terminal phenylalanine group (Log Po/w = 0.7 vs 2.2). As partitioning is intimately associated with solubility/ lipophilicity, it follows that it is very likely that the partitioning is lower for MMAF than for MMAE. To further support this, it was shown that measured log Dow for cys-mcMMAF across range pH 4 to 7 was 0.10 to -1.25. Extrapolation from this trend strongly suggests that the log Dow across the environmentally relevant pH spectrum (pH 5-9) is unlikely to exceed 4.5. Quantitative structure-activity relationships (QSAR) predictions support this assumption. The applicant considers that based on the weight of evidence provided, MMAF is unlikely to exceed the log Kow of 4.5 and a PBT assessment is not required. This is endorsed.

2.5.7. Conclusion on the non-clinical aspects

Overall, the pharmacology, pharmacokinetics and toxicology of belantamab mafodotin is adequately characterised. Relevant information has been included in the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with 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**

Study; Phase	**Study design Objectives**	**Healthy participants or diagnosis of patients**	**Total number of participants by group (ITT/Safety analysis set)**	**Study reporting status**
Registrational studies on triplet combination therapy				
207503 (DREAMM-7); Phase 3	Randomised, open-label; Efficacy, safety and tolerability	RRMM Participants had to have at least 1 prior line of MM therapy	Total 494/488 Study Group A (BVd): 243/242 Study Group B (DVd): 251/ 246	Ongoing (primary cut-off date: 02 October 2023)
207499 (DREAMM-8); Phase 3	Randomised, open-label; Efficacy and safety	RRMM Participants had to have at least 1 prior line of MM therapy including lenalidomide	Total 302/295 Study Group A (BPd): 150 participants Study Group B (PVd): 145 participants	Ongoing (primary cut-off date: 29 January 2024)
Supportive studies on triplet combination therapy				

Study; Phase	Study design Objectives	Healthy participants or diagnosis of patients	Total number of participants by group (ITT/Safety analysis set)	Study reporting status
207497 (DREAMM-6); Phase 1/2[a, b]	Non-randomised, open-label, dose escalation and dose expansion; Safety, tolerability, and clinical activity	RRMM Participants had to have at least 1 prior line of MM therapy	Study Arm B (BVd): 107 1.9 mg/kg Q6W Stretch: 12 1.9 mg/kg Q3W Single: 12 2.5 mg/kg Q6W Step Down Stretch: 12 2.5 mg/kg Q6W Stretch: 12 2.5 mg/kg Q3W Split: 13 2.5 mg/kg Q3W Single: 18 3.4 mg/kg Q3W Split: 12 3.4 mg/kg Q3W Single: 16	Ongoing (primary cut-off date: 28 February 2023)
209418 (ALGONQUIN) NCT03715478; Phase 1/2	Open-label, dose expansion; Recommended Part 2 dose, safety and efficacy	RRMM Participants had to have at least 1 prior line of MM therapy	Single arm, multiple dosing cohorts (BPd): 87/87 participants (All Treated Population) Part 1 dose-exploration phase: 61/87 participants Part 2 dose-expansion phase: 26/87 participants (BPd 2.5 mg/kg Q8W) RP2D treatment 38/87 participants (12 in Part 1 and 26 in Part 2)	Ongoing
Supportive studies on monotherapy				
117159 (DREAMM-1); Phase 1	Part 1: Determine RP2D, safety, PK, PD and immunogenicity Part 2: Safety, PK, immunogenicity and clinical activity	RRMM and NHL	Total: 79 enrolled (73MM) Part 1: MM 38 enrolled/33 completed Part 2: MM 35 enrolled/22 completed NHL: 6 enrolled/3 completed	Completed
207495 (DREAMM-3); Phase 3	Randomized, open-label; Safety and efficacy	Participants had to have at least 2 prior lines of MM therapy	Study Group A (Belantamab mafodotin 2.5 mg/kg): 217 participants Study Group B (Pomalidomide/dexamethasone): not relevant for this submission	Ongoing (primary efficacy analysis: 12 September 2022), OS IA 2: 01 March 2024

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Population PK model

The PPK model for belantamab mafodotin ADC and cys-mcMMAF was built using data from studies DREAMM-2, DREAMM-3, DREAMM-6, DREAMM-7, DREAMM-12, DREAMM-14 (total n=977). Samples below the limit of quantification (BLQ) were excluded (4.7% of all ADC samples and 31.5% of all cys-mcMMAF samples).

The model for belantamab mafodotin ADC was developed using a previous model as a starting point. The final model for ADC was a two-compartment model with time-varying CL and the following covariate effects using baseline covariate values: weight (WT), albumin, sBCMA, and body mass index (BMI) on central volume of distribution (V1); WT, albumin, sBCMA, IgG, and race on CL; WT and albumin on ADC peripheral volume of distribution (V2); WT on intercompartmental CL (Q); sBMCA, IgG, and combination therapy on maximum fold-change from baseline in clearance (IMAX). Parameter estimates are summarised in **Table 7**.

The final model for cys-mcMMAF was a two-compartment model with cys-mcMMAF formed from the clearance of belantamab mafodotin ADC and dependent on a drug-antibody ratio (DAR) that declined over time after the previous dose with the following covariate effects using baseline covariate values: sBCMA, IgG, WT, albumin, race, and BMI on the cys-mcMMAF central volume of distribution (V3); sBCMA and WT on the cys-mcMMAF CL (CLMMAF). The estimated disposition parameters were CLMMAF, V3, the distribution rate constant from the central to the peripheral compartment (K34), and the distribution rate constant from the peripheral to the central compartment (K43). Interoccasion variability (IOV) on CLMMAF and on V3 was included in the model. Parameter estimates are summarised in **Table 8**.

Visual evaluation of the final belantamab mafodotin and cys-mcMMAF population PK models with Goodness of Fit and Visual Predictive Check plots (data not shown) indicated that the models adequately described the concentration data.

Table 7. Population PK model parameter estimates of belantamab mafodotin (ADC) during treatment of RRMM (Final Model).

PK parameter (unit)	Estimate	% RSE	% Shrinkage	Lower 95% CI	Upper 95% CI
Typical value					
CL (L/Day)	0.926	1.45	-	0.899	0.952
V1 (L)	4.21	0.813	-	4.15	4.28
Q (L/Day)	0.711	3.64	-	0.660	0.761
V2 (L)	6.63	2.58	-	6.29	6.96
IMAX	–0.403	7.01	-	–0.458	–0.347
TI50 (Day)	66.4	2.21	-	63.5	69.2
Gamma	2.87	7.11	-	2.47	3.27
Covariate effects					
Weight on V1 and V2 (θ_{V_WTBL})	0.929	4.57	-	0.845	1.01
Weight on CL and Q (θ_{CL_WTBL})	0.542	8.71	-	0.449	0.635
Albumin on CL (θ_{CL_ALBBL})	–0.698	10.3	-	–0.839	–0.557

Albumin on V1 (θ_{V1_ALBBL})	−0.302	17.9	-	−0.407	−0.19
Albumin on V2 (θ_{V2_ALBBL})	0.567	25.3	-	0.285	0.849
sBCMA on V1 (θ_{V1_BsBCMA})	0.0401	14.2	-	0.0289	0.0513
sBCMA on CL (θ_{CL_BsBCMA})	0.113	6.34	-	0.0988	0.127
IgG on CL (θ_{CL_IGGBL})	0.170	5.10	-	0.153	0.187
BMI on V1 (θ_{V1_IBMIBL})	−0.459	12.4	-	−0.571	−0.348
Asian race on CL (θ_{CL_RACEA})	0.913	2.55	-	0.867	0.958
AA race on CL (θ_{CL_RACEB})	0.861	3.53	-	0.801	0.921
Combo therapy on Imax (θ_{IMAX_COMBO})	1.44	7.55	-	1.23	1.66
IgG on Imax (θ_{IMAX_IGGBL})	0.192	19.8	-	0.117	0.266
sBCMA on Imax (θ_{IMAX_BsBCMA})	0.160	21.6	-	0.0920	0.227
Between participant variability CV%					
On CL (%)	26.1	3.92	14.9	24.0	28.0
On V1 (%)	20.0	3.60	15.7	18.5	21.3
V1-CL covariance[a]	0.0328	8.69	-	0.0272	0.0383
On Q (%)	19.0	41.0	69.1	NA	31.0
On V2 (%)	30.6	8.47	50.1	25.1	35.4
On IMAX (%)	29.0	10.4	40.6	22.5	34.5
On TI50 (%)	69.3	7.76	53.7	58.4	79.6
Residual error, additive variance on log scale ((log(ng/mL))^2)	0.0633	6.52	12.6	0.0553	0.0714

[a] Correlation coefficient of 0.646

Notes: The 95% CI was calculated using standard errors from the estimation.

Abbreviations: η=individual deviation from the population value; θ=fixed effect parameter (typical value); Ω=between-subject variability variance; ADC=antibody-drug conjugate; ALBBL=baseline albumin; BMI=body mass index; CL=clearance; Combo=combination; CV%=percent coefficient of variation; i=individual subject index; IBMIBL=baseline body mass index; IgG=immunoglobulin G; IGGBL=baseline immunoglobulin G; IMAX=natural log of the maximum fold-change from baseline in clearance; IPRED=individual prediction; Q=intercompartmental clearance; RSE%=percent relative standard error; sBCMA=soluble B-cell maturation antigen; SBCMABL=baseline SBCMA; SQRT=square root; TI50=time from first dose to half-maximal fold-change in clearance on the natural log scale; V1=antibody-drug conjugate central volume of distribution; V2=antibody-drug conjugate peripheral volume of distribution; WTBL=baseline body weight

For a typical patient with RRMM in the analysis population, belantamab mafodotin (ADC) has an initial systemic CL of 0.926 L/day, a Vss of 10.8 L, and an elimination phase half-life of 13.0 days for a typical participant with RRMM in the analysis population. Following monotherapy treatment, CL is reduced by 33.2% to 0.619 L/day over time, resulting in an elimination half-life of 16.8 days. Following combination treatment, CL is reduced by 44.0% to 0.518 L/day, resulting in an elimination half-life of 19.1 days.

In the entire analysis population, the geometric mean (CV%) ADC initial systemic CL was 0.901 L/day (40.0%), Vss was 10.8 L (22.2%), and the elimination half-life was 13.2 days (25.5%). Following treatment, steady-state CL was 0.605 L/day (43.2%) or approximately 32.9% lower than initial systemic CL with an elimination half-life of 17.0 days (31.2%).

Table 8. Population PK parameter estimates from the final cys-mcMMAF model during treatment of RRMM.

Parameter	Estimate	RSE%	95% CI	Shrinkage (%)
Typical values				
CLMMAF (L/day)	642	2.76	607, 677	-
V3 (L)	12.3	22.4	6.91, 17.7	-
K34 (1/day)	186	23.9	98.9, 273	-
K43 (1/day)	5.97	5.34	5.34, 6.6	-
RATE-DAR (1/day)	0.0381	4.01	0.0351, 0.0411	-
Covariate effects				
sBCMABL on CLMMAF (ΘCL_SBCMABL)	-0.0448	33.9	-0.0746, -0.0151	-
Weight on CLMMAF (ΘCL_WTBL)	0.701	12.6	0.528, 0.875	-
Albumin on V3 (ΘV3_ ALBBL)	-0.533	28.8	-0.835, -0.232	-
IgG on V3 (ΘV3_IGGBL)	0.184	9.93	0.148, 0.22	-
sBCMABL on V3 (ΘV3_SBCMABL)	0.107	16	0.0732, 0.14	-
Weight on V3 (ΘV3_WTBL)	1.24	13.5	0.912, 1.57	-
Asian race on V3 (ΘV3__RACEA)	0.816	5.74	0.724, 0.908	-
AA race on V3 (ΘV3__RACEB)	0.746	9.58	0.606, 0.886	-
BMI on V3 (ΘV3_BMI)	-0.853	23.8	-1.25, -0.455	-
Between-subject and interoccasion variability CV%				
On CLMMAF	29.6	10.6	22.4, 35.5	35.7
CLMMAF-V3 covariance[a]	0.0816	13.7	0.0597, 0.103	-
On V3	65.2	3.7	59.5, 70.7	17.3
V3-K43 covariance[b]	0.372	11.5	0.288, 0.456	-
On K43	137	4.11	119, 155	30.1
On IOV CLMMAF	56.7	2.86	53, 60.3	42.7
On IOV V3	45	2.41	42.7, 47.3	36.1
Residual error				
Proportional error CV%	26.2	1.05	25.6, 26.7	27
Additive error SD (nmol/L)	1×10^{-6} FIXED	-	-	-

a *Correlation coefficient of 0.474*
b *Correlation coefficient of 0.609*
Notes: The 95% CI was calculated using standard errors from the estimation.
Abbreviations: η=individual deviation from the population value; θ=fixed effect parameter (typical value); Ω=between-subject variability variance; AA=African American; ALBBL=baseline albumin; BMI=body mass index; CI=confidence interval; CL=clearance; CLMMAF=cys-mcMMAF clearance; CV%=percent coefficient of variation; i=individual subject index; IBMIBL=baseline body mass index; IgG=immunoglobulin G; IGGBL=baseline immunoglobulin G; IOV=interoccasion variability; IPRED=individual prediction; K34=distribution rate constant from the central to the peripheral compartment; K43=distribution rate constant from the peripheral to the central compartment; RATE-DAR=rate change in drug-antibody ratio over time since most recent dose; RSE%=percent relative standard error; sBCMABL=baseline soluble B-cell maturation antigen; SD=standard deviation; SQRT=square root; V3=cysmcMMAF central volume of distribution; WTBL=baseline body weight

For belantamab mafodotin (ADC) at dose of 2.5 mg/kg, the GeoMean (geometric CV%) Cmax was 43.7 µg/mL (22.1%), Cavg21 was 7.83 µg/mL (30.6%), Ctau was 2.03 µg/mL (62.5%), and AUC(0-21days) was 3950 µg·h/mL (30.6%) at the end of first Q3W dosing interval. For cys-mcMMAF, the GeoMean (geometric CV%) Cmax was 0.976 ng/mL (45.3%), Cavg21 was 0.243 ng/mL (42.4%), and AUC(0-7days) was 94.2 ng·h/mL (42.3%) at the end of first Q3W dosing interval.

Absorption

Bioavailability of belantamab mafodotin is 100% since it is administered by IV infusion which occurred at or shortly after the end of infusion while cys-mcMMAF concentrations peaked ~24 hours after dosing.

Distribution

Based on the population PK (PPK) analysis, the geometric mean (CV%) volume of distribution at steady-state is 10.8 L (22.2%) for belantamab mafodotin antibody-drug compound (ADC). The cytotoxic small drug component cys-mcMMAF exhibited low protein binding *in vitro* in human plasma in a concentration-dependent manner, the unbound percentages ranged from 49 to 62% at 0.5 ng/mL and from 69 to 71% at 5 ng/mL.

Metabolism

Belantamab mafodotin antibody component is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes.

Cys-mcMMAF exhibited very limited Phase I/II enzymatic biotransformation *in vitro*, which indicates that it is unlikely to be a victim of a drug-drug interaction (DDI) with inhibitors or inducers of CYP enzymes.

Cys-mcMMAF was an *in vitro* substrate of OATP1B1, OATP1B3, MRP1, MRP2, and MRP3, a borderline substrate of BSEP, and possibly a substrate of P-gp. Cys-mcMMAF was not an *in vitro* inhibitor of human BSEP, BCRP, MDR1, MRP1, MRP2, MRP3, MRP4, MRP5, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 transporters at concentrations up to 200 nM.

Elimination

The monoclonal antibody component of belantamab mafodotin is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Results of *in vitro* and non-clinical studies in rats indicate that enzymatic metabolism of cys-mcMMAF is very limited and the main pathway of elimination is excretion of intact cys-mcMMAF into the bile. In study DREAMM-12, the amount of cys-mcMMAF excreted in urine over 504 h was approximately 18% of the dose in patients with normal renal function or mild renal impairment.

Dose proportionality and time dependencies

In study DREAMM-2, clearance and volume of distribution of belantamab mafodotin (calculated using non-compartmental methods) were comparable at doses 2.5 mg/kg and 3.4 mg/kg (

Table *9* and

Table *10*).

Table 9. Belantamab Mafodotin PK Parameter Values at Cycle 1 (DREAMM-2)

	2.5 mg/kg Frozen (N=95)		3.4 mg/kg Frozen (N=99)		3.4 mg/kg Lyo (N=24)	
	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)
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)

Table 10. Belantamab Mafodotin PK Parameter Values at Cycle 3 (DREAMM-2)

	2.5 mg/kg Frozen (N=95)		3.4 mg/kg Frozen (N=99)		3.4 mg/kg Lyo (N=24)	
	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)
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	11.64 (40)

Geometric mean (%CVb) accumulation ratio values from cycle 1 to cycle 3 following 2.5 mg/kg Q3W were 1.69 (50) and 1.09 (20) for AUC_{0-T} and C_{max}, respectively. Decreasing clearance over time was observed, which was also seen in the PPK analysis.

Cys-mcMMAF trough concentrations were consistently below or very close to the lower limit of quantification and no accumulation was observed.

Study DREAMM-1 was a first time in human study, in which doses from 0.03 mg/kg to 4.6 mg/kg were evaluated in small number of patients (n=1 to 8 per dose category). The power model approach was applied to evaluate dose proportionality. Cycle 1 C_{max} and AUC_{0-T} values for belantamab mafodotin appeared to increase proportionally with dose. The 90% CIs for the slopes for these parameters included the value 1.0, indicating that the results were consistent with dose proportionality.

In study DREAMM-6 Arm B, however, cycle 1 exposure to belantamab mafodotin appeared to increase slightly less than in proportion to the dose over the range 1.9 mg/kg to 3.4 mg/kg.

Special populations

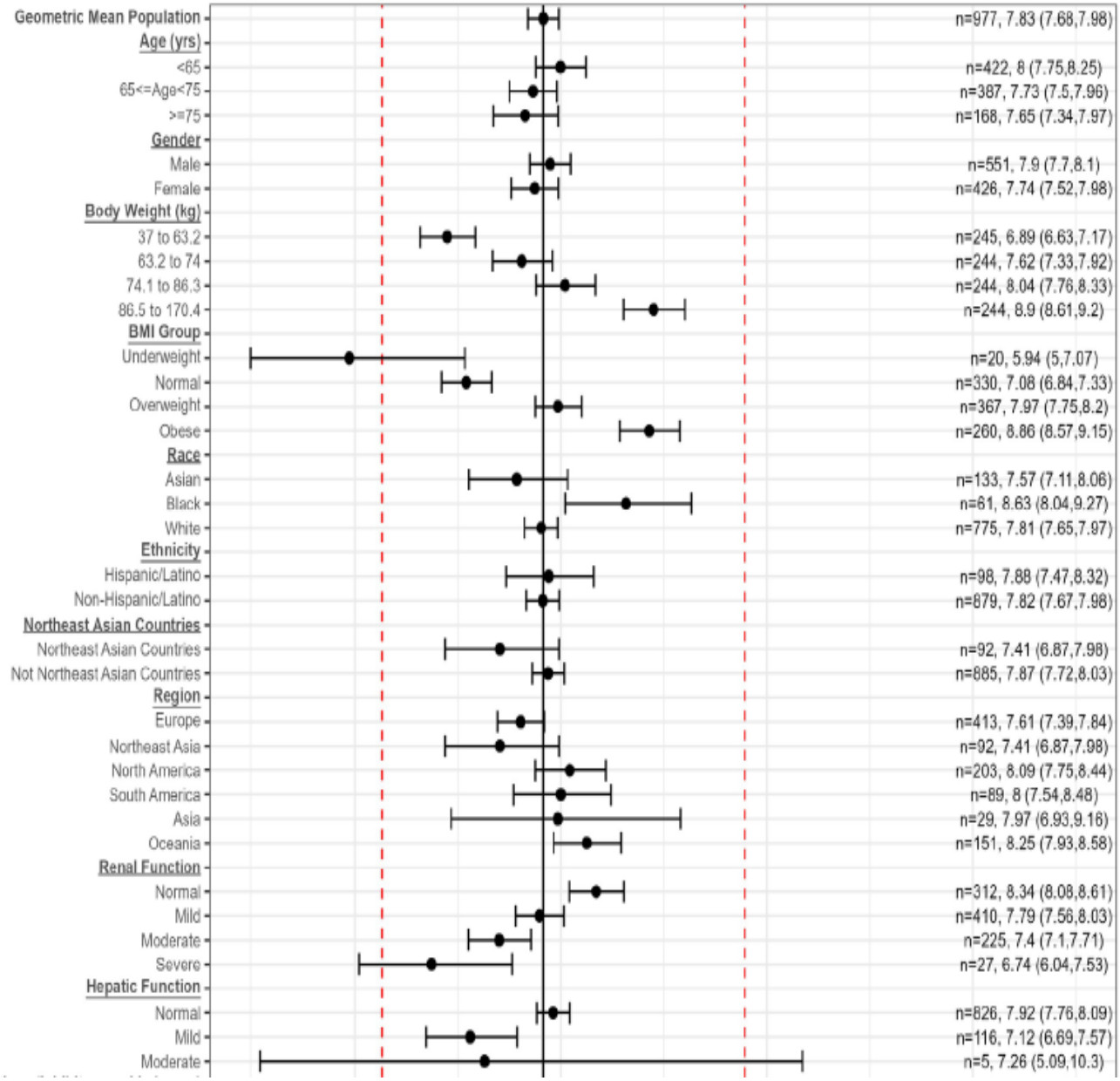
Pharmacokinetics in special populations was evaluated using PPK models for belantamab mafodotin ADC and cys-mcMMAF. Post hoc exposure measures were simulated for Cycle 1 using the actual dose administered to each participant with their specific demographic and empirical Bayes estimates from the final population PK models. Exposure (C_{avg}) to belantamab mafodotin and cys-mcMMAF (normalised to a 2.5 mg/kg dose) in special populations is summarized in **Figure 4** and

The solid black circle represents the geometric mean, and the error bar represents the 95% confidence interval. The solid black line represents the geometric mean value of all participants. The dashed red lines represent an interval of 0.8 to 1.25 times the geometric mean of all participants. N=sample size and the numbers represent the geometric mean and 95% confidence interval for that subgroup. All the participant exposures were normalized to a 2.5 mg/kg dose. Subgroups with <5 participants were

omitted from the plot. Missing data were imputed at the median value for the population.
BMI groupings: Underweight≤18.5, Normal=18.5 to 24.9, Overweight=25 to 29.9, Obese=30+.

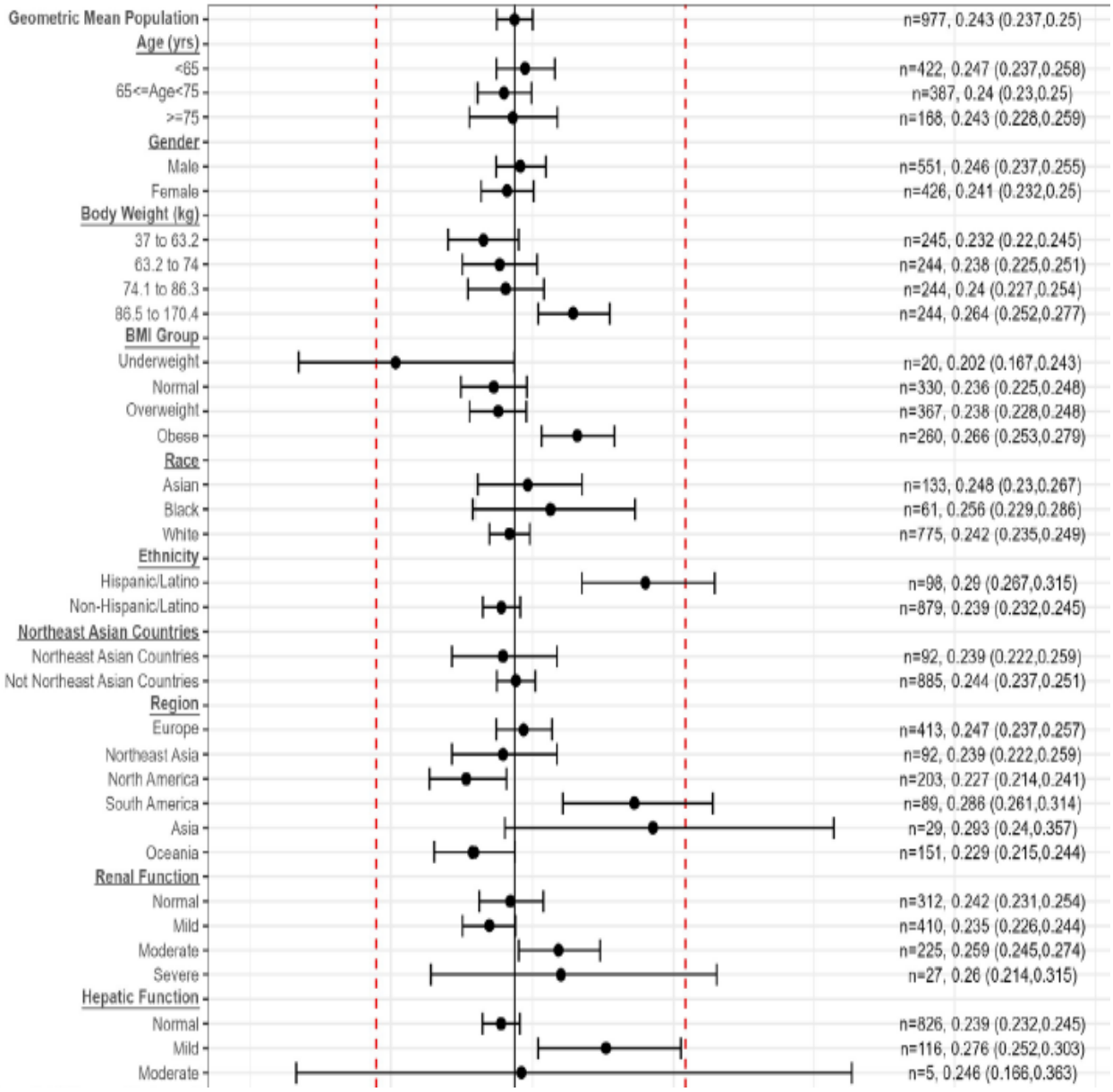
Figure *5*, respectively.

Figure 4. Forest plot of post hoc Cycle 1 belantamab mafodotin average concentration (C_{avg}) in various sub-populations.



The solid black circle represents the geometric mean, and the error bar represents the 95% confidence interval. The solid black line represents the geometric mean value of all participants. The dashed red lines represent an interval of 0.8 to 1.25 times the geometric mean of all participants. N=sample size and the numbers represent the geometric mean and 95% confidence interval for that subgroup. All the participant exposures were normalized to a 2.5 mg/kg dose. Subgroups with <5 participants were omitted from the plot. Missing data were imputed at the median value for the population.
BMI groupings: Underweight≤18.5, Normal=18.5 to 24.9, Overweight=25 to 29.9, Obese=30+.

Figure 5. Forest plot of post hoc Cycle 1 cys-mcMMAF average concentration (C_{avg}) in various special populations.



The solid black circle represents the geometric mean, and the error bar represents the 95% confidence interval. The solid black line represents the geometric mean value of all participants. The dashed red lines represent an interval of 0.8 to 1.25 times the geometric mean of all participants. N=sample size and the numbers represent the geometric mean and 95% confidence interval for that subgroup. All the participant exposures were normalized to a 2.5 mg/kg dose. Subgroups with <5 participants were omitted from the plot. Missing data were imputed at the median value for the population.
BMI groupings: Underweight≤18.5, Normal=18.5 to 24.9, Overweight=25 to 29.9, Obese=30+.

Pharmacokinetics of belantamab mafodotin and cys-mcMMAF in patients with severe renal impairment (GFR 15-29 mL/min) and patients with normal or mildly impaired renal function were compared in study DREAMM-12 Part 1. Following the first 2.5 mg/kg dose, patients with severe renal impairment had on average lower plasma exposures of belantamab mafodotin ADC (**Table 11**) and cys-mcMMAF (**Table 12**) than participants with normal or mildly impaired renal function.

Table 11. Cycle 1 Belantamab Mafodotin (ADC) PK Parameters (DREAMM-12)

PK parameter	Group 1 (Normal or mild renal impairment) (N=8)		Group 2 (Severe renal impairment) (N=8)		Comparison Group 2 vs. Group 1
	n	PK values	n	PK values	Geometric LS mean ratio (90% CI)
AUC(0-tlast) (h·µg/mL)	8	4021.3 (54.3)	8	3704.7 (32.4)	-
tlast (h)	8	396.3 (163.0, 579.9)	8	506.4 (503.3, 528.4)	-
AUC(0-τ) (h·µg/mL)	4	4379.2 (32.4)	8	3683.1 (32.6)	0.841 (0.591, 1.196)
C-EOI (µg/mL)	8	54.43 (31.5)	7	45.66 (20.8)	-
Cmax (µg/mL)	8	62.01 (38.4)	8	47.62 (24.8)	0.768 (0.582, 1.013)
tmax (h)	8	1.508 (0.650, 2.083)	8	3.000 (0.667, 7.400)	-
Ctrough (µg/mL)	4	1.954 (63.8)	8	2.178 (39.9)	-
Note 1: Data presented as GeoMean (%CVb), except tlast and tmax, presented as median (minimum, maximum). Note 2: Tau was 504 h postdose.					

Table 12. Cycle 1 cys-mcMMAF PK Parameters (DREAMM-12)

	Group 1 (Normal or mild renal impairment) (N=8)		Group 2 (Severe renal impairment) (N=8)		Comparison Group 2 vs. Group 1
	n	PK values	n	PK values	Geometric LS mean ratio (90% CI)
AUC(0-tlast) (h·ng/mL)	8	127.3 (81.3)	8	77.1 (53.1)	-
tlast[a] (h)	8	190.6 (163.0, 359.5)	8	167.7 (166.6, 334.3)	
AUC(0-168) (h·ng/mL)	6	134.7 (99.8)	8	75.2 (48.2)	0.558 (0.301, 1.034)
Cmax (ng/mL)	8	1.63 (64.0)	8	0.71 (48.2)	0.436 (0.274, 0.693)
tmax[a] (h)	8	16.017 (0.917, 92.600)	8	23.400 (7.400, 30.700)	-
Data presented as GeoMean (%CVb), except tlast and tmax, presented as median (minimum, maximum).					

The Geometric LS mean ratio (90% CI) for the comparison between end stage renal disease-not on dialysis (N=3) and Group 1 was 0.867 (0.534, 1.409) and 1.054 (0.731, 1.519) for the AUC(0-T) and Cmax respectively for belantamab mafodotin and 1.973 (0.902, 4.312) and 1.836 (0.874, 3.855) for AUC(0-168) and Cmax respectively for cys-mcMMAF.

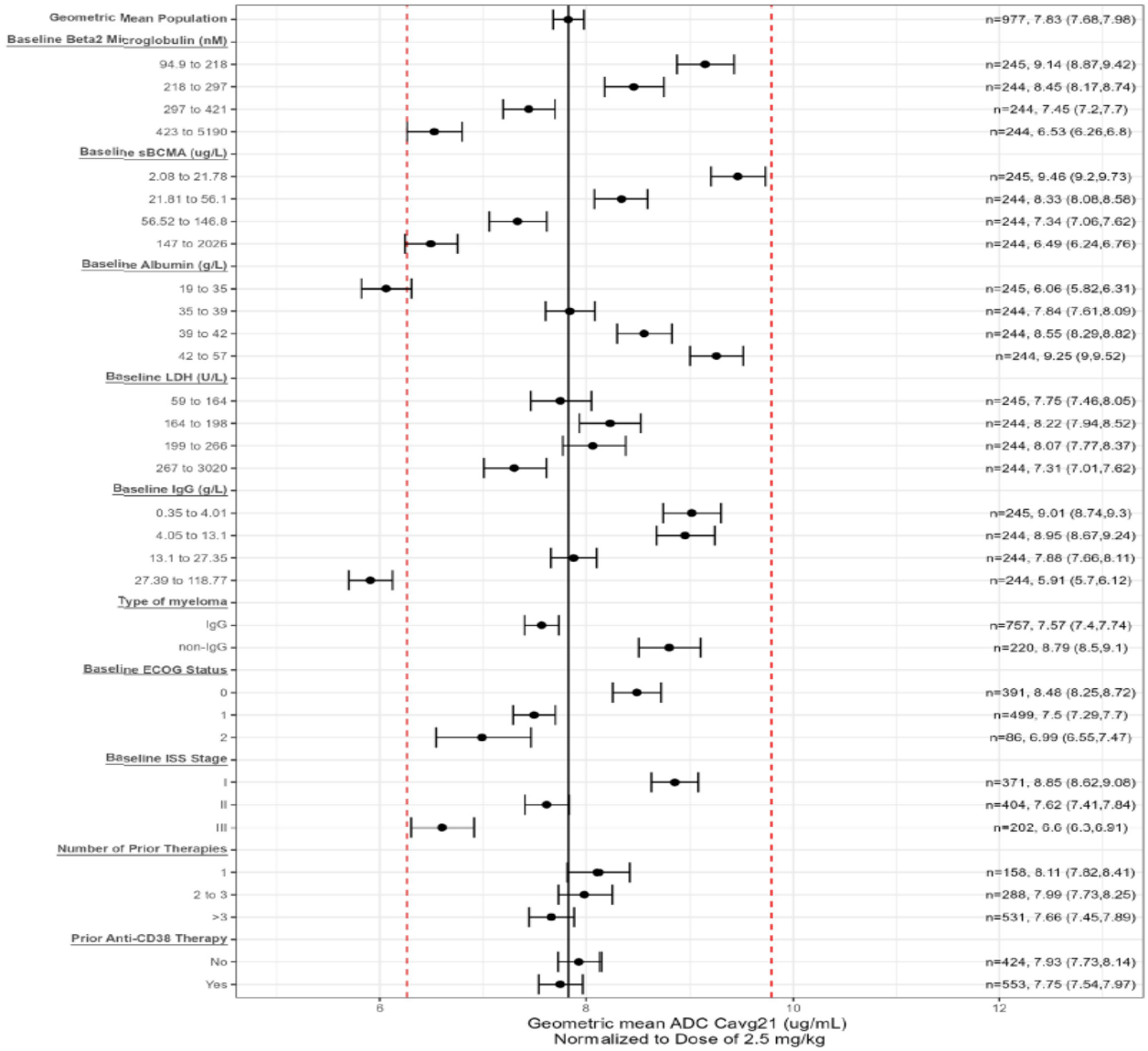
The Geometric LS mean ratio (90% CI) for the comparison between end stage renal disease-on dialysis (N=5) and Group 1 was 1.186 (0.684, 2.055) and 0.841 (0.618, 1.144) for the AUC(0-T) and Cmax respectively for belantamab mafodotin and 0.759 (0.308, 1.873) and 0.574 (0.308, 1.073) (0.874, 3.855) for AUC(0-168) and Cmax respectively for cys-mcMMAF.

The number of elderly subjects included in the PPK analysis dataset is summarised below.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Population PK analysis dataset	387 / 977	158 / 977	10 / 977

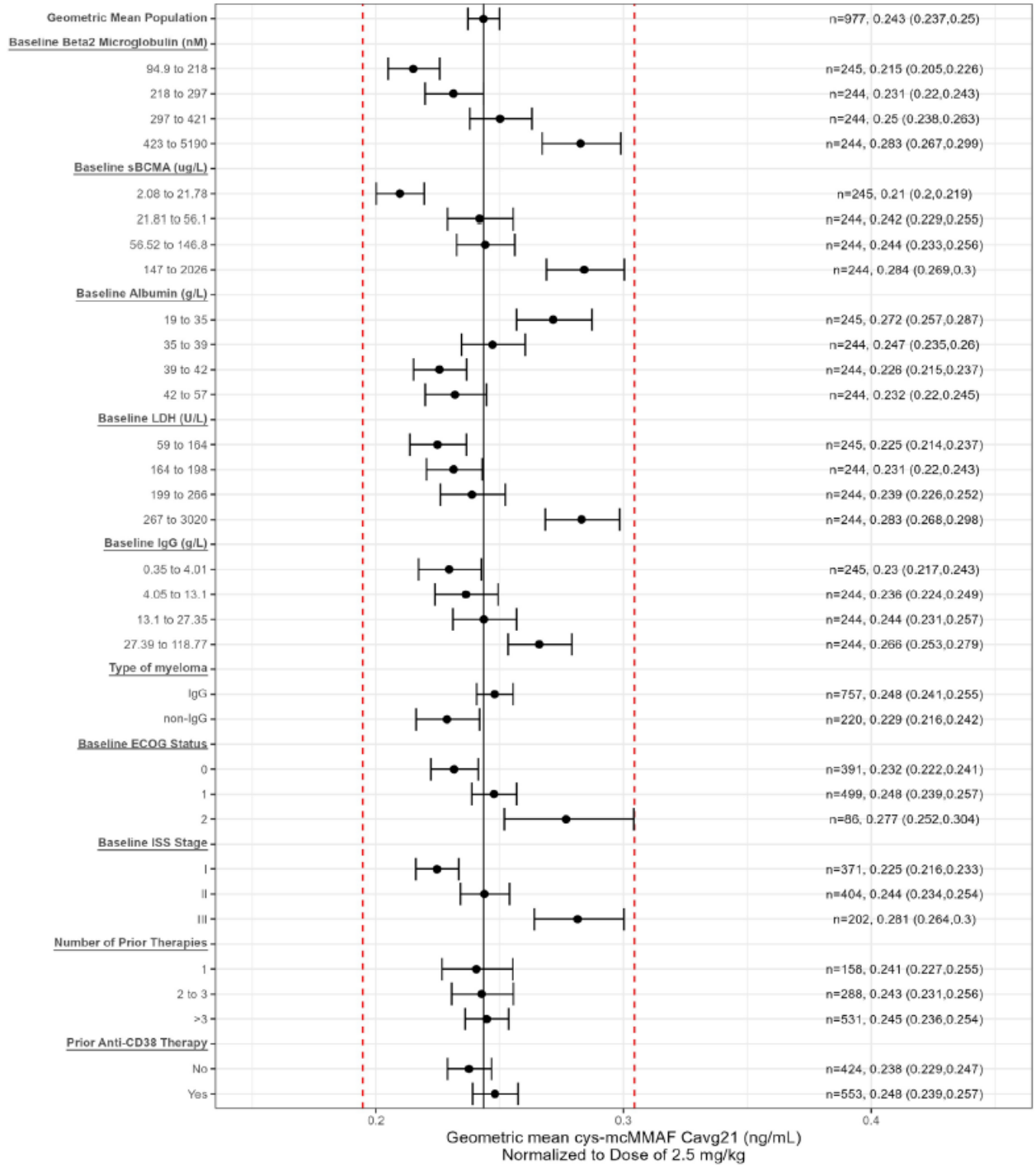
Several disease-related characteristics were statistically significant covariates in PPK models, including baseline sBCMA, IgG, and albumin. Forest plots of the post hoc predicted Cycle 1 belantamab mafodotin and cys-mcMMAF C_{avg} normalized to a 2.5 mg/kg dose for disease characteristics are shown in **Figure 6** and **Figure 7**, respectively.

Figure 6 . Forest plot of post hoc Cycle 1 belantamab mafodotin average concentration in various disease characteristics subgroups.



The solid black circle represents the geometric mean, and the error bar represents the 95% confidence interval. The solid black line represents the geometric mean value of all participants. The dashed red lines represent an interval of 0.8 to 1.25 times the geometric mean of all participants. N=sample size and the numbers represent the geometric mean and the 95% confidence interval for that subgroup. Subgroups with <5 participants were omitted from the plot. Missing data were imputed at the median value for the population. ADC=antibody-drug conjugate; Cavg=average concentration over a dosing interval; Cavg21=Cavg of 21 days; CD=cluster of differentiation; ECOG=Eastern Cooperative Oncology Group; IgG=immunoglobulin G; ISS=International Staging System; LDH=lactate dehydrogenase; sBCMA=soluble B-cell maturation antigen.

Figure 7. Forest plot of post hoc Cycle 1 cys-mcMMAF average concentration in various disease characteristics subgroups.



The solid black circle represents the geometric mean, and the error bar represents the 95% confidence interval. The solid black line represents the geometric mean value of all participants. The dashed red lines represent an interval of 0.8 to 1.25 times the geometric mean of all participants. N=sample size and the numbers represent the geometric mean and the 95% confidence interval for that subgroup. Subgroups with <5 participants were omitted from the plot. Missing data were imputed at the median value for the population. ADC=antibody-drug conjugate; Cavg=average concentration over a dosing interval; Cavg21=Cavg of 21 days; CD=cluster of differentiation; ECOG=Eastern Cooperative Oncology Group; IgG=immunoglobulin G; ISS=International Staging System; LDH=lactate dehydrogenase; sBCMA=soluble B-cell maturation antigen.

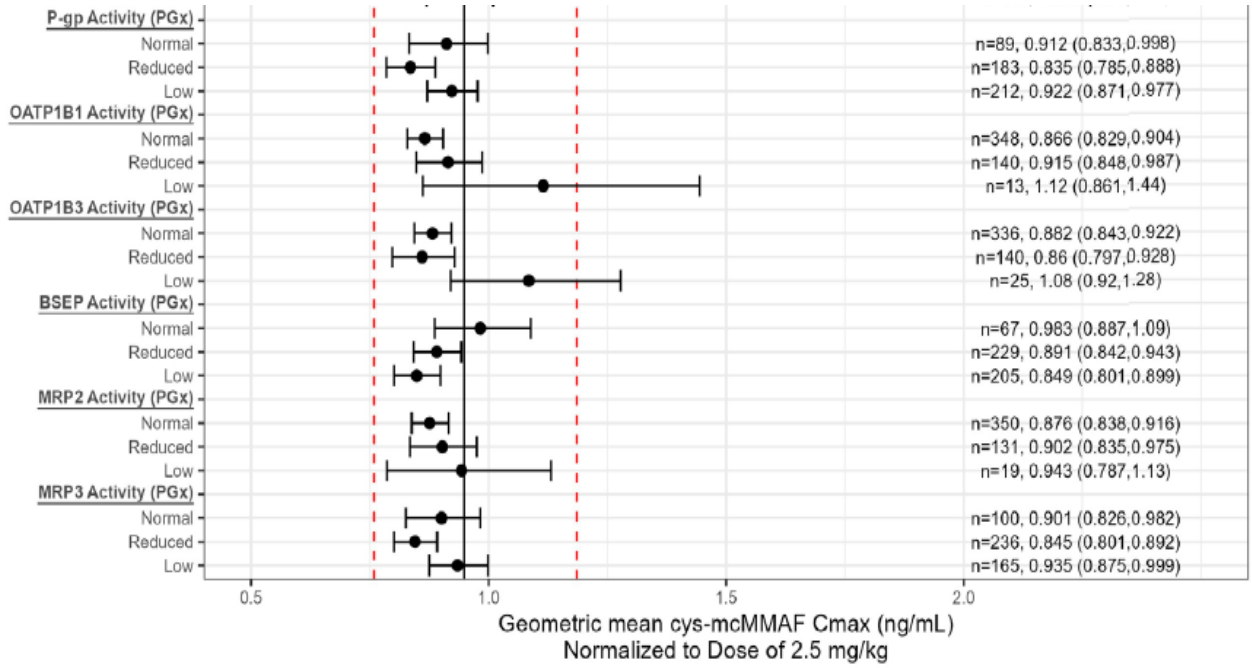
Pharmacokinetic interaction studies

Dedicated clinical drug-drug interaction studies were not submitted. Belantamab mafodotin was co-administrated with bortezomib and dexamethasone (Vd) in DREAMM-6 Arm B and DREAMM-7 Arm A, with pomalidomide and dexamethasone (Pd) in DREAMM-8 Arm A, and with lenalidomide and dexamethasone (Rd) in DREAMM-6 Arm A in participants with RRMM. In these studies, PK parameters of belantamab mafodotin and cys-mcMMAF following the first dose of belantamab mafodotin in combination with Vd, Pd, or Rd were generally comparable to those in studies where belantamab mafodotin was given as monotherapy at the same dose level. Observed exposures to bortezomib, pomalidomide, and lenalidomide in the three studies were comparable with published historical data.

Consequences of possible genetic polymorphism

Genotype data for genes encoding P-gp, OATP1B1, OATP1B3, MRP2, MRP3, and BSEP transporters was available for a subset of patients in the PPK analysis dataset. Post hoc Cycle 1 cys-mcMMAF exposures were graphically explored in these subjects (**Figure 8**); the proportion of missing pharmacogenomic data was too high to allow formal covariate analysis.

Figure 8. Forest plot of post hoc Cycle 1 cys-mcMMAF peak concentration (C_{max}) by transporter activity.



The solid black circle represents the geometric mean (GeoMean), and the error bar represents the 95% CI. The solid black line represents the GeoMean value of all participants. The dashed red lines represent an interval of 0.8 to 1.25 times the GeoMean of all participants. n=sample size and number represent the GeoMean and the 95% CI for that subgroup. All participant exposures were normalized to 2.5 mg/kg dose. Patients with unknown genotype (activity) were excluded.

2.6.2.2. Pharmacodynamics

Mechanism of action

Belantamab mafodotin is an anti-BCMA immunoconjugate with an afucosylated, humanized immunoglobulin G1 anti-BCMA monoclonal antibody conjugated by a protease-resistant maleimidocaproyl linker to a microtubule disrupting agent, monomethyl auristatin F. Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell, disrupting the microtubule network and leading to cell cycle arrest and apoptosis, in its function as an antibody-drug conjugate. Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells, which can kill 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.

The mechanism of action of belantamab mafodotin enables antitumor activity of cells by ADCC/ADCP activity (non-dividing cells) as well as ADC activity (dividing cells). The normal function of BCMA is to promote cell survival by transduction of signals from two known ligands (B-cell activating factor from the tumour necrosis factor [TNF] family [BAFF/BLyS] and a proliferation-inducing ligand [APRIL]). BCMA expression is restricted to B cells at later stages of differentiation, with expression on germinal centre B cells in tonsil, blood plasma blasts, and long-lived plasma cells.

Primary and Secondary pharmacology

Primary and secondary pharmacology is discussed in the non-clinical aspects section of this report.

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.

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

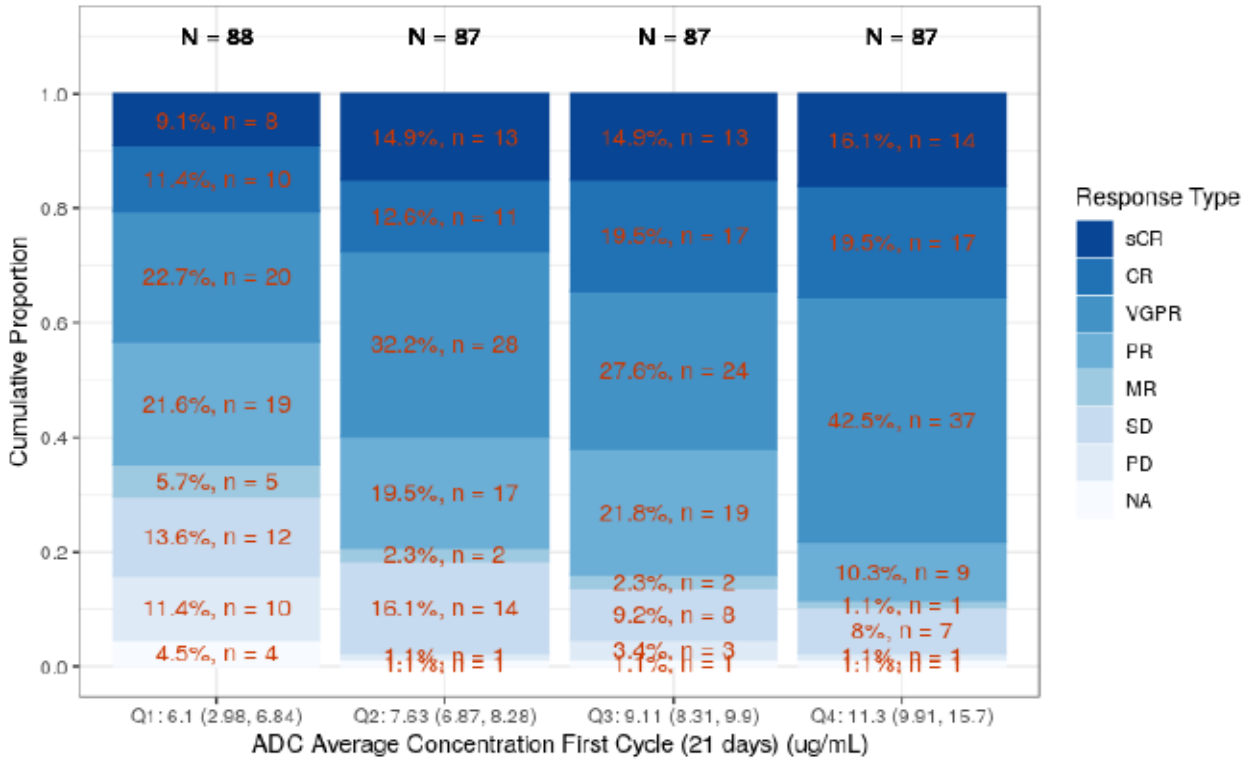
Exposure-response (E-R) analyses were conducted separately for belantamab mafodotin in combination with Vd (pooled data of DREAMM-7 and DREAMM-6 Part B) and for belantamab mafodotin in combination with Pd (DREAMM-8). Exposure measures for Cycle 1 were derived using the individual post hoc estimates obtained from the PPK analysis. Logistic regression models were used to assess the

probability of efficacy or safety endpoints occurring, while Cox proportional hazard models were used to assess time-to-event endpoints.

Belantamab mafodotin in combination with Vd

The best response category by Cycle 1 belantamab mafodotin (ADC) C_{avg} quartile is shown in **Figure 9**.

Figure 9. Best Response by Cycle 1 ADC C_{avg} Quartile (DREAMM-7 and DREAMM-6 Arm B).



Notes: The summary statistics for each quartile are reported on the x-axis as median (minimum, maximum).
Abbreviations: ADC=antibody-drug conjugate; Cavg=average concentration over a dosing interval of 21 days; CR=complete response; MR=minimal response; N=number of subjects; n=number of subjects in the subgroup; NA=missing; PD=progressive disease; PR=partial response; Q1=1st quartile; Q2=2nd quartile; Q3=3rd quartile; Q4=4th quartile; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response

In participants of DREAMM-7, the probability of a Grade ≥2 or a Grade ≥3 ocular adverse events of special interest (AESI) (Common Terminology Criteria for Adverse Events (CTCAE) grade) was not statistically significantly associated with Cycle 1 ADC exposure or with Cycle 1 cys-mcMMAF exposure. Participants of DREAMM-6 were not included in the analysis because different criteria were used for reporting ocular AESI of DREAMM-6 and DREAMM-7.

The analyses for unilateral and bilateral worsening of best corrected visual acuity (BCVA) to 20/50 or worse were conducted only for participants of DREAMM-7. Participants who experienced unilateral worsening of BCVA to 20/50 or worse on average tended to have higher ADC exposures and lower cys-mcMMAF exposures compared to participants who did not. The final model for probability of probability of unilateral worsening of BCVA to 20/50 or worse included baseline BCVA for the worst eye and Cycle 1 cys-mcMMAF C_{max}. Higher baseline BCVA for the worst eye and lower Cycle 1 cys-mcMMAF C_{max} were associated with a higher probability of unilateral worsening of BCVA to 20/50 or worse. Likewise, participants who experienced bilateral worsening of BCVA to 20/50 or worse on average tended to have higher ADC exposures and lower cys-mcMMAF exposures compared to participants who did not. However, the final model for probability of bilateral worsening of BCVA to 20/50 or worse included only

baseline BCVA for the best eye. Higher baseline BCVA for the best eye was associated with a higher probability of bilateral worsening in BCVA to 20/50 or worse.

In pooled analysis of DREAMM-7 and DREAMM-6 Arm B data, probabilities of Grade ≥2 and Grade ≥3 corneal event (KVA scale) and of Grade ≥2 and Grade ≥3 corneal exam finding (KVA scale) increased with increasing Cycle 1 belantamab mafodotin exposure. Other covariates were not found to be statistically significantly associated with these endpoints.

In pooled analysis of DREAMM-7 and DREAMM-6 Arm B data, none of the explored Cycle 1 ADC and cys-mcMMAF exposure measures were statistically significantly associated with Grade ≥3 thrombocytopenia. The final model for probability of Grade ≥3 thrombocytopenia included only baseline platelet count. Higher baseline platelet count was associated with a lower probability of Grade ≥3 thrombocytopenia.

In pooled analysis of DREAMM-7 and DREAMM-6 Arm B, 89.4% of participants experienced a Grade 3-4 treatment-emergent adverse event (TEAE). No exposure measures or other covariates were statistically significantly associated with the probability of a Grade 3-4 TEAE.

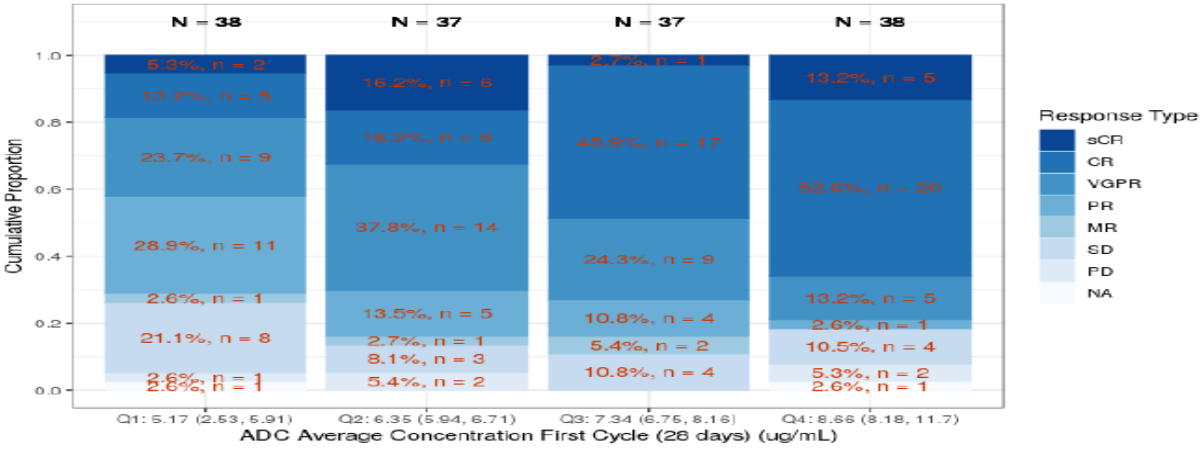
E-R analyses for a fatal serious adverse event (SAE) were not performed due to the low incidence rate (3.2%).

In DREAMM-7, 220 (90.9%) of the 242 participants, whereas in DREAMM-6 Arm B, 94 (87.9%) of the 107 participants experienced a treatment-emergent adverse event (TEAE) led dose modification (dose discontinuation, dose delay/interruption, or dose reduction). E-R analyses were not performed for any dose modification due to the high incidence rate, but they were performed separately for dose discontinuation, dose delay/interruption, and dose reduction. Higher Cycle 1 ADC exposure measures were associated with a higher probability of dose delay/interruption. Cycle 1 ADC and cys-mcMMAF exposure measures were not statistically significantly associated with probabilities of dose discontinuation or of dose reduction.

Belantamab mafodotin in combination with Pd

The best response category by Cycle 1 belantamab mafodotin (ADC) C_{avg} quartile is shown in **Figure 10**.

Figure 10. Best Response by Cycle 1 ADC C_{avg} Quartile (DREAMM-8).



None of the Cycle 1 exposure measures were statistically significantly associated with the probability of a Grade ≥2 or a Grade ≥3 Ocular AESI (CTCAE grade). Lower Cycle 1 cys-mcMMAF C_{max} were

associated with a higher probability of unilateral worsening of BCVA to 20/50 or worse; no other covariates were included in the final model. No exposure measures or other covariates were statistically significantly associated with the probability of bilateral worsening of BCVA to 20/50 or worse.

Probabilities of Grade ≥2 corneal event (KVA scale) and of Grade ≥2 corneal exam finding (KVA scale) increased with increasing Cycle 1 belantamab mafodotin exposure. Other covariates were not found to be statistically significantly associated with these endpoints. No exposure measures or other covariates were found to be statistically significantly associated with Grade ≥3 corneal event (KVA scale) or Grade ≥3 corneal exam finding (KVA scale).

None of the explored Cycle 1 ADC and cys-mcMMAF exposure measures were statistically significantly associated with Grade ≥3 thrombocytopenia. The final model for probability of Grade ≥3 thrombocytopenia included only baseline platelet count. Higher baseline platelet count was associated with a lower probability of Grade ≥3 thrombocytopenia.

E-R analyses for a Grade 3-4 TEAE were not performed due to the high incidence rate (92%).

No exposure measures or other covariates were statistically significantly associated with the probability of a fatal serious adverse event (SAE).

In DREAMM-8, 124 (82.7%) of the 150 participants experienced a TEAE led dose modification. Probability of a dose modification appeared to increase with increasing Cycle 1 ADC exposure and decrease with increasing Cycle 1 cys-mcMMAF exposure. The final logistic regression analysis model included only Cycle 1 cys-mcMMAF C_{max}. Higher Cycle 1 cys-mcMMAF C_{max} was associated with a lower probability of dose modification led by TEAE. Higher Cycle 1 ADC exposure measures were associated with a higher probability of dose delay/interruption. Cycle 1 ADC and cys-mcMMAF exposure measures were not statistically significantly associated with probabilities of dose discontinuation or of dose reduction.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

PPK models for belantamab mafodotin (ADC) and cys-mcMMAF were developed using PK datasets from 6 clinical studies and commonly used methodology and software. Parameters of the ADC PPK model were estimated with generally good precision. ETA shrinkage was low for CL and V1 (14.9% and 15.7%, respectively) but high for Q, V2, Imax, and TI50 (40.6% to 69.1%). Time-varying clearance (decreasing CL over time) was captured by the model. Parameters of the cys-mcMMAF PPK model were estimated with good to moderate precision. ETA shrinkage was low for V3 (17.3%) but high for other parameters (30.1% to 42.7%).

The PPK models for belantamab mafodotin (ADC) and cys-mcMMAF are considered appropriate to evaluate the effects of covariates on PK and to provide exposure measures for exposure-response analyses.

Clinical PK information are mostly from efficacy and safety studies with relatively sparse PK sampling. Therefore, evaluation of PK relies heavily on population PK analysis and is partly supported by noncompartmental analysis of individual study data.

Bioavailability of belantamab mafodotin is complete because it is administered intravenously. The geometric mean (CV%) volume of distribution of belantamab mafodotin is 10.8 L (22.2%), based on the population PK (PPK) analysis, suggesting limited distribution.

The IgG moiety of belantamab mafodotin ADC is a protein which is expected to be degraded to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Elimination pathways of the protein component were not investigated, which is acceptable. Elimination pathways of the cytotoxic moiety cys-mcMMAF have not been characterised in a human mass-balance study. In rats, excretion of intact cys-mcMMAF into the bile was the major route of elimination. Results of study DREAMM-12 demonstrated that renal excretion of cys-mcMMAF is a minor elimination pathway in humans, representing <20% of total clearance. *In vitro* studies indicated that phase I/II enzymatic biotransformation of cys-mcMMAF is limited. Overall data indicate that biliary excretion of unmetabolized cys-mcMMAF is the main pathway of elimination in humans as in rats.

Dose proportionality has not been thoroughly investigated in a dedicated study. Results of DREAMM-1 and DREAMM-2 indicated approximately dose proportional PK for belantamab mafodotin, whereas results of DREAMM-6 suggested less than dose proportional increase in exposure over the range 1.9 mg/kg to 3.4 mg/kg. Results of PPK analysis indicated no effects of dose on PK. Considering that the proposed dose range is narrow (2.5 mg/kg with bortezomib and dexamethasone; first dose 2.5 mg/kg followed by 1.9 mg/kg with pomalidomide and dexamethasone) and no major deviations from dose proportionality are expected with the proposed dose regimens, supplemental analyses are not expected to affect dose regimens and benefit/risk assessment.

Clearance of belantamab mafodotin decreases over time and was associated with minimal to moderate accumulation of belantamab mafodotin (the ratio from cycle 3 to cycle 1 was 1.13 for Cmax and 1.58 for AUC) and accumulation of cys-mcMMAF was negligible as observed in clinical trials with a every 3 weeks dosing regimen. PPK analysis suggested that the steady-state clearance was slightly lower following combination therapy compared with monotherapy (0.518 L/day vs 0.619 L/day, respectively). This small difference is not expected to have clinical implications. The reasons for decreasing clearance over time are not known but might include decreasing target-mediated clearance. Pre-dose concentrations of cys-mcMMAF following the first and multiple doses were consistently below or close to the limit of quantification following the proposed dose regimens. Clearance of cys-mcMMAF did not change over time.

PK in special populations was evaluated using PPK models for belantamab mafodotin ADC and cys-mcMMAF. Results of these simulations indicated that dose adjustment is not required based on age, gender, race/ethnicity, renal function (normal to severe impairment [estimated GFR 15 to <30 mL/min]), and hepatic function (normal to moderate impairment). Body weight (37 to 170 kg) was a significant covariate in population pharmacokinetic analyses, but this effect was adjusted by the weight proportional dosing regimen, which decreases the between-subject variability in exposure.

In patients with severe renal impairment (eGFR 15-29 mL/min, n = 8), belantamab mafodotin Cmax decreased by 23% and AUC(0-tau) decreased by 16% compared with patients with normal renal function or mild renal impairment (eGFR ≥ 60 mL/min, n = 8). For cys-mcMMAF, Cmax and AUC(0-168h) decreased by 56% and 44%, respectively compared to patients with normal renal function or mild renal impairment. Renal function was not a significant covariate in population pharmacokinetic analyses that included patients with normal renal function (eGFR 12-150 mL/min), mild (eGFR 60-89 mL/min), moderate (eGFR 30-59 mL/min), or severe renal impairment (eGFR < 30 mL/min not requiring dialysis). No impact on belantamab mafodotin PK was observed for patients with end stage renal disease (eGFR < 15 mL/min requiring dialysis, n = 5). Belantamab mafodotin is not expected to be removed via dialysis due to its molecular size. While free cys-mcMMAF may be removed via dialysis, cys-mcMMAF systemic exposure is very low and has not been shown to be associated with efficacy or safety based on exposure-response analysis. PK in patients with end-stage renal disease (eGFR <15 mL/min) is investigated in an ongoing study 209626 (DREAMM-12) Part 2. Exposure to belantamab mafodotin antibody-drug compound (ADC) was comparable in Group 1 (normal or mild renal function, n=8), Group 3 (eGFR <15 mL/min, not on dialysis, n=3), and Group 4 (eGFR <15

mL/min, on dialysis, n=5). Exposure to cys-mcMMAF appeared to be higher in Group 3 compared with Group 1 but was similar in Group 4 and Group 1. Based on the overall results and knowing that renal excretion is a minor elimination pathway for cys-mcMMAF (~18% of the dose in patients with normal or mildly impaired renal function), it is agreed with the applicant that no dose adjustment is to be recommended for patients with eGFR <15 mL/min, including patients with end-stage renal disease on dialysis. The CHMP recommended that results from this study should be submitted when available.

Hepatic function as per the National Cancer Institute Organ Dysfunction Working Group classification, was not a significant covariate in population pharmacokinetic analyses that included patients with normal hepatic function, mild (total bilirubin > ULN to ≤ 1.5 × ULN and any AST or total bilirubin ≤ ULN with AST > ULN) or moderate hepatic impairment (total bilirubin > 1.5 x ULN to ≤ 3 × ULN and any AST). Limited data are available for patients with moderate hepatic impairment (n = 5) or severe hepatic impairment (n = 1, total bilirubin > 3 × ULN and any AST) in the population pharmacokinetic analyses. Belantamab mafodotin should only be used in these patients if the potential benefits outweigh any potential risks which is reflected in the SmPC.

Belantamab mafodotin is proposed to be used in combination with bortezomib and dexamethasone (Vd) or with pomalidomide and dexamethasone (Pd), these combinations were used in the pivotal Phase 3 studies. Comparisons of exposure measures between combination therapy studies, monotherapy studies, and published literature data indicated that bortezomib, lenalidomide, pomalidomide, and/or dexamethasone do not affect the PK of belantamab mafodotin and vice versa.

In vitro studies demonstrated that cys mcMMAF is not an inhibitor, an inducer, or a sensitive substrate of cytochrome P450 enzymes, but is a substrate of organic anion transporting polypeptide (OATP)1B1 and OATP1B3, multidrug resistance-associated protein (MRP)1, MRP2, MRP3, bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P gp). Clinically relevant drug-drug interactions with inhibitors or inducers of these enzymes and transporters are not expected. Population PK analysis indicated that subjects with genotypes associated with reduced function of these transporters did not have clinically relevantly increased exposure to cys-mcMMAF. Clinically relevant drug interactions with inhibitors of these transporters are unlikely, impaired function of one transporter is expected to be compensated by others.

Exposure-response analyses

In the exposure-response (E-R) analyses for efficacy and safety, individual Cycle 1 exposure measures of belantamab mafodotin and cys-mcMMAF were simulated using the final PPK models. Separate analyses were conducted for combination therapy with Vd (analysis population from DREAMM-6 Arm B and DREAMM-7) and with Pd (analysis population from DREAMM-8).

In both Vd and Pd combination therapy populations, Cycle 1 exposure to belantamab mafodotin was not statistically significantly associated with PFS, which was the primary endpoint of the pivotal Phase 3 studies DREAMM-7 and DREAMM-8. Several other efficacy endpoints were also tested, statistically significant associations were seen for some of them (Overall response and very good partial response or better (VGPR+) for the VD combination and VGPR+ response, CR+ response, and MRD negativity (sCR/CR) for the PD combination), indicating better response with increasing Cycle 1 exposure to belantamab mafodotin.

Associations between Cycle 1 exposure and numerous ocular AEs were evaluated in both Vd and Pd combination therapy populations. Statistically significant associations were seen for some of them, especially for corneal AEs (KVA scale), indicating higher probability of some ocular AEs with increasing Cycle 1 exposure to belantamab mafodotin. Interestingly, lower Cycle 1 exposure to cys-mcMMAF seemed to be associated with higher probability of some ocular AEs.

Overall, results of the E-R analyses for efficacy and safety should be interpreted cautiously. Firstly, there was little to no variation in dose levels: approximately 85% of patients treated with belantamab mafodotin + Vd in DREAMM-6 Arm B and DREAMM-7 had Cycle 1 dose of 2.5 mg/kg, and all patients treated with belantamab mafodotin + Pd in DREAMM-8 had Cycle 1 dose of 2.5 mg/kg. Several baseline characteristics associated with disease severity (e.g., sBCMA, IgG, and albumin levels) affect the PK of belantamab mafodotin, which hinders making conclusions on relationships between exposure measures and efficacy. Furthermore, the exposure measures used in the exposure-response analyses were the predicted exposure at Cycle 1, whereas the efficacy and safety response parameters were typically observed at markedly later treatment cycles. It was not taken into account in the E-R analyses that approximately 83% to 91% of patients in studies DREAMM-6 Arm B, DREAMM-7, and DREAMM-8 had a dose modification due to TEAEs (dose discontinuation, dose reduction, and/or dose delay/interruption). Finally, it should be noted for the combination of belantamab mafodotin + Pd that the Cycle 1 dose (2.5 mg/kg) is higher than the dose of subsequent doses (1.9 mg/kg). This causes further uncertainty for the E-R analyses for belantamab mafodotin + Pd.

Results of the concentration-QTc analysis do not indicate significant potential for prolongation of QTc interval. The analysis has data from patients treated with 3.4 mg/kg dose, which is 36% higher than the proposed dose. It is also noted that *in vitro* cys-mcMMAF had no detectable effect on hERG channels.

2.6.4. Conclusions on clinical pharmacology

The PK and PD of belantamab mafodotin have been sufficiently investigated.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

DREAMM-7, BVd dosing regimen

Belantamab mafodotin starting dose of 2.5 mg/kg on a Q3W schedule was selected in combination with bortezomib and dexamethasone. In case of toxicities, dose delays and dose reductions (to 1.9 mg/kg) could be implemented based on the participant's individual tolerability.

This dosing schedule was based on the results from DREAMM-2 that evaluated 2 doses of belantamab mafodotin (2.5 mg/kg and 3.4 mg/kg) administered Q3W where the 2.5 mg/kg dose showed a more favourable benefit:risk profile. Interim data from DREAMM-6 had demonstrated that a belantamab mafodotin dose of 2.5 mg/kg Q3W combination with bortezomib and dexamethasone was shown to have an acceptable safety profile, with an AE profile consistent with each of the AE profiles for bortezomib, dexamethasone, and belantamab mafodotin monotherapy.

Additional dosing regimen exploration (including different doses and dosing schedules) were conducted in DREAMM-6; none of the explored regimens appeared to be superior and lead to further improvement of the benefit:risk profile, based on clinical observation and E-R analyses (see clinical pharmacology section). In addition, the interim PK data of belantamab mafodotin evaluated in combination with Vd in DREAMM-6 did not appear to impact the PK of bortezomib, while Vd did not appear to alter the PK of belantamab mafodotin.

Dose modifications for ocular events were consistent with DREAMM-2 and based on the KVA scale, where a KVA Grade 2 would require a dose hold (until resolution to baseline or Grade 1) and a KVA Grade 3 would require a dose reduction to 1.9 mg/kg upon resolution.

DREAMM-8, BPd dosing regimen

The proposed dosing regimen for belantamab mafodotin in combination with Pd in the treatment of participants with RRMM with at least 1 prior line of therapy including lenalidomide is 2.5 mg/kg in Cycle 1 and 1.9 mg/kg in Cycle 2+ Q4W as an IV infusion until disease progression or unacceptable toxicity.

Initial dose-finding was based on very limited clinical data from the ALGONQUIN study, where belantamab mafodotin at multiple dose levels and different dosing schedule was evaluated in combination with Pd in RRMM participants who have failed at least 1 prior line of therapy. The dosing schedule of Q4W was chosen to match the 28-day cycle required for Pd dosing. It is expected to provide sustained belantamab mafodotin (ADC) PK exposure based on the PK profile.

Only 11 patients received 1.92 mg/kg Q4W dosing, and five patients regimen of 2.5 mg/kg in Cycle 1 followed by 1.92 mg/kg Q4W from Cycle 2 onwards. The interim data demonstrated that 1.92 mg/kg Q4W was better tolerated but with reduced efficacy compared to 2.5 mg/kg Q4W dose of belantamab mafodotin in combination with Pd. Rates of grade 3–4 keratopathy, objective decrease in BCVA by the KVA scale and symptomatic grade ≥2 blurred vision by the National Cancer Institute Common Terminology Criteria for Adverse Events grading were 33.3% (4 of 12), 41.7% (5 of 12) and 25% (3 of 12), respectively, for the 1.92 mg/kg dose and 100% (7 of 7), 71.4% (5 of 7) and 57.2% (4 of 7), respectively, for the 2.5 mg/kg Q4W cohort. Given the totality of data available for the BPd combination, and to maximize tolerability and efficacy while limiting the need for dose modification, a dosing regimen of belantamab mafodotin 2.5 mg/kg in Cycle 1, to elicit an early and deep response, followed by 1.9 mg/kg in Cycle 2 and beyond, Q4W, in combination with Pd was chosen for the DREAMM-8 clinical study.

The integrated E-R analyses provide limited support for the selected maintenance dosing, as only Cycle 1 exposure metrics were used with clinical data from DREAMM-8.

To further improve tolerability on an individual participant's level and still allow meaningful target engagement, given the reduction of belantamab mafodotin clearance and disease burden over time and in the context of continued administration of Pd, dose modification allowed for a dose reduction (by extension of dosing interval) to 1.9 mg/kg Q8W in the event of a KVA Grade 2, and a dose reduction to 1.4 mg/kg Q8W in the event of KVA Grade 4.

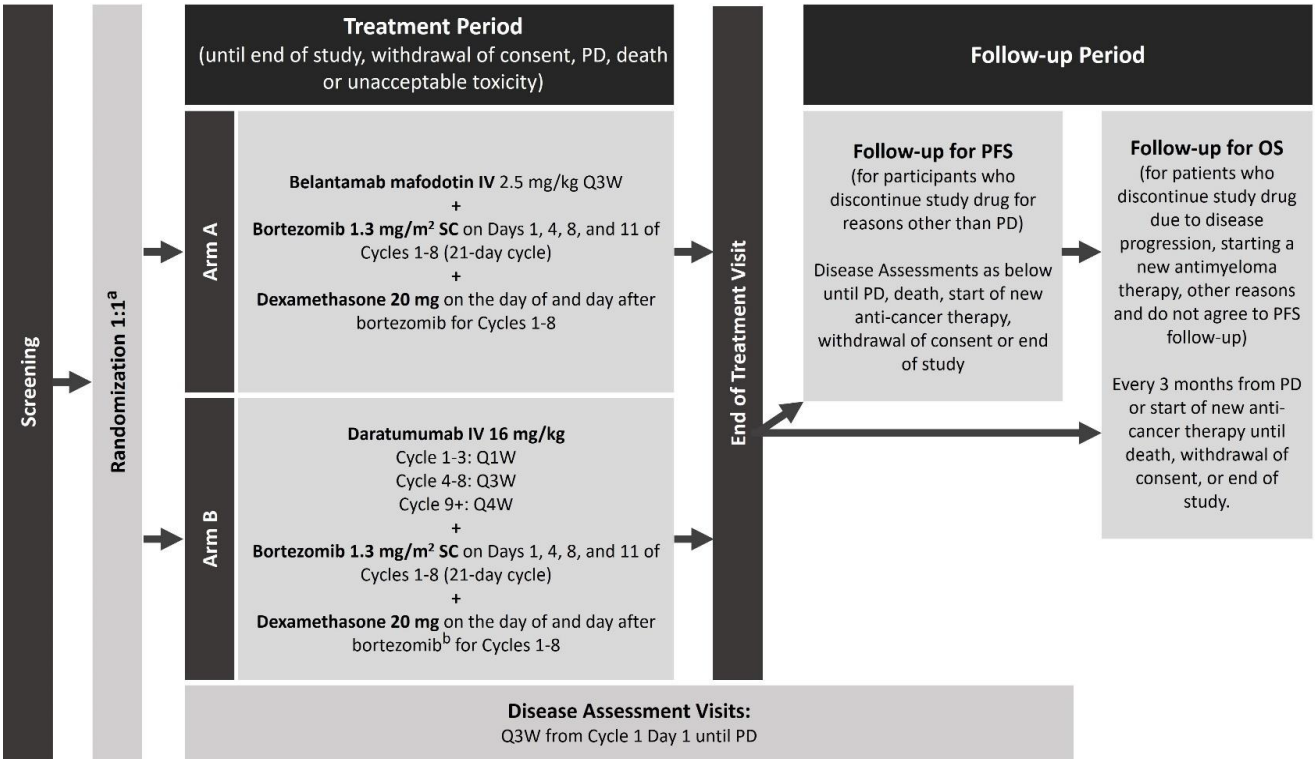
2.6.5.2. Main studies

Study 207503 (DREAMM-7): A multicenter, open-label, randomized study to evaluate the efficacy and safety of the combination of belantamab mafodotin, bortezomib, and dexamethasone (BVd) compared with the combination of daratumumab, bortezomib and dexamethasone (DVd) in participants with relapsed/refractory multiple myeloma.

Methods

A diagrammatic representation of the phase 3 part of the study is presented in **Figure 11**.

Figure 11. DREAMM-7 study design



Participants were stratified based on the number of prior lines of therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (yes vs. no), and the Revised-International Staging System (R-ISS) stage (I vs. II/III), and centrally randomised in a 1:1 ratio to either arm. No cross-over was allowed and no more than 50% of participants with ≥2 prior lines of treatment were enrolled.

Treatment was continued in both arms until progressive disease (PD) per International Myeloma Working Group (IMWG) criteria, death, unacceptable toxicity, investigator's discretion, withdrawal of consent, or end of study, whichever occurred first. For participants who discontinued study treatment for reasons other than PD or death, disease evaluations were performed Q3W (±3 days) until confirmed PD (documented), death, start of a new anti-myeloma treatment, withdrawal of consent, loss to follow-up, or end of the study, whichever occurred first. In case of PD, participants were followed to ascertain subsequent anti-myeloma therapy, PFS2, and survival status Q12W (±14 days) until withdrawal of consent, loss to follow-up, death, or the end of the study.

- **Study Participants**

The key inclusion criteria were the following:

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Male or female, 18 years or older (at the time consent is obtained).

3. Confirmed diagnosis of multiple myeloma as defined by the IMWG criteria [Rajkumar, 2014].

4. Previously treated with at least 1 prior line of MM therapy and must have documented disease progression during or after their most recent therapy according to the IMWG criteria [Kumar, 2016]. Note: induction + ASCT + maintenance is 1 line of therapy

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

6. Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:

    a. ASCT was >100 days prior to initiating study treatment, and

    b. No active bacterial, viral, or fungal infection(s) present.

7. Must have at least ONE aspect of measurable disease, defined as one the following:

    a. Urine M-protein excretion ≥200 mg/24h, or

    b. Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or

    c. 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).

8. All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] v5.0) must be ≤ Grade 1 at the time of enrolment, except for alopecia.

9. Adequate, prespecified organ system functions

The key exclusion criteria were the following:

1. Intolerant to daratumumab.

2. Refractory to daratumumab or any other anti-CD38 therapy (defined as progressive disease during treatment with anti-CD38 therapy, or within 60 days of completing that treatment).

3. Intolerant to bortezomib, or refractory to bortezomib (defined as progressive disease during treatment with a bortezomib-containing regimen of 1.3 mg/m2 twice weekly, or within 60 days of completing that treatment). Note: participants with progressive disease during treatment with a weekly bortezomib regimen are allowed.

4. Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain.

5. Prior treatment with anti-BCMA therapy.

6. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs, or treatment with an investigational agent or approved systemic antimyeloma therapy (including systemic steroids) within 14 days or 5 half-lives of receiving the first dose of study drugs, whichever is shorter.

7. Plasmapheresis within 7 days prior to the first dose of study drug.

8. Has received radiotherapy to a large pelvic area (check with sponsor). Bridging radiotherapy otherwise is allowed. NOTE: Disease assessment should be repeated if RT is done prior to first dose of study drug within screening window.

9. Prior allogenic stem cell transplant. NOTE – Participants who have undergone syngeneic transplant will be allowed, only if no history of GvHD.

10. Any major surgery within 4 weeks prior to the first dose of study drug. Exception allowed for bone stabilizing surgery after consultation with medical monitor.

11. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil prespecified criteria

12. 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.

13. Evidence of active mucosal or internal bleeding.

14. Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice. NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable if participant otherwise meets entry criteria.

15. Previous or concurrent malignancies other than multiple myeloma, unless the second malignancy has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease.

16. Evidence of cardiovascular risk including any of the following:

    a. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including second degree (Mobitz Type II) or third degree atrioventricular (AV) block.

    b. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of Screening.

    c. Class III or IV heart failure as defined by the New York Heart Association functional classification system.

    d. Uncontrolled hypertension.

- **Treatments**

Arm A

- Belantamab mafodotin administered intravenously (IV) at the recommended combination dose of 2.5 mg/kg on Day 1 (D1) of every 21-day cycle until confirmed PD, unacceptable toxicity, death, withdrawal of consent or study end, whichever occurs first.

  Ocular prophylaxis is required throughout treatment.

- Bortezomib 1.3 mg/m2 administered subcutaneously (SC) on Days 1, 4, 8, and 11 of every 21-day cycle for a total of 8 cycles. Bortezomib should be administered approximately 1 hour after the belantamab mafodotin infusion is complete, assuming the participant is clinically stable.

- Dexamethasone 20 mg (PO or IV) should be administered on the day of and the day after bortezomib treatment. For participants with contraindications or intolerance to this dose, a dose of 20 mg weekly should be used (Section 6.1.6). On days where bortezomib administration coincides with administration of belantamab mafodotin, dexamethasone should be administered PO or IV 1-3 hours prior to the infusion of belantamab mafodotin.

  Efficacy assessments were performed every 3 weeks (± 3 days), irrespective of dosing.

  Ocular prophylaxis should be instituted for all participants on Treatment Arm A as detailed in the SoA. Ocular prophylaxis includes:

- Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily, beginning on Cycle 1 Day 1 until the end of belantamab mafodotin treatment.

- At the start of each belantamab mafodotin infusion, participants may apply cooling eye masks to their eyes for as long as tolerated, up to 4 hours.

Arm B

- Daratumumab 16 mg/kg IV administered according to the approved label schedule in combination with bor/dex weekly for Cycles 1 through 3 (21-day cycles, total of 9 doses), on Day 1 of Cycles 4 thorough 8 (21-day cycles, total of 5 doses), and then every 4 weeks from Cycle 9 onwards (28-day cycles). For the first dose of daratumumab dosing at Week 1 only, in accordance with the label and institutional guidance and to facilitate administration, the single infusion of daratumumab may be split over 2 days.

- Bortezomib 1.3 mg/m2 administered SC on Days 1, 4, 8, and 11 of every 21-day cycle for a total of 8 cycles. Bortezomib should be administered approximately 1 hour after the daratumumab infusion is complete, assuming the participant is clinically stable.

- Dexamethasone 20 mg (PO or IV) should be administered on the day of and the day after bortezomib treatment. Administration should be IV prior to the first dose of daratumumab. For participants with contraindications or intolerance to this dose, a dose of 20 mg weekly should be used. On days where bortezomib administration coincides with administration of daratumumab, dexamethasone should be administered prior to the IV infusion of daratumumab. Corticosteroids are required as part of pre/post-medication for daratumumab infusions.

- **Objectives**

The primary objective of this study is to compare the efficacy of belantamab mafodotin in combination with bortezomib and dexamethasone (B-Vd) with that of daratumumab in combination with bortezomib and dexamethasone (D-Vd) in participants with RRMM, to demonstrate superiority of B-Vd compared to D-Vd in Progression Free Survival (PFS).

The key secondary objective of this study is to compare the efficacy of B-Vd with that of D-Vd in participants with RRMM, to demonstrate superiority of B-Vd compared to D-Vd in terms of Overall Survival (OS), Duration of Response (DoR) and Minimal residual disease (MRD) negativity.

- **Outcomes/endpoints**

The primary endpoint is PFS, defined as the time from the date of randomisation until the earliest date of documented disease progression, determined by an IRC, according to IMWG criteria [Kumar, 2016], or death due to any cause.

The key secondary endpoints are OS (defined as the time from the date of randomisation until the date of death due to any cause), DoR (defined as the time from first documented evidence of PR or better until progressive) and MRD negativity rate (defined as the percentage of participants who are MRD negative by next-generation sequencing (NGS)).

Secondary endpoints included:

- Complete response rate (CRR), defined as the percentage of participants with a confirmed CR or better (i.e., CR, sCR)
- Overall response rate (ORR), defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, sCR)
- Clinical Benefit Rate (CBR), defined as the percentage of participants with a confirmed MR or better per IMWG
- Time to response (TTR), defined as the time between the date of randomisation and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better
- Time to progression (TTP), defined as the time from the date of randomisation until the earliest date of documented PD or death due to PD
- PFS2, defined as time from randomisation to disease progression after initiation of new anti-myeloma therapy or death from any cause whichever is earlier. If disease progression after new anti-myeloma therapy could not be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier.

- **Sample size**

Based on data from the CASTOR study, the median PFS in Treatment Arm B was expected to be approximately 16.7 months [Spencer, 2018]. It was expected that treatment with belantamab mafodotin in combination with bor/dex would lead to a 33% reduction in the risk of progression or death, i.e., an expected HR of 0.67, which corresponds to an increase in median PFS from 16.7 months to 25 months under the exponential assumption.

The primary PFS analysis was conducted after observing approximately 280 PFS events. With ~280 events, the study has a power of 92% to detect a hazard ratio of 0.67 at 1-sided alpha of 0.025 (corresponding to a critical value of 0.783 for the hazard ratio).

Assuming that a total of 478 participants were randomized in a 1:1 ratio to Arm A or Arm B and a uniform enrolment rate of 30 participants per month, enrolment would continue for approximately 16 months. It was estimated that the targeted 280 PFS events would be observed approximately 37 months from the time when the first participant is randomized under H1, assuming an annual dropout rate of 5%.

Key Secondary Endpoint: Overall Survival

Using available data from literature, the median OS in the daratumumab-bortezomib-dexamethasone (DVd) arm was expected to be around 49 months [Spencer, 2018; Sonneveld, 2023 (CASTOR); Meletios, 2023 (POLLUX); Stewart, 2017 (ASPIRE)].

It was hypothesised that treatment with belantamab mafodotin would result in a 27% reduction in the hazard rate for OS, i.e., an expected HR of 0.73 (which corresponds to an increase in median OS to 67 months under the exponential model assumption). In order to ensure 80% power to test the null hypothesis: OS HR = 1, versus the specific alternative hypothesis: OS HR = 0.73, a total of 355 deaths need to be observed (~84% power). This calculation assumed analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomised to the two treatment arms in a 1:1 allocation ratio, and a group sequential design with a Lan DeMets (O' Brien-Fleming) alpha spending function [Lan, 1983] using information fractions of (0.4, 0.5, 0.75, 1). The information fraction may shift dependent on the actual timing of analyses and the observed OS events at that time and the boundaries will be adjusted accordingly. If OS is tested at the 2% level, under the same assumptions as stated above the study would provide approximately 81% power to demonstrate superiority of OS for B-Vd vs. D-Vd.

Key Secondary Endpoint: Duration of Response

Duration of Response (DoR), as one of the key secondary endpoints, would be formally statistically tested, provided that the primary endpoint PFS is statistically significant. Comparison of restricted mean DOR (RMDOR) between the two treatment arms was based on a one-sided Z test at the overall 0.5% level of significance.

Key Secondary Endpoint: MRD Negativity

Based on available data from literature, the proportion of participants with MRD Negativity as assessed by NGS with a 10-5 sensitivity, in the Dara/bor/dex arm was expected to be around 12% [Spencer, 2018]. It was hypothesised that treatment with belantamab mafodotin would result in a 15% absolute increase in MRD negativity to 27%. Based on the same number of participants that are planned to be enrolled in this study to provide sufficient power for the primary endpoint (i.e., 478 participants), the power to detect a difference in the MRD negativity between the 2 treatment arms would be approximately 99%. This calculation assumed analysis by a 1-sided Fisher' s exact test at the overall

2.5% level of significance, participants randomised to the 2 treatment arms in a 1:1 allocation ratio. Assuming MRD negativity is tested at the 2% level of significance, the study would provide approximately 86% power to detect a difference in MRD negativity between the two treatment arms.

- **Randomisation and Blinding (masking)**

This is an open-label study.

All participants were centrally randomised using a central Interactive Response Technology (IRT) system.

- **Statistical methods**

The analyses of PFS were based on the ITT Analysis Set, unless otherwise specified. The non-parametric Kaplan-Meier method were used to estimate the survival curves for PFS. Kaplan-Meier plots of PFS were presented by treatment arm. Kaplan-Meier estimates for the median PFS and the first and third quartiles were presented, along with 95% CIs. CIs for quartiles were estimated using Brookmeyer-Crowley method [Brookmeyer, 1982].

The treatment difference in PFS was compared by the one-sided stratified log-rank test. The stratified log-rank test (stratified by randomisation factors) was only performed for the primary analysis of primary estimand of PFS (i.e. based on IRC assessed response and primary event and censoring rules) based on ITT Analysis Set. Hazard ratio (HR) and its corresponding 95% CI were estimated from Cox proportional hazard model stratified by randomisation factors with treatment arm as the sole explanatory variable. The Cox models was fitted using SAS PROC PHREG with the Efron method to control for ties.

The type of events (progressions, deaths) and censoring reasons were summarised. Depending on data maturity, PFS rate at 6, 12, and 18 months with corresponding 95% CI were estimated from the Kaplan-Meier analysis. Stratification factors entered for randomisation using the Randomization and Trial Supply Management (RTSM) system were used in the primary analysis. If there is any mis-stratification, supplementary analyses were performed using the stratification data based on the clinical database (eCRF).

Primary analysis were conducted at the time of the planned interim analysis I (IA1), when approximately ~250 PFS events (~89% PFS information fraction) have been observed. If PFS alpha ≤0.018 (PFS stat. significant), split 0.025 between DoR and OS: 1) Test DoR at alpha=0.005, if DoR is significant test OS at overall alpha 0.025 (across all looks) so OS alpha=0.00037 in this look. If DoR is not significant, test OS at overall alpha 0.02 (across all looks) so OS alpha=0.0001 in this look. 2) If OS is significant, test MRD at same alpha. Alpha=0.02 if DoR is not significant Alpha=0.025 if DoR is significant Supportive secondary endpoints were analysed but not tested.

Sensitivity analyses were conducted using alternative PFS censoring rules and using investigator-assessed responses. Sensitivity analyses were also performed using the mITT analysis population, allowing use of local labs at baseline, considering COVID-19 censoring, and based on actual/corrected strata information.

Subgroup analyses for SAP specified disease characteristics were conducted for PFS.

The analyses of OS were based on the ITT Analysis Set, unless otherwise specified. When calculating overall survival, all deaths following subsequent anti-cancer therapy were included. This is the primary estimand of OS, and there is no supplementary estimand of OS. In addition, pending on maturity of

data, the survival probability at 6, 12 and 18 months with 95% CI was estimated using Kaplan-Meier method.

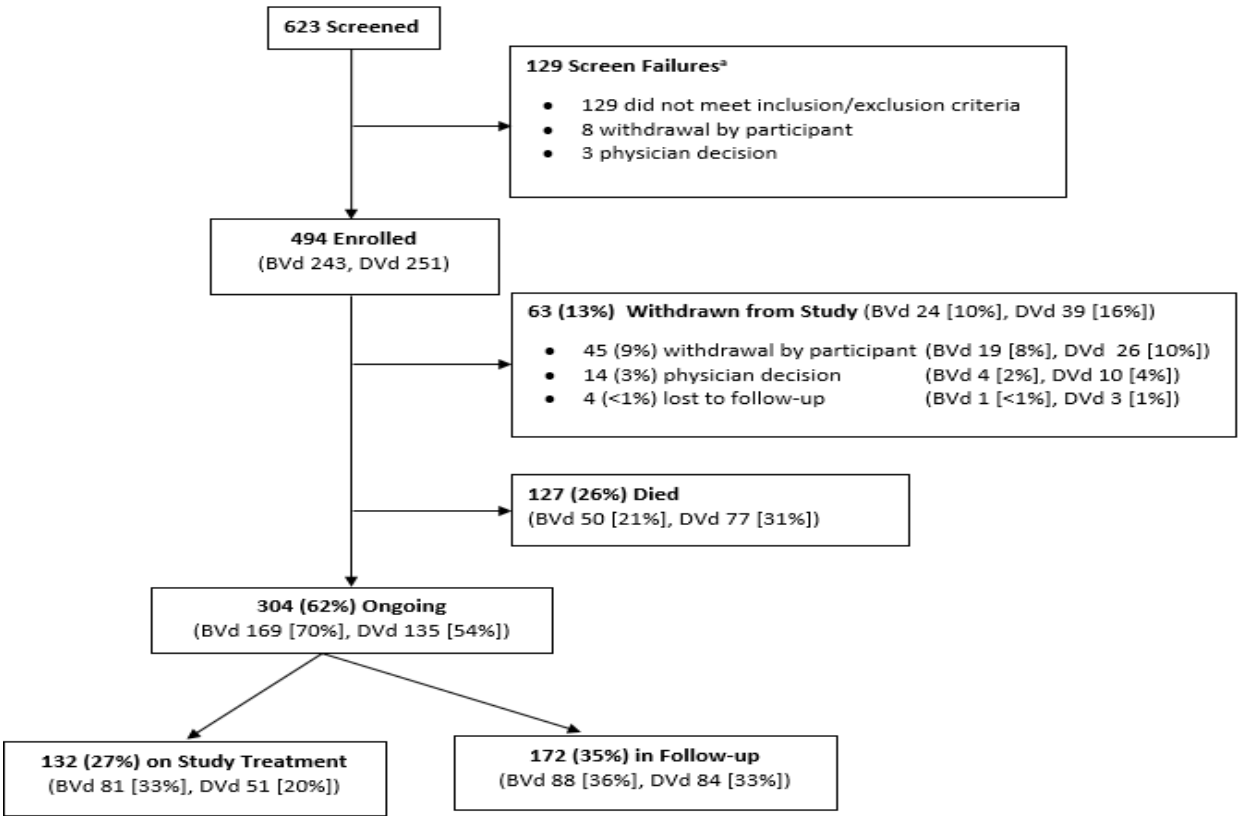
For the primary analysis of DoR, all participants were included in the analysis regardless of response status, to enable a valid statistical comparison between the two arms. Response was based on IRC-assessment per IMWG criteria [Kumar, 2016]. DoR was analyzed based on the restricted mean DoR (RMDoR) using a non-parametric approach [Huang, 2022]. Using this approach, non-responders had an observed DoR of zero. The approach accounts for TTR, ORR and DoR where the summary measure is the time from response to progression or death. The RMDoR for a treatment arm is the difference between the KM curves of PFS and response/progression-free survival (RPFS). The RMDoR and the corresponding 95% confidence interval will be calculated for each arm. The difference in the RMDoR and the associated 95% CI and one-sided p-value will be provided. Additionally, the ratio of the RMDoRs (Arm A/Arm B) and associated 95% CI will be calculated.

The number and percentage of participants who are MRD negative were summarised by treatment arms. The corresponding exact 95% CI for MRD negativity rate and associated p-value(s) were provided.

The cutoff date for inclusion of clinical information in from DREAMM 7 is 02 October 2023 (IA1), unless otherwise stated.

Results

- **Participant flow**



- **Recruitment**

Study initiation (first participant first dose): 21 May 2020

The study is ongoing.

- **Conduct of the study**

The original protocol dated 13 December 2019, was amended 6 times. The main changes are summarised below:

With amendment 1 (dated 16 July 2020), MRD was changed from a secondary to a key secondary endpoint.

Amendment 3 (dated 15 July 2021) removed the first of two interim analyses that were planned for the study based on ~25% of PFS events, allowing for early stopping due to harm (inferior efficacy). This was removed as the trial has accrued faster than anticipated.

Amendment 4 (dated 15 July 2022) updated the statistical analyses to include Clinical Benefit Rate (CBR) as a secondary endpoint and sustained MRD negativity rate as an exploratory endpoint. The key secondary endpoint of MRD negativity was clarified to state that the analysis would be conducted in participants with CR or better, and a sensitivity analysis would be conducted in patients with a best overall response of VGPR.

Amendment 5 (dated 19 December 2022) removed the interim analysis for futility and superiority that was planned at 80% information. Enrolment was completed for the Intent-To-Treat population in June 2021. The protocol was also amended to introduce an Independent Review Committee (IRC) and to document that the analysis of efficacy endpoints will be based on assessments determined by an IRC instead of derived confirmed response based on an algorithm. In addition, Duration of Response and Overall Survival, which were secondary endpoints for the study, were now classified as key secondary endpoints.

Amendment 6 (dated 20 September 2023) updated the number of PFS events required to trigger the primary PFS analysis and to include an interim analysis for PFS at ~89% information fraction to allow for a longer duration of follow up and increasing OS data maturity at the time of the primary PFS analysis.

Protocol deviations

All protocol deviations were assessed for importance by the study team based on a pre-defined protocol deviation management plan. Important deviations were defined as deviations that directly or indirectly had an impact on the participant's rights, safety, or well-being, and/or on data integrity and/or regulatory compliance as per ICH E3.

Important efficacy-related deviations included missed or out of window disease assessments resulting in censorship and MRD sample not collected at the time of CR or better. Important ocular-related deviations included administration of study treatment (belantamab mafodotin) when an ocular exam was missed or was out of window by ≥7 days prior to the dose, and administration of study treatment (belantamab mafodotin) when the KVA grade was ≥2. Protocol waivers or exemptions were not allowed.

The percentage of participants with any important protocol deviation was higher in the BVd group compared with the DVd group (78% vs. 63%). The most common types of protocol deviation in both treatment groups were related to assessment or, time point completion, wrong study treatment/administration/dose, informed consent, and study procedures. The difference in protocol

deviations between treatment groups was driven by missing ocular exams and incorrect dose modification based on ocular exams.

Five participants in the DVd group were assigned to the subcategory wrong study treatment; however, 2 of these deviations were related to bortezomib dosing. One participant in the DVd group was administered belantamab mafodotin due to an error and was subsequently discontinued from DVd treatment in accordance with the protocol; the deviation was categorized as study treatment not administered per protocol. Noncompliance with dose modification due to KVA grading or missed ocular exams were categorized under the subcategory study treatment not administered per protocol.

- **Baseline data**

Demographic disease characteristics are summarised in **Table 13** and **Table 14** respectively.

Table 13. Demographic Characteristics – Study DREAMM 7 (ITT Population)

	BVd (N=243)	DVd (N=251)	Total (N=494)
Sex, n (%)			
Female	115 (47%)	107 (43%)	222 (45%)
Male	128 (53%)	144 (57%)	272 (55%)
Age (years)[a]			
Mean (SD)	64.5 (9.47)	63.6 (10.11)	64.0 (9.80)
Median (min, max)	65.0 (34, 86)	64.0 (32, 89)	64.5 (32, 89)
Age Group (years), n (%)[a]			
18 to <65	121 (50%)	126 (50%)	247 (50%)
65 to <75	85 (35%)	95 (38%)	180 (36%)
≥75	37 (15%)	30 (12%)	67 (14%)
Ethnicity, n (%)			
n	243	249	492
Hispanic or Latino	30 (12%)	41 (16%)	71 (14%)
Not Hispanic or Latino	213 (88%)	208 (83%)	421 (85%)
High level race, n (%)			
n	242	249	491
American Indian or Alaska Native	0	0	0
Asian	28 (12%)	33 (13%)	61 (12%)
Black or African American	8 (3%)	12 (5%)	20 (4%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	206 (85%)	203 (81%)	409 (83%)
Mixed race	0	1 (<1%)	1 (<1%)
Race detail, n (%)			
n	242	249	491
American Indian or Alaska Native	0	0	0
Asian – Central/South Asian heritage	1 (<1%)	4 (2%)	5 (1%)
Asian – East Asian heritage	21 (9%)	28 (11%)	49 (10%)
Asian – Japanese heritage	3 (1%)	0	3 (<1%)
Asian – South East Asian heritage	3 (1%)	1 (<1%)	4 (<1%)
Black or African American	8 (3%)	12 (5%)	20 (4%)
Native Hawaiian or Other Pacific Islander	0	0	0
White – Arabic/North African heritage	13 (5%)	6 (2%)	19 (4%)
White – White/Caucasian/European heritage	193 (79%)	197 (78%)	390 (79%)

	BVd (N=243)	DVd (N=251)	Total (N=494)
Mixed Asian race	0	0	0
Mixed White race	0	0	0
Mixed race	0	1 (<1%)	1 (<1%)
Height (cm)			
n	243	248	491
Mean (SD)	165.7 (10.90)	167.0 (10.46)	166.4 (10.69)
Median (min, max)	164.0 (128, 199)	167.0 (138, 193)	166.0 (128, 199)
Weight (kg)			
n	243	250	493
Mean (SD)	76.25 (16.626)	78.15 (16.286)	77.21 (16.465)
Median (min, max)	73.10 (43.7, 133.0)	79.30 (42.9, 136.9)	77.00 (42.9, 136.9)
BMI (kg/m²)			
n	243	248	491
Mean (SD)	27.681 (5.0907)	27.842 (4.7463)	27.763 (4.9154)
Median (min, max)	27.131 (18.63, 47.53)	27.254 (18.29, 50.90)	27.182 (18.29, 50.90)

a. Age was imputed when full date of birth was not provided.
Note: There were 2 participants in the ITT Population who were randomized, not treated, re-screened, and re-randomized. They were counted as 4 unique participants in this table.

Table 14. Disease Characteristics at Screening Study DREAMM 7 (ITT Population)

	BVd (N=243)	DVd (N=251)	Total (N=494)
Revised-International Staging System (R-ISS) at screening, n (%)			
I	102 (42%)	103 (41%)	205 (41%)
II	130 (53%)	132 (53%)	262 (53%)
III	9 (4%)	14 (6%)	23 (5%)
Unknown	2 (<1%)	2 (<1%)	4 (<1%)
Relapsed or refractory disease (categorized per IMWG based on investigator assessment), n (%)			
n	242	251	493
Relapsed[a]	131 (54%)	137 (55%)	268 (54%)
Refractory[b]	104 (43%)	107 (43%)	211 (43%)
Unknown[c]	7 (3%)	7 (3%)	14 (3%)
Extramedullary disease, n (%)			
No	230 (95%)	226 (90%)	456 (92%)
Yes	13 (5%)	25 (10%)	38 (8%)
Lytic bone lesions, n (%)			
No	62 (26%)	66 (26%)	128 (26%)
Yes	181 (74%)	185 (74%)	366 (74%)
Myeloma immunoglobulin, n (%)[d, e]			
IgA	55 (23%)	50 (20%)	105 (21%)
IgD	2 (<1%)	4 (2%)	6 (1%)
IgE	0	0	0
IgG	161 (66%)	159 (63%)	320 (65%)
IgM	1 (<1%)	2 (<1%)	3 (<1%)
None present	23 (9%)	34 (14%)	57 (12%)
Missing	1 (<1%)	2 (<1%)	3 (<1%)

Myeloma light chain, n (%)			
Yes: Kappa light chain	151 (62%)	172 (69%)	323 (65%)
Yes: Lambda light chain	92 (38%)	77 (31%)	169 (34%)
No myeloma light chain	0	2 (<1%)	2 (<1%)
Type of multiple myeloma, n (%)			
Nonsecretory	0	0	0
Secretory	243 (100%)	251 (100%)	494 (100%)
Lines of therapy completed prior to screening, n (%)			
1 Line	125 (51%)	125 (50%)	250 (51%)
2 Lines	54 (22%)	63 (25%)	117 (24%)
3 Lines	34 (14%)	36 (14%)	70 (14%)
4 Lines	18 (7%)	13 (5%)	31 (6%)
5 Lines	5 (2%)	9 (4%)	14 (3%)
6 Lines	5 (2%)	3 (1%)	8 (2%)
7 Lines	2 (<1%)	2 (<1%)	4 (<1%)
Lines of therapy completed prior to screening			
Mean (SD)	2.0 (1.29)	1.9 (1.25)	2.0 (1.27)
Median (min, max)	1.0 (1, 7)	2.0 (1, 7)	1.0 (1, 7)
Prior stem cell transplant, n (%)			
No	79 (33%)	78 (31%)	157 (32%)
Yes	164 (67%)	173 (69%)	337 (68%)
High-risk cytogenetic abnormalities, n (%)[d, e]			
t(4;14)	41 (17%)	42 (17%)	83 (17%)
t(14;16)	8 (3%)	6 (2%)	14 (3%)
17p13del	30 (12%)	35 (14%)	65 (13%)
Other cytogenetic abnormalities, n (%)[d, e]			
del 13	18 (7%)	28 (11%)	46 (9%)
del 1p	22 (9%)	31 (12%)	53 (11%)
Hyperdiploidy	33 (14%)	28 (11%)	61 (12%)
t(11;14)	13 (5%)	15 (6%)	28 (6%)
t(14;20)	1 (<1%)	1 (<1%)	2 (<1%)
1q21+	94 (39%)	79 (31%)	173 (35%)
Other	30 (12%)	24 (10%)	54 (11%)
Cytogenetic risk categories, n (%)			
High risk[f]	67 (28%)	69 (27%)	136 (28%)
Standard[g]	175 (72%)	175 (70%)	350 (71%)
Missing or not evaluable	1 (<1%)	7 (3%)	8 (2%)
Double Hit Multiple Myeloma (2 or more high-risk cytogenetic abnormalities), n (%)			
Yes	11 (5%)	13 (5%)	24 (5%)
No	232 (95%)	238 (95%)	470 (95%)
Time to relapse after completion of 1L treatment, n (%)[h]			
≤12 Months	49 (20%)	50 (20%)	99 (20%)
>12 Months	194 (80%)	201 (80%)	395 (80%)
Actual time since initial diagnosis at randomization (years)			
Median (min, max)	4.28 (0.2, 26.0)	3.94 (0.1, 23.4)	4.09 (0.1, 26.0)
1st quartile	2.52	2.71	2.64
3rd quartile	6.71	6.17	6.42
ECOG performance status[i]			
n	242	246	488
0	121 (50%)	112 (46%)	233 (48%)
1	111 (46%)	123 (50%)	234 (48%)
2	10 (4%)	11 (4%)	21 (4%)

a. Collected in the CRF as follows: PD after >60 days of stopping treatment (includes eCRF categories: relapsed <6, 6 to 12 and >12 months).
b. Collected in the CRF as follows: PD on treatment or within 60 days of stopping treatment (includes eCRF categories: relapsed <60 days, refractory, primary refractory, relapsed and refractory).
c. Includes CRF category: relapsed (time period unknown).
d. Participants could be included in more than 1 category.
e. Only positive results are summarized.
f. If the participant had at least 1 high-risk abnormality: t(4;14), t(14;16), or 17p13del.
g. If the participant had negative results for all high-risk abnormalities: t(4;14), t(14;16), or 17p13del.
h. Time to relapse was defined as the time between start date of first line of therapy to PD date on 1L treatment. If no PD date was available, start date of second line of treatment was used. If no PD date nor start date of second line of treatment was available, date of randomization into study was used.
i. Analyzed using Safety Population.

Prior anti-myeloma therapy

The types of prior anti-myeloma therapies participants received were similar between treatment groups **Table 15**.

Table 15. Prior Anti-myeloma Therapy and Percentage of Participants Who Were Refractory by Drug Class of Agents- DREAMM 7 (ITT Population)

	Participants with prior anti-myeloma therapy		Participants refractory to prior anti-myeloma therapy	
Drug Class, n (%)	BVd (N=243)	DVd (N=251)	BVd (N=243)	DVd (N=251)
Immunomodulator	198 (81%)	216 (86%)	94 (39%)	104 (41%)
Lenalidomide	127 (52%)	130 (52%)	79 (33%)	87 (35%)
Thalidomide	121 (50%)	144 (57%)	16 (7%)	22 (9%)
Pomalidomide	25 (10%)	19 (8%)	17 (7%)	12 (5%)
Steroids	241 (>99%)	247 (98%)	65 (27%)	66 (26%)
Chemotherapy	198 (81%)	206 (82%)	30 (12%)	28 (11%)
Proteasome inhibitor	218 (90%)	216 (86%)	22 (9%)	24 (10%)
Carfilzomib	31 (13%)	35 (14%)	12 (5%)	17 (7%)
Ixazomib	13 (5%)	11 (4%)	7 (3%)	8 (3%)
Bortezomib	210 (86%)	211 (84%)	4 (2%)	0
Monoclonal antibody	9 (4%)	7 (3%)	2 (<1%)	3 (1%)
Elotuzumab	4 (2%)	3 (1%)	1 (<1%)	3 (1%)
Nivolumab	1 (<1%)	0	1 (<1%)	0
HDAC inhibitor	0	2 (<1%)	0	1 (<1%)
Engineered T/NK cell therapy	1 (<1%)	0	1 (<1%)	0
Small molecular kinase inhibitor	1 (<1%)	0	-	-
Other	8 (3%)	5 (2%)	3 (1%)	2 (<1%)

Note 1: There were 2 participants in the ITT Population who were randomized, not treated, re-screened, and re-randomized. They were counted as 4 unique participants in this table.
Note 2: Multiple categories per participant possible, total may add to more than 100%.
Note 3: Of the 4 participants in the BVd group reported as refractory to PI, 1 was confirmed refractory and reported as an eligibility protocol deviation, 2 were data entry errors and 1 was refractory to once weekly bortezomib, whereas the protocol cited refractoriness to bortezomib in a twice-weekly regimen as an exclusion criterion.

Follow-up anti-myeloma therapy

At the data cut-off (02 October 2023), 66% of participants in the BVd group and 78% in the DVd group had discontinued study treatment respectively.

The median time from study treatment discontinuation to start of subsequent anti-myeloma therapy was longer in the BVd group compared with the DVd group (69.0 days vs. 44.0 days).

Any and first line of subsequent therapy are summarised in **Table 16**.

Table 16. Follow-Up Anti-Myeloma Therapy- DREAMM 7 (ITT Population)

Drug Class, n (%)	Any Subsequent Anti-Myeloma Therapy		First Subsequent Anti-Myeloma Therapy	
	BVd (N=243)	DVd (N=251)	BVd (N=243)	DVd (N=251)
Any anti-myeloma therapy	62 (26%)	110 (44%)	62 (26%)	110 (44%)
Steroids	52 (21%)	88 (35%)	47 (76%)	85 (77%)
Immunomodulator	43 (18%)	79 (31%)	35 (56%)	63 (57%)
Proteasome inhibitor	29 (12%)	61 (24%)	23 (37%)	51 (36%)
Chemotherapy	16 (7%)	33 (13%)	8 (13%)	27 (25%)
Monoclonal antibody	37 (15%)	16 (6%)	33 (53%)	9 (8%)
Other	8 (3%)	9 (4%)	3 (5%)	4 (4%)
Missing	1 (<1%)	1 (<1%)	1 (2%)	1 (<1%)
Antibody drug conjugate	1 (<1%)	20 (8%)	1 (2%)	15 (14%)
Bi-specific antibody	5 (2%)	11 (4%)	1 (2%)	5 (5%)
Engineered T/NK cell therapy	0	2 (<1%)	0	1 (<1%)
Stem cell transplant	2 (<1%)	2 (<1%)	0	1 (<1%)

Note 1: Drug class contains all medications taken for the specific follow-up anti-cancer line of therapy.
Note 2: Drug class percentages are based off the number of participants who received the subsequent line of therapy number.

At the latest DCO date of 07 October 2024 (IA2), more participants remained on study treatment in the BVd group (25%) compared to the DVd group (15%). Hence, with more participants having discontinued study treatment in the DVd group, more had the need to start subsequent therapy, which is reflected in the higher percentage of participants in the DVd group starting subsequent therapy (BVd: 36%; DVd: 52%). For participants who started subsequent therapy, the median time from study treatment discontinuation to the start of subsequent anti-myeloma therapy was 83.0 days in the BVd group and 51.5 days in the DVd group.

- **Numbers analysed**

Table 17. DREAMM 7 Study Populations

Population, n (%)	Screen Failure (N=129)	BVd (N=243)	DVd (N=251)	Total (N=623)
All screened	129 (100%)	243 (100%)	251 (100%)	623 (100%)
Enrolled	0	243 (100%)	251 (100%)	494 (79%)
Safety	0	242 (>99%)	246 (98%)	488 (78%)
Intent-to-treat	0	243 (100%)	251 (100%)	494 (79%)
Modified ITT	0	241 (>99%)	243 (97%)	484 (78%)
Pharmacokinetic	0	242 (>99%)	0	242 (39%)

Note 1: All randomized participants were included in the Intent-to-Treat population (ITT) regardless of whether they received study treatment.
Note 2: Participants were included in the Modified ITT Population if they received at least 1 line of prior therapy, had evidence of measurable disease at baseline and were randomized and received at least 1 dose of their planned study treatment.
Note 3: All participants in the Safety Population from whom at least 1 PK sample had been obtained and analyzed were included in the Pharmacokinetic Population.

- **Outcomes and estimation**

Progression-free survival

PFS primary analysis

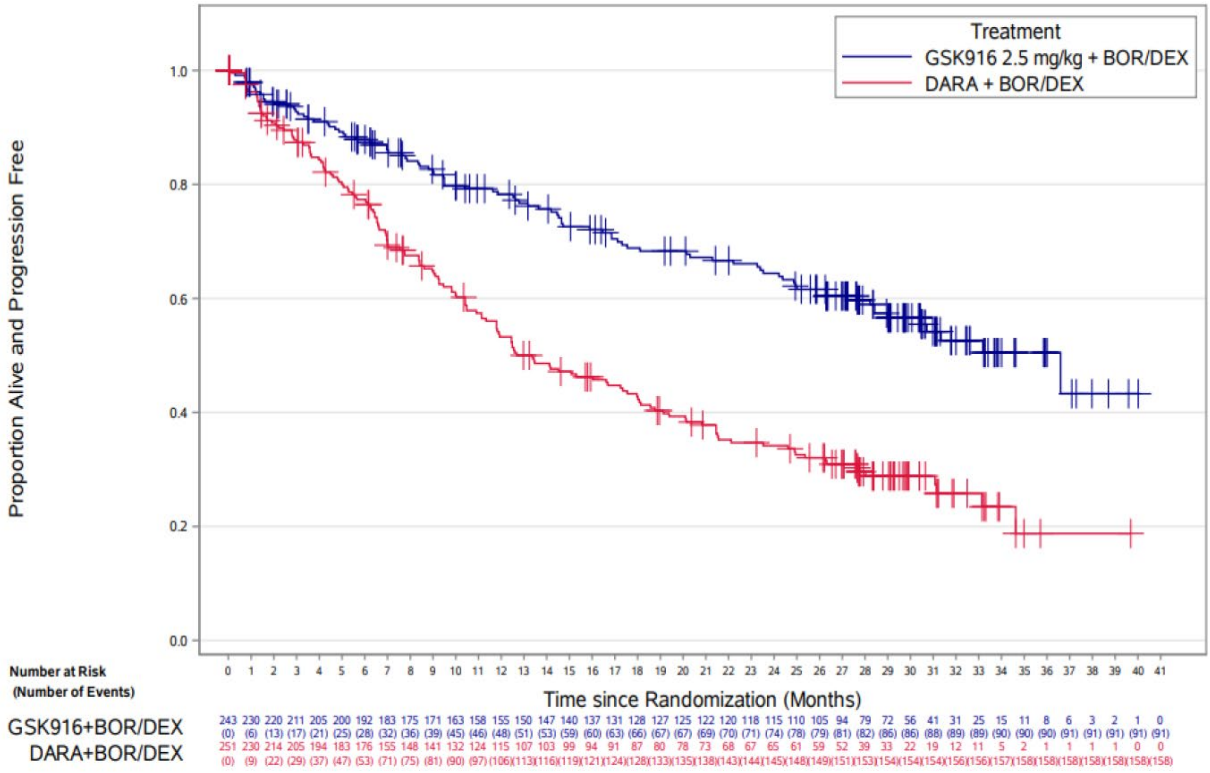
Table 18. Progression-Free Survival Based on Independent Reviewer-Assessed Response-DREAMM 7 (ITT Population)

	BVd (N=243)	DVd (N=251)
Number of participants, n (%)		
Progressed or died (event)	91 (37%)	158 (63%)
Censored, follow-up ended	44 (18%)	41 (16%)
Censored, follow-up ongoing	108 (44%)	52 (21%)
Event summary, n (%)		
Disease progression	67 (28%)	139 (55%)
Death	24 (10%)	19 (8%)
Estimates for time variable (months)[a]		
1st Quartile	14.5	6.4
95% CI	(9.5, 17.5)	(4.9, 7.0)
Median	36.6	13.4
95% CI	(28.4, -)	(11.1, 17.5)
3rd Quartile	-	33.1
95% CI	(-, -)	(26.3, -)
Hazard ratio[b]		
Number of participants in the model	243	251
Estimate	0.41	
95% CI	(0.31, 0.53)	
Stratified log-rank[c]		
P-value	<0.00001	
Progression-free survival rate		
Time-to-event endpoint at 6 months	0.88	0.77
95% CI	(0.83, 0.91)	(0.71, 0.82)
Time-to-event endpoint at 12 months	0.78	0.53
95% CI	(0.72, 0.83)	(0.47, 0.60)
Time-to-event endpoint at 18 months	0.69	0.43
95% CI	(0.62, 0.75)	(0.36, 0.49)

a. CIs were estimated using the Brookmeyer Crowley method.
b. Hazard ratios were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III), with a covariate of treatment.
c. P-value from 1-sided stratified log-rank test.

Landmark analysis of PFS at 18 months showed a higher PFS rate in the BVd group compared with the DVd group (69% vs. 43%). The median duration of follow-up was 8.2 months. Follow-up is ongoing for the majority of censored participants/events (44% vs. 21% in the BVd and DVd groups, respectively).

Figure 12. Kaplan Meier Curves of Progression-Free Survival Based on Independent Reviewer-Assessed Response-DREAMM 7 (ITT Population)



PFS analysis based on investigator-assessed responses was consistent with IRC results (data not shown).

Sensitivity analysis

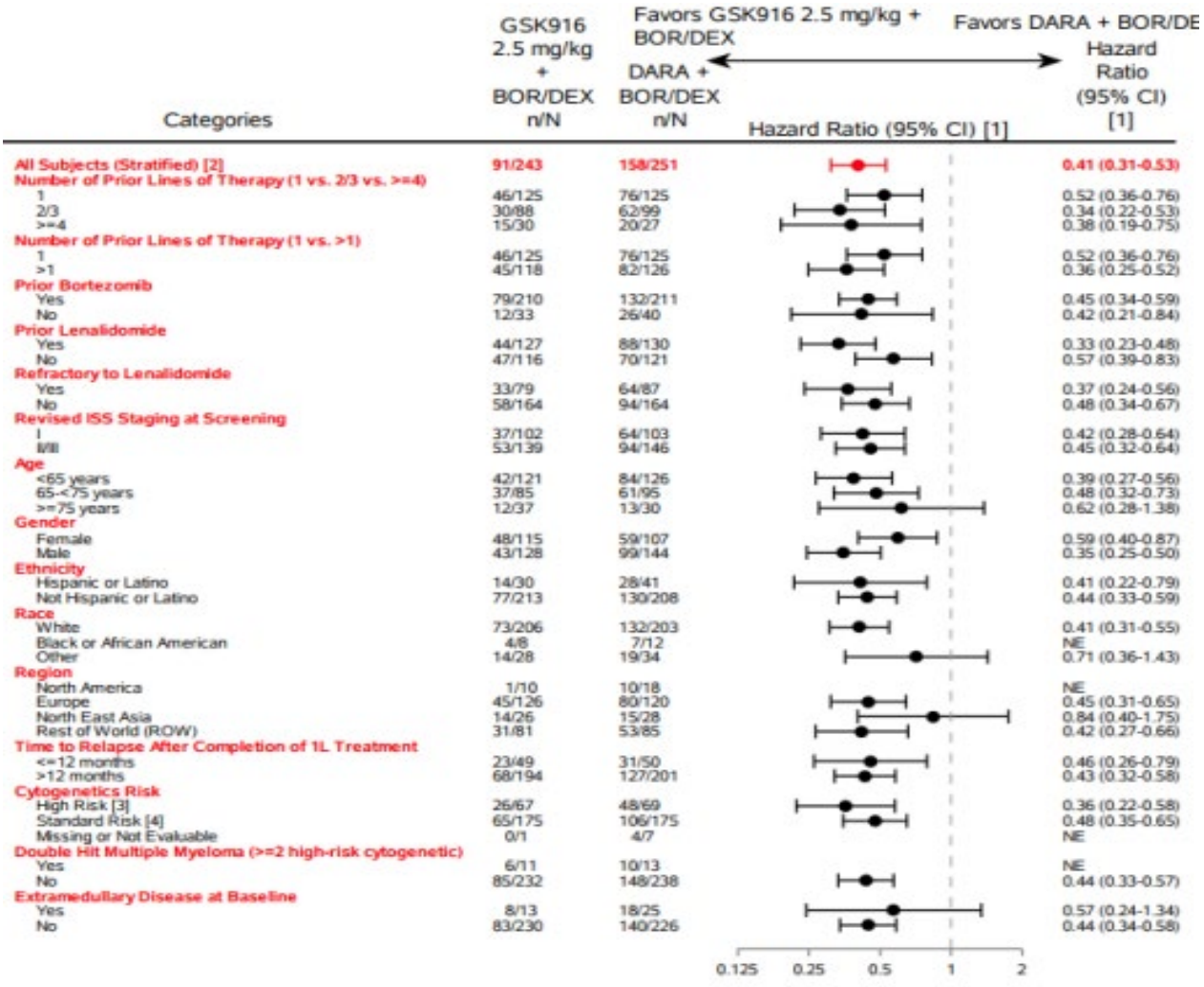
Results of all supplementary and sensitivity analyses were consistent with the primary PFS analysis with HR ranging from 0.48 to 0.54 and restricted mean survival time 22.8 months vs. 16.5 months (restricted to the common truncation time of 34.1 months) with a ratio of 1.37 favoring BPd group. In the BPd and PVd groups, new anti-myeloma therapy prior to observing a PFS event was initiated in 8 (5%) and 19 (13%) of participants. This indicated that more participants on the PVd group may have deteriorated, with a documented progression expected imminently had the new anti-myeloma therapy not been initiated.

The pre-specified supplementary analysis 2 considered the initiation of new anti-myeloma therapy as an event, which yielded a HR of 0.48 (95% CI: 0.35, 0.65) in favor of BPd, reaffirming the results of the primary analysis.

Subgroup analysis

PFS benefit was consistent across subgroups including those exposed or refractory to lenalidomide with HR point estimates ranging from 0.33 to 0.84 (**Figure 13**).

Figure 13. Forest Plot – Progression-Free Survival Based on Independent Reviewer-Assessed Response-DREAMM 7 (ITT Population)



[1] HRs for subgroups were only plotted if number of events ≥20 in total across both treatments. HRs for subgroups were estimated using Cox Proportional Hazard models, without adjustment for stratification variables.

[2] Stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes), and R-ISS at screening (I vs. II/III) according to IVRS strata with a covariate of treatment.

[3] A participant was considered as high risk if the participant had any of the following cytogenetics: t(4;14), t(14;16), or 17p13del.

[4] A participant was considered standard risk if the participant had negative results for all high-risk abnormalities: t(4;14), t(14;16), or 17p13del.

Note: There were 2 participants in the ITT Population who were randomized, not treated, re-screened, and re-randomized. They were counted as 4 unique participants in this figure.

Key secondary efficacy endpoints

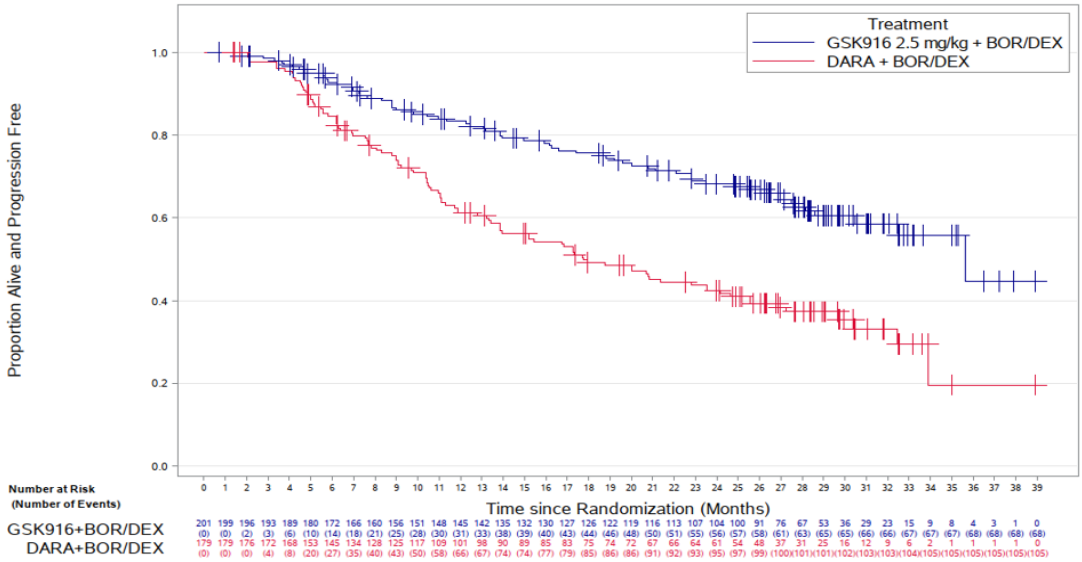
Duration of response

Conventional assessment of duration of response

The median DoR was longer in the BVd group compared with the DVd group (35.6 months vs. 17.8 months). In the BVd group, 53% of participants with response had not progressed or died at the data cut-off compared with 29% of participants with response in the DVd group.

The KM curves for DoR is shown in (**Figure 14**).

Figure 14. Kaplan Meier Curves of Duration of Response Based on Independent Reviewer-Assessed Response-DREAMM 7 (ITT Population)

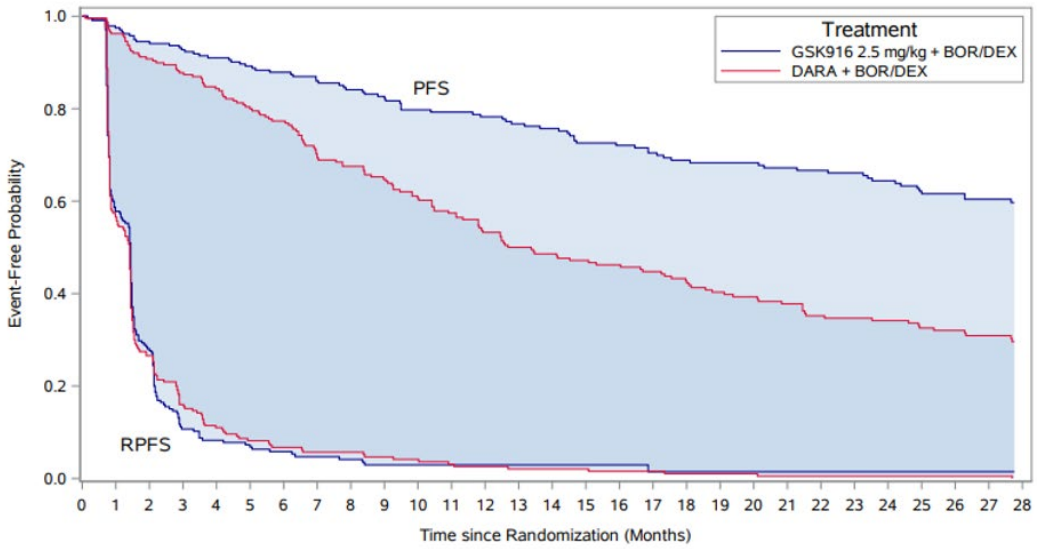


Restricted mean duration of response

The restricted mean DoR is a composite endpoint that uses information from both the overall response data (including non-responders) as well as PFS (progression/death) data. The shaded area between the curves (

Figure *15*) is the mean RMDoR based on IRC assessment, which was larger for the BVd group compared with the DVd group (19.0 months vs. 13.2 months) with a difference of 5.9 months and a ratio of 1.45). The results were considered statistically significant with a p-value of <0.00001.

Figure 15. Restricted Mean Duration of Response based on Independent Reviewer-Assessed Response-DREAMM 7 (ITT Population)



Note 1: RPFS=Response/progression-free survival.
Note 2: The common truncation time (t*) was calculated using the algorithm defined in Huang and Tian [Huang, 2022].

Overall survival

At the PFS data cut-off, OS benefit favored the BVd group vs. the DVd group with a nominal p-value of 0.00049 (HR=0.57; 95% CI: 0.40, 0.80) (**Table 19**).

Table 19. Summary of Overall Survival- DEAMM 7 (ITT Population)

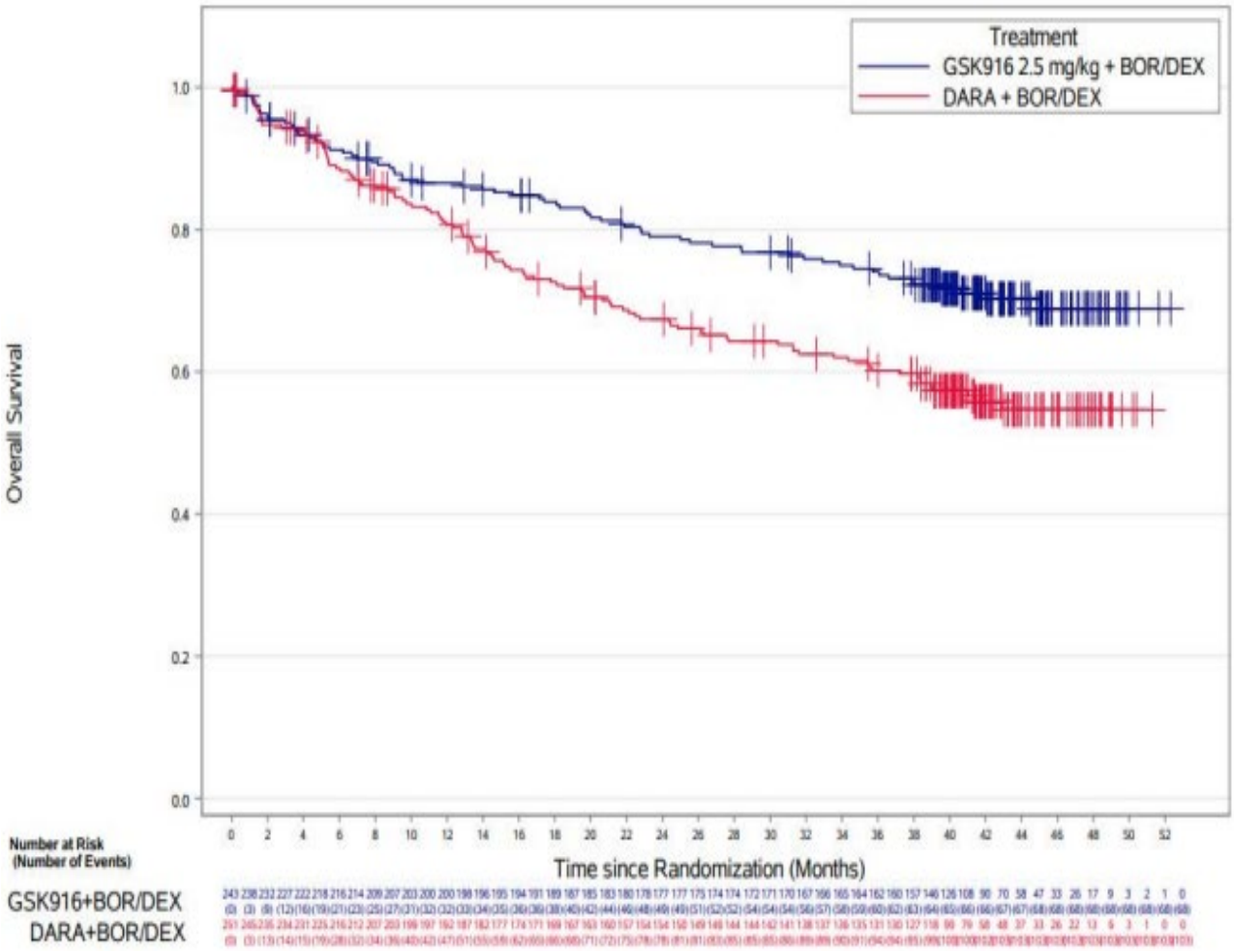
	IA1 (DCO 02 October 2023)		IA2 (DCO 07 October 2024)	
	BVd (N=243)	DVd (N=251)	BVd (N=243)	DVd (N=251)
Number of participants, n (%)				
Died (event)	54 (22%)	87 (35%)	68 (28%)	103 (41%)
Censored, follow-up ended	20 (8%)	28 (11%)	26 (11%)	33 (13%)
Alive date obtained	6 (2%)	12 (5%)	12 (5%)	16 (6%)
No alive date obtained	14 (6%)	16 (6%)	14 (6%)	17 (7%)
Censored, follow-up ongoing	169 (70%)	136 (54%)	149 (61%)	115 (46%)
Event summary, n (%)				
Death	54 (22%)	87 (35%)	68 (28%)	103 (41%)
Estimates for time variable (months)[a]				
1st quartile (95% CI)	33.9 (21.9, -)	15.2 (12.3, 21.1)	33.9 (21.9, 44.5)	15.2 (12.3, 21.1)
Median (95% CI)	– (–,–)	– (–,–)	– (–,–)	– (41.0, –)
3rd quartile (95% CI)	– (–,–)	– (–, –)	– (–, –)	– (–, –)
Hazard ratio[b]				
Number of participants in the model	243	251	243	251
Estimate (95% CI)	0.57 (0.40, 0.80)		0.58 (0.43, 0.79)	
Stratified log-rank[c]				
p-value	0.00049[d]		0.00023[e]	
Overall survival rate				
Time-to-event endpoint at 6 months (95% CI)	0.91 (0.87, 0.94)	0.89 (0.84, 0.92)	0.91 (0.87, 0.94)	0.89 (0.84, 0.92)
Time-to-event endpoint at 12 months (95% CI)	0.87 (0.81, 0.90)	0.81 (0.75, 0.85)	0.87 (0.81, 0.90)	0.81 (0.75, 0.85)
Time-to-event endpoint at 18 months (95% CI)	0.84 (0.79, 0.88)	0.73 (0.67, 0.78)	0.84 (0.79, 0.88)	0.73 (0.67, 0.78)
Time-to-event endpoint at 24 months (95% CI)	-	-	0.79 (0.73, 0.84)	0.67 (0.61, 0.73)
Time-to-event endpoint at 36 months (95% CI)	-	-	0.74 (0.68, 0.79)	0.60 (0.54, 0.66)

Median OS was not reached in either treatment group. OS data have reached 29% (141/494 participants) overall maturity and IF equal to 40% (141/355), where 355 were the planned deaths for OS analysis according to the SAP. Follow up for OS is ongoing.

The next planned OS IA occurred with a DCO date of 07 October 2024 (IA2). As of that date, 30 additional participants had died, OS data had reached 35% (171/494 participants) maturity (**Table 19**). A statistically significant OS benefit continued to favor the BVd group vs. the DVd group with an HR of 0.58 (95% CI: 0.43, 0.79; p-value=0.00023). Median OS was not reached in either treatment group. Follow up for OS is ongoing.

The KM curves for OS are shown in **Figure 16**.

Figure 16. Kaplan-Meier Curves of Overall Survival- DREAMM 7 (ITT Population)



Minimal residual disease

The proportion of participants who achieved MRD negativity was higher in the BVd group compared with the DVd group at the time of primary PFS analysis (**Table 20**).

Table 20. Summary of MRD Negativity Based on Independent Reviewer-Assessed Responses- DREAMM 7 (ITT Population)

Best Response		BVd (N=243)	DVd (N=251)
sCR/CR	MRD negativity rate	60 (24.7%)	24 (9.6%)
	95% CI	(19.4%, 30.6%)	(6.2%, 13.9%)
	P-value[a]	<0.00001	
	P-value[b]	<0.00001	

a. MRD negativity rate compared between treatment groups using CMH test, adjusting for stratification factors: number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III).
b. MRD negativity rate compared between treatment groups using unadjusted Fisher's exact test. CIs are based on the exact method. P-values presented are 2-sided 5% and as such significance only declared if MRD negativity Rate is in favor of belantamab mafodotin 2.5 mg/kg (which is equivalent to 1-sided 2.5%).

Results of MRD negativity analysis using investigator-confirmed response or in participants with VGPR or better were consistent with the primary MRD analysis. MRD negativity by best response based on IRC assessment showed higher MRD negativity rate in the BVd group compared with the DVd group in all response categories (**Table 21**).

Table 21. MRD Negativity Rate by Best Response Based on Independent Reviewer-Assessed Response- DREAMM 7 (ITT Population)

Best Confirmed Response		BVd (N=243)	DVd (N=251)
Stringent complete response (sCR)	n	34	13
	Number of sCR participants with MRD data	32	11
	MRD negativity rate	24 (70.6%)	6 (46.2%)
	95% CI	(52.5%, 84.9%)	(19.2%, 74.9%)
Complete response (CR)	n	50	30
	Number of CR participants with MRD data	46	27
	MRD negativity rate	35 (70.0%)	18 (60.0%)
	95% CI	(55.4%, 82.1%)	(40.6%, 77.3%)
Very good partial response (VGPR)	n	76	73
	Number of VGPR participants with MRD data	55	54
	MRD negativity rate	30 (39.5%)	15 (20.5%)
	95% CI	(28.4%, 51.4%)	(12.0%, 31.6%)
sCR/CR	n	84	43
	Number of CR+ participants with MRD data	78	38
	MRD negativity rate	60 (71.4%)	24 (55.8%)
	95% CI	(60.5%, 80.8%)	(39.9%, 70.9%)
sCR/CR/VGPR	n	160	116
	Number of VGPR+ participants with MRD data	133	92
	MRD negativity rate	94 (58.8%)	43 (37.1%)
	95% CI	(50.7%, 66.5%)	(28.3%, 46.5%)

Note 1: Percentages are based on the subgroup 'n' values.
Note 2: CIs are based on the exact method.

Secondary efficacy endpoints

Secondary endpoints of CRR, ORR, CBR, TTR, and TTP were based on IRC results (**Table 22**).

Table 22. Summary of Independent Reviewer-Assessed Best Response with Confirmation (IMWG Criteria)- DREAMM 7 (ITT Population)

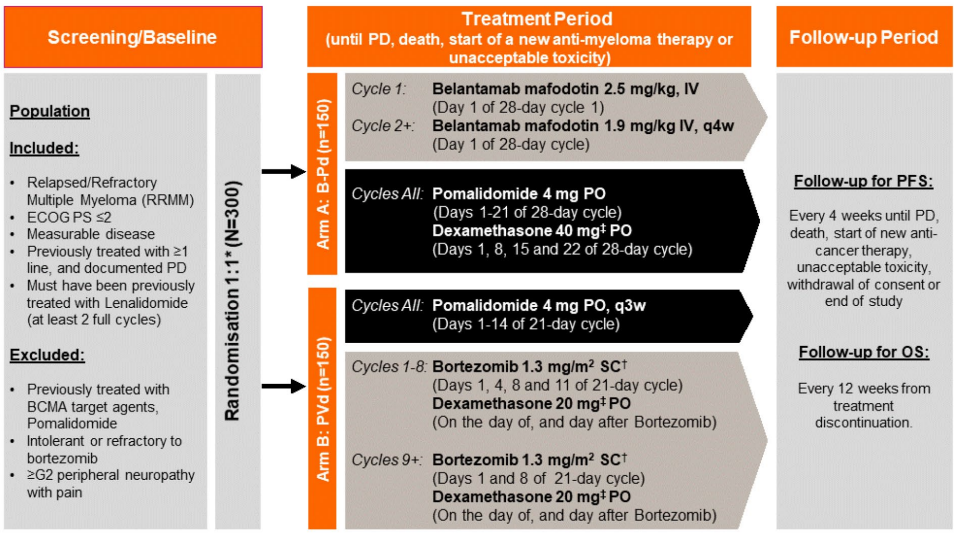
	BVd (N=243)	DVd (N=251)
Best response, n (%)		
Stringent complete response (sCR)	34 (14.0%)	13 (5.2%)
Complete response (CR)	50 (20.6%)	30 (12.0%)
Very good partial response (VGPR)	76 (31.3%)	73 (29.1%)
Partial response (PR)	41 (16.9%)	63 (25.1%)
Minimal response (MR)	8 (3.3%)	11 (4.4%)
Stable disease	25 (10.3%)	36 (14.3%)
Progressive disease (PD)	4 (1.6%)	12 (4.8%)
Not evaluable (NE)	5 (2.1%)	13 (5.2%)
Complete response rate, n (%)		
sCR+CR	84 (34.6%)	43 (17.1%)
95% CI	(28.6%, 40.9%)	(12.7%, 22.4%)
Difference in complete response rate		
Difference	17.4%	
95% CI for difference	(8.6%, 26.1%)	
Overall response rate, n (%)		
sCR+CR+VGPR+PR	201 (82.7%)	179 (71.3%)
95% CI	(77.4%, 87.3%)	(65.3%, 76.8%)
Difference in overall response rate		
Difference	11.4%	
95% CI for difference	(2.6%, 20.1%)	
VGPR+ rate, n (%)		
sCR+CR+VGPR	160 (65.8%)	116 (46.2%)
95% CI	(59.5%, 71.8%)	(39.9%, 52.6%)
Difference in VGPR+ rate		
Difference	19.6%	
95% CI for difference	(10.8%, 28.2%)	
Clinical benefit rate, n (%)		
sCR+CR+VGPR+PR+MR	209 (86.0%)	190 (75.7%)
95% CI	(81.0%, 90.1%)	(69.9%, 80.9%)
Difference in clinical benefit rate		
Difference	10.3%	
95% CI for difference	(1.4%, 19.1%)	

Study 207499 (DREAMM-8): A multicenter, open-label, randomised study evaluating the efficacy and safety of belantamab mafodotin in combination with pomalidomide and dexamethasone (B-Pd) vs pomalidomide plus bortezomib and dexamethasone (PVd) in participants with RRMM.

Methods

A diagrammatic representation of the phase 3 part of the study is presented in **Figure 17** .

Figure 17. DREAMM-8 study design



* Stratification: Prior lines of treatment (1 vs. 2 / 3 vs. ≥4), prior bortezomib treatment (yes or no) and prior anti-CD38 treatment (yes or no). No more than 50% of participants with 2 or more prior lines of treatment were enrolled. It was anticipated that no more than 15% of participants with 4 or more prior lines of treatment would be enrolled. No cross-over was allowed. Prior to Protocol Amendment 1, stratification included ISS status (I vs. II/III) instead of anti-CD38 treatment.
† SC administration of bortezomib only.
‡ The dose level of dexamethasone was reduced by half if participant age >75 years or had comorbidities or were intolerant to 40 mg dose in Arm A or 20 mg dose in Arm B, respectively.

- **Study Participants**

<u>The key inclusion criteria were the following:</u>

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Male or female, 18 years or older (at the time consent is obtained).

3. Confirmed diagnosis of multiple myeloma as defined by the IMWG criteria [Rajkumar, 2016].

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

5. Have been previously treated with at least 1 prior line of MM therapy including a lenalidomide-containing regimen (lenalidomide must have been administered for at least 2 consecutive cycles) and must have documented disease progression during or after their most recent therapy.

6. Note: Participants intolerant or refractory to bortezomib at 1.3 mg/m2 dose twice weekly dosing schedule are not eligible.

7. Must have at least ONE aspect of measurable disease, defined as one the following:

a. Urine M-protein excretion ≥200 mg/24h, or

b. Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or

c. 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).

8. Have undergone autologous stem cell transplant (SCT) or are considered transplant ineligible. Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:

a. ASCT was >100 days prior to initiating study treatment, and

b. No active bacterial, viral, or fungal infection(s) present.

8. All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] v5.0) must be ≤Grade 1 at the time of enrollment, except for alopecia.

9. Adequate, prespecified organ system functions.

The key exclusion criteria were the following:

1. Active plasma cell leukemia at the time of screening. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, and skin changes).

2. Participants after prior allogeneic SCT.

- NOTE: Participants who have undergone syngeneic transplant will be allowed only if no history of or no currently active graft versus host disease (GvHD).

3. Systemic anti-myeloma therapy (including chemotherapy and systemic steroids) or 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 monoclonal antibody drug within 30 days of receiving the first dose of study drugs.

4. Plasmapheresis within 7 days prior to the first dose of study drug.

5. Received prior treatment with or intolerant to pomalidomide.

6. Prior treatment with anti-BCMA therapy.

7. Intolerant to bortezomib or refractory to bortezomib (i.e., participant experienced progressive disease during treatment, or within 60 days of completing treatment, with a bortezomib-containing regimen of 1.3 mg/m2 twice weekly).

8. Evidence of cardiovascular risk including any of the following:

a. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including 2nd degree (Mobitz Type II) or 3rd degree atrioventricular (AV) block.

b. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of Screening.

c. Class III or IV heart failure as defined by the New York Heart Association functional classification system.

9. Any major surgery within 4 weeks prior to the first dose of study drug

10. Previous or concurrent malignancies other than multiple myeloma, unless the second malignancy has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease.

11. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to belantamab mafodotin or drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.

12. Evidence of active mucosal or internal bleeding.

13. Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice.

14. Active infection requiring treatment.

15. Known human immunodeficiency virus (HIV) infection.

16. 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).

17. 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.

18. Intolerance or contraindications to anti-viral prophylaxis.

19. Presence of active renal conditions (e.g. infection, severe renal impairment requiring dialysis or any other condition that could affect participant's safety).

20. Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain

21. Active or history of venous thromboembolism within the past 3 months.

22. Contraindications to or unwilling to undergo protocol-required anti-thrombotic prophylaxis

23. Current corneal disease except for mild punctate keratopathy

- **Treatments**

Arm A

- Belantamab mafodotin was administered intravenously (IV) over at least 30 minutes at a single dose of 2.5 mg/kg dose on Day 1 (D1) of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2+ in each 28-day cycle until confirmed PD or unacceptable toxicity. The dose administered was based on actual body weight calculated at baseline. However, if the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing.
- Pomalidomide was taken orally 4 mg per day on Days 1-21 of each 28-day cycle until disease progression, death, unacceptable toxicity, withdrawal of consent, initiation of another anti-cancer therapy or end of study, whichever occurs first. On C1D1, pomalidomide should be administered as close as possible to the end of the 1-hour rest period after administration of belantamab mafodotin and no later than 4 hours after the end of the rest period after administration of belantamab mafodotin. On subsequent pomalidomide and belantamab mafodotin co-administration days such as C2D1, C3D1 and thereafter, pomalidomide should be administered after the end of the 1-hour rest period after administration of belantamab mafodotin.
- Dexamethasone was administered orally at a dose of 40 mg per day on Days 1, 8, 15, and 22 of each 28-day cycle. For participants who are >75 years old or have comorbidities or are intolerant to 40 mg, dexamethasone may be administered at the lower dose of 20 mg in Arm A

at the discretion of the investigator.

Efficacy assessments was performed every 4 weeks (±3 days), irrespective of dosing.

Arm B

- Pomalidomide was administered orally at 4 mg daily on Days 1 to 14 of each 21-day cycle, with bortezomib injected subcutaneously (SC) at 1.3 mg/m2 on Days 1, 4, 8, 11, of each 21-day cycle for C1-8, and on Days 1, 8, of each 21-day cycle for C9+ until disease progression, death, unacceptable toxicity, withdrawal of consent, initiation of another anti-cancer therapy or end of study, whichever occurs first.
- Dexamethasone was administered orally at a dose of 20 mg on the day of and day after bortezomib, of each 21-day cycle or on Days 1, 2, 4, 5, 8, 9, 11, 12, of each 21-day cycle for C1-8 and then on Days 1, 2, 8, 9, q3w for C9+. For participants who are >75 years old or have comorbidities or are intolerant to 20 mg, dexamethasone may be administered at the lower dose of 10 mg on the day of and day after bortezomib in Arm B at the discretion of the investigator.

Efficacy was performed every 4 weeks (±3 days), irrespective of dosing. If either pomalidomide or bortezomib is permanently discontinued due to an AE(s), the participant would be allowed to continue on the study with the remaining doublet in PVd treatment regimen.

- **Objectives**

The primary objective of this study is to compare the efficacy of B-Pd with that of PVd in participants with RRMM, to demonstrate superiority of B-Pd compared to PVd in PFS.

The key secondary objective of this study is to compare the efficacy of B-Vd with that of D-Vd in participants with RRMM, to demonstrate superiority of B-Pd with that of PVd in participants with RRMM, in terms of OS, DoR, and MRD negativity.

- **Outcomes/endpoints**

The primary endpoint is PFS, defined as the time from randomisation until the earliest date of PD based on IRC-assessment per IMWG criteria, or death due to any cause.

The keys secondary endpoints are:

- OS defined as the time from the date of randomisation until the date of death due to any cause;
- DoR defined as the time from first documented evidence of PR or better until progressive disease or death die to any cause based on IRC-assessment per IMWG criteria;
- MRD negativity rate defined as the percentage of participants who achieve MRD negative status as assessed by NGS at the 10^{-5} threshold at least once during the time of confirmed CR or better response based on IRC-assessment per IMWG.

Secondary endpoint include:

- ORR, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR CR, and sCR) based on IRC-assessment per IMWG criteria
- CRR, defined as the percentage of participants with a confirmed CR or better (i.e., CR and sCR)

based on IRC-assessment per IMWG criteria

- VGPR or better rate, defined as the percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, and sCR) based on IRC assessment per IMWG criteria
- TTBR, defined as the interval of time between the date of randomisation and the earliest date of achieving best response among participants with a confirmed PR or better based on IRC assessment per IMWG criteria
- TTR, defined as the time between the date of randomisation and the first documented evidence of response (PR or better) among participants who achieve response (i.e., confirmed PR or better) based on IRC-assessment per IMWG criteria
- TTP, defined as the time from the date of randomisation until the earliest date of documented PD based on IRC-assessment per IMWG criteria, or death due to PD
- PFS2, defined as time from randomisation to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier.

- **Sample size**

Based on data from the OPTIMISMM study [Richardson, 2019], the median PFS in the lead to a 40% reduction in the risk of progression or death, i.e., an expected PFS HR of 0.6, which corresponds to an increase in median PFS from 12 months to 20 months under the exponential assumption.

To ensure >90% power to test the null hypothesis: PFS HR = 1, versus the specific alternative hypothesis: PFS HR = 0.6, a total of approximately 173 PFS events are needed. The calculation assumes a comparison of PFS by log-rank test at overall 1-sided alpha level of 2.5% with 1:1 randomization ratio, and two interim analyses: an interim analysis for harm using gamma spending function with parameter of -3 when observing ~25% PFS events and an early efficacy analysis using Lan De Mets O'Brien Fleming alpha spending function [Lan, 1983]. The calculation further assumes approximately 302 participants to be randomized in a 1:1 ratio to receive B-Pd or PVd, with a uniform enrolment rate of 11.2 participants per month and enrolment period of approximately 27 months. It is estimated that the targeted 173 PFS events would be observed approximately 35 months from the time when the first participant is randomized under H1, assuming an annual dropout rate of 5%. These calculations were conducted using the software package EAST v6.5.

- **Randomisation and Blinding (masking)**

This is an open-label study.

- **Statistical methods**

The distribution of PFS for each treatment arm, at each planned analysis, was estimated using the non-parametric Kaplan-Meier method. Kaplan-Meier plots of PFS were presented by treatment arm. The median, 25th and 75th percentiles of PFS was estimated and corresponding 95% confidence intervals were estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982].

The treatment relative effect in PFS was compared by the one-sided stratified log-rank test. The stratified log-rank test (stratified by applicable randomization factors) were performed for the primary

analysis of primary estimand of PFS (i.e., based on IRC assessed response and primary event and censoring rules) based on the ITT Analysis Set. The hazard ratio (HR) and its corresponding 95% CI was estimated from a Cox proportional hazard model stratified by applicable randomization factors with treatment arm as the sole explanatory variable. Cox models were fitted using SAS PROC PHREG with the Efron method to control for ties.

The type of events (progressions, deaths) and censoring reasons were summarised. Depending on data maturity, PFS rate at 6, 12, and 18 months with corresponding 95% CI was estimated from the Kaplan-Meier analysis.

Stratification factors entered for randomisation in the interactive voice recognition system (IVRS) was used in the primary analysis. If there was any mis-stratification, sensitivity analyses were performed using the stratification data based on the clinical database (eCRF/vendor data).

PFS, was tested across 3 planned analyses: Two interim analyses, the first one, interim analysis 1 (IA1), when approximately 35 PFS events (approximately 25% PFS information fraction) had occurred and the second one, (IA2) when approximately 145 PFS events (approximately 84% PFS information fraction) had occurred and the primary PFS analysis/IA3. The Lan DeMet approach that approximates the O'Brien and Fleming spending function [Lan, 1983] was used to maintain an overall one-sided 2.5% type I error when testing PFS across IA2 and the Primary PFS analysis/IA3, since these analyses provide the opportunity to make a claim of efficacy. If PFS demonstrates statistical significance at IA2 the rationale for Primary PFS analysis was driven by the requirements for OS (PFS not retested).

Sensitivity analyses were conducted using alternative PFS censoring rules (including rules for COVID-19 censoring) and using investigator-assessed responses. Sensitivity analyses were performed using the mITT analysis population, based on the stratification data from clinical database (eCRF/vendor data) and using methods to account for the changes in the stratification factors (ISS and prior anti-CD38 use) following Protocol Amendment 1. Subgroup analyses, were done with subgroups identified based on clinically relevant baseline demography and disease characteristics as specified in the statistical analysis plan.

The analysis of OS was based on the ITT Analysis Set, unless otherwise specified. In addition, pending on maturity of data, the survival probability at 6, 12 and 18 months with 95% CI was estimated using Kaplan-Meier method. Kaplan-Meier plots of OS were presented by treatment arm. A listing of participants OS status was produced. OS was tested across 4 planned analyses: IA2, Primary PFS analysis/IA3, IA4, and the final analysis.

For the primary analysis of DoR, all participants were included in the analysis regardless of response status, to enable a valid statistical comparison between the two arms. Response was based on IRC-assessment per IMWG criteria [Kumar, 2016].

DoR was analyzed based on the restricted mean DoR (RMDoR) using a nonparametric approach [Huang, 2022]. Using this approach, non-responders had an observed DoR of zero. The approach accounts for TTR, ORR and DoR where the summary measure is the time from response to progression or death. The RMDOR for a treatment arm is the difference between the KM curves of PFS and response/progression free survival (RPFS). The RMDOR and the corresponding 95% confidence interval were calculated for each arm. The difference in the RMDOR and the associated 95% CI and one-sided p-value (descriptive only) were provided. Additionally, the ratio of the RMDORs (Arm A/Arm B) and associated 95% CI were calculated. A listing of duration of response was produced.

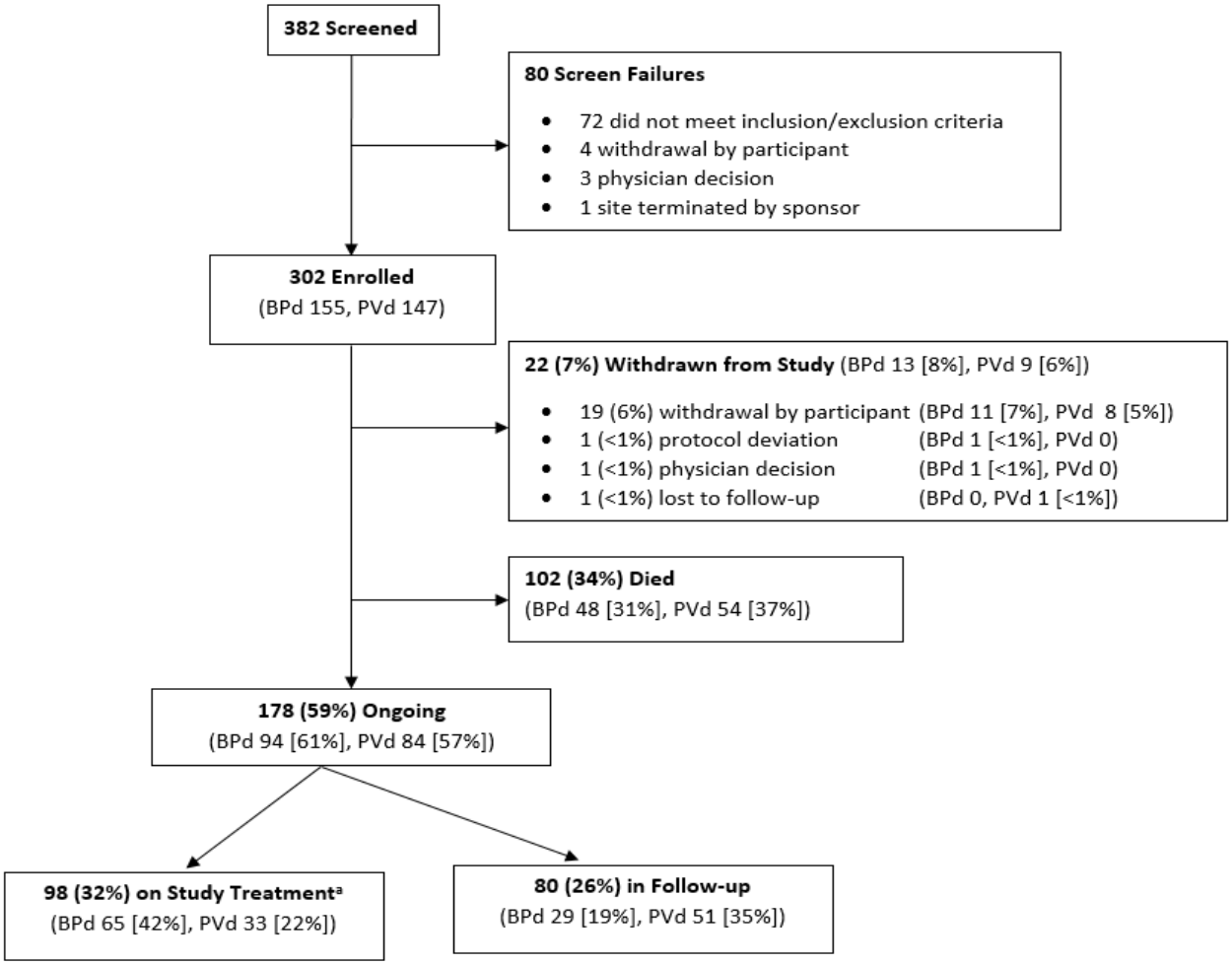
The number and percentage of participants who are MRD negative was summarized by treatment arms. The corresponding exact 95% CI for MRD negativity rate and associated p-value(s) was provided. Information of MRD was included in the listing of response.

The primary analysis and formal testing of MRD negativity was based on data available at the time of IA2, regardless of the timing of PFS statistical significance. At the time of primary PFS analysis, data was analyzed descriptively without formally being tested based on the data available at the data cut-off.

The cut-off date for inclusion of clinical information in from DREAMM 8 is 29 January 2023 (IA2), unless otherwise stated.

Results

- **Participant flow**



- **Recruitment**

Study initiation date: first subject was treated on 13 October 2020.

The study is ongoing.

- **Conduct of the study**

The original protocol was dated 16 April 2020.

Substantial changes in the conduct of the study are described below:

Protocol Amendment 1 (dated 20 April 2021)

• Update of the stratification strategy to include prior anti-CD38 treatment instead of ISS stage.

• Use of KVA scale for grading corneal events associated with belantamab mafodotin and base dose modifications for belantamab mafodotin-related ocular toxicity on KVA grade instead of CTCAE grade.

• Inclusion of a step-down dose levels for belantamab mafodotin following onset of corneal events: with a Dose Level –1 of belantamab mafodotin 1.9 mg/kg Q8W and a Dose Level –2 of 1.4 mg/kg Q8W.

Protocol Amendment 2 (dated 12 July 2022)

• Reduction of the total number of participants to be randomized in the study from 450 to approximately 300, to keep at least 50% of participants with 1 prior lines of therapy in ITT population, while required number of PFS events, power, etc. remained the same.

• Update and clarification of key secondary endpoint definition of MRD negativity rate which will be as assessed in participants with CR or better.

Protocol Amendment 3 (dated 23 February 2023)

• Change of the primary analysis of efficacy endpoints to be based on IRC-assessed response and dates per IMWG criteria, instead of on a proprietary algorithm-derived response and date.

• Addition of DoR and OS as key secondary endpoints.

Protocol Amendment 4 (dated 28 September 2023)

• Delay of primary PFS analysis for a longer duration of follow-up and increase of OS data maturity.

• Inclusion of an additional IA2 for PFS (opportunity to test efficacy early).

• Due to the above changes, increase of the targeted number of PFS events from approximately 139 to approximately 173 events and modified multiplicity strategy to account for multiple testing.

• Inclusion of additional details regarding planned OS IA.

• Modification of testing hierarchy such that OS was to be tested prior to MRD negativity, recognizing the importance of OS as both an efficacy and safety endpoint.

Protocol deviations

All protocol deviations were assessed for importance by the study team based on a predefined Protocol Deviation Management Plan. Important deviations were defined as deviations that directly or indirectly had an impact on the participant's rights, safety, or well-being, and/or on data integrity and/or regulatory compliance as per ICH E3.

Important efficacy deviations included deviations related to missed or out of window disease assessments resulting in censorship and MRD sample not collected at the time ofCR or better. Important SAE deviations included deviations related to SAE reporting criteria and other deviations related to safety, i.e., administration of study treatment (belantamab mafodotin) when an ocular exam was missed or was out of window by≥5 days prior to the dose. Important investigational product compliance deviations included deviations related to investigational product administration, i.e., administration of study treatment (belantamab mafodotin) when the KVA grade was ≥2. Protocol waivers or exemptions were not allowed.

The percentage of participants with any important protocol deviation was higher in the BPd group compared with the PVd group (70% vs. 50%).

The most common types of protocol deviation in both treatment groups were related to investigational product compliance and SAE criteria. Protocol deviations due to investigational product compliance and SAE criteria were reported in more participants in the BPd group than in the PVd group. The difference in protocol deviations between treatment groups was driven by noncompliance with dose modification due to KVA grading (investigational product compliance) or missed ocular exams (SAE criteria). The following factors contributed to the imbalances in protocol deviations between the treatment groups.

- **Baseline data**

Demographic characteristics were balanced between the BPd and PVd groups (

Table *23*).

Table 23. Demographic Characteristics-DREAMM 8 study (ITT Population)

	BPd (N=155)	PVd (N=147)	Total (N=302)
Sex, n (%)			
Female	56 (36%)	65 (44%)	121 (40%)
Male	99 (64%)	82 (56%)	181 (60%)
Age (years)[a]			
Mean (SD)	65.5 (8.56)	66.7 (10.03)	66.1 (9.31)
Median (min, max)	67.0 (40, 82)	68.0 (34, 86)	67.0 (34, 86)
Age Group (years)[a], n (%)[a]			
19 to <65	64 (41%)	53 (36%)	117 (39%)
65 to <75	72 (46%)	59 (40%)	131 (43%)
≥75	19 (12%)	35 (24%)	54 (18%)
Ethnicity, n (%)			
n	155	146	301
Hispanic or Latino	10 (6%)	7 (5%)	17 (6%)
Not Hispanic or Latino	145 (94%)	139 (95%)	284 (94%)
High level race, n (%)			
n	155	146	301
American Indian or Alaska Native	0	0	0
Asian	20 (13%)	17 (12%)	37 (12%)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	1 (<1%)	2 (1%)	3 (<1%)
White	133 (86%)	127 (87%)	260 (86%)
Mixed race	1 (<1%)	0	1 (<1%)
Race detail, n (%)			
n	155	146	301
American Indian or Alaska Native	0	0	0
Asian – Central/South Asian heritage	1 (<1%)	1 (<1%)	2 (<1%)
Asian – East Asian heritage	16 (10%)	8 (5%)	24 (8%)
Asian – Japanese heritage	3 (2%)	6 (4%)	9 (3%)
Asian – South East Asian heritage	0	2 (1%)	2 (<1%)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	1 (<1%)	2 (1%)	3 (<1%)
White – Arabic/North African heritage	9 (6%)	14 (10%)	23 (8%)
White – White/Caucasian/European heritage	124 (80%)	113 (77%)	237 (79%)
Mixed Asian race	0	0	0
Mixed White race	0	0	0
Mixed race	1 (<1%)	0	1 (<1%)
Geographical Region, n (%)			
North America[b]	4 (3%)	1 (<1%)	5 (2%)
Europe[c]	105 (68%)	109 (74%)	214 (71%)
North East Asia[d]	18 (12%)	14 (10%)	32 (11%)
Rest of the World[e]	28 (18%)	23 (16%)	51 (17%)
Height (cm)			
Mean (SD)	168.16 (10.221)	166.10 (10.856)	167.16 (10.568)
Median (min, max)	169.00 (139.6, 194.0)	167.00 (137.5, 187.5)	168.00 (137.5, 194.0)
Weight (kg)			
Mean (SD)	77.03 (15.387)	76.90 (15.992)	76.97 (15.658)
Median (min, max)	76.00 (46.0, 123.0)	76.00 (45.0, 122.4)	76.00 (45.0, 123.0)

	BPd (N=155)	PVd (N=147)	Total (N=302)
BMI (kg/m²)			
Mean (SD)	27.216 (4.8351)	27.779 (4.7658)	27.490 (4.8018)
Median (min, max)	26.913 (17.60, 42.98)	27.673 (17.58, 46.09)	27.106 (17.58, 46.09)

a. Age was imputed when full date of birth was not provided.
b. North America: United States.
c. Europe: Czech Republic, France, Germany, Greece, Italy, Poland, Russian Federation, Spain, Turkey, United Kingdom.
d. North East Asia: China, Japan, Republic of Korea.
e. Rest of the World: Australia, Brazil, Israel, New Zealand.

Disease characteristics at baseline are summarised in

Table *24*.

Table 24. Disease Characteristics at Screening-DREAMM 8 study (ITT Population)

	BPd (N=155)	PVd (N=147)	Total (N=302)
International Staging System (ISS) at screening, n (%)			
I	93 (60%)	85 (58%)	178 (59%)
II	39 (25%)	40 (27%)	79 (26%)
III	22 (14%)	22 (15%)	44 (15%)
Unknown	1 (<1%)	0	1 (<1%)
Extramedullary disease, n (%)			
No	135 (87%)	136 (93%)	271 (90%)
Yes	20 (13%)	11 (7%)	31 (10%)
Lytic bone lesions, n (%)			
No	37 (24%)	40 (27%)	77 (25%)
Yes	118 (76%)	107 (73%)	225 (75%)
Myeloma immunoglobulin, n (%)			
IgA	42 (27%)	25 (17%)	67 (22%)
IgD	2 (1%)	1 (<1%)	3 (<1%)
IgE	0	0	0
IgG	86 (55%)	102 (69%)	188 (62%)
IgM	2 (1%)	1 (<1%)	3 (<1%)
Not present	23 (15%)	18 (12%)	41 (14%)
Missing	0	0	0
Myeloma light chain, n (%)			
Yes: Kappa light chain	94 (61%)	94 (64%)	188 (62%)
Yes: Lambda light chain	57 (37%)	52 (35%)	109 (36%)
No myeloma light chain	4 (3%)	1 (<1%)	5 (2%)
Type of multiple myeloma, n (%)			
Nonsecretory	0	0	0
Secretory	155 (100%)	147 (100%)	302 (100%)
Lines of therapy completed prior to screening, n (%)			
1 Line	82 (53%)	77 (52%)	159 (53%)
2 Lines	32 (21%)	33 (22%)	65 (22%)
3 Lines	22 (14%)	15 (10%)	37 (12%)
4 Lines	12 (8%)	13 (9%)	25 (8%)
5 Lines	5 (3%)	5 (3%)	10 (3%)
6 Lines	2 (1%)	1 (<1%)	3 (<1%)
7 Lines	0	2 (1%)	2 (<1%)
8 Lines	0	0	0
9 Lines	0	1 (<1%)	1 (<1%)
Lines of therapy completed prior to screening			
Mean (SD)	1.9 (1.22)	2.0 (1.44)	2.0 (1.33)
Median (min, max)	1.0 (1, 6)	1.0 (1, 9)	1.0 (1, 9)
Prior stem cell transplant, n (%)			
No	56 (36%)	65 (44%)	121 (40%)
Yes	99 (64%)	82 (56%)	181 (60%)
High-risk cytogenetic profile by FISH, n (%)[a]			
t(4;14)	23 (15%)	20 (14%)	43 (14%)
t(14;16)	7 (5%)	11 (7%)	18 (6%)
17p13del	32 (21%)	26 (18%)	58 (19%)
Other cytogenetic abnormalities by FISH, n (%)[a,b]			
Amp(1q)	40 (26%)	33 (22%)	73 (24%)
1pdel	11 (7%)	12 (8%)	23 (8%)
Other	10 (6%)	8 (5%)	18 (6%)

High-risk cytogenetic profile categories, n (%)			
High risk[c]	52 (34%)	47 (32%)	99 (33%)
Double hit multiple myeloma[d]	9 (6%)	7 (5%)	16 (5%)
Standard risk[e]	72 (46%)	75 (51%)	147 (49%)
Missing or not evaluable	31 (20%)	25 (17%)	56 (19%)
Time to relapse after initiation of 1L treatment, n (%)[f]			
≤12 Months	22 (14%)	20 (14%)	42 (14%)
>12 Months	133 (86%)	127 (86%)	260 (86%)
Actual time since initial diagnosis at randomization (years)			
Median (min, max)	4.04 (0.4, 16.7)	3.43 (0.4, 17.7)	3.63 (0.4, 17.7)
1st quartile	2.48	2.11	2.33
3rd quartile	6.60	5.22	6.04
ECOG performance status, n (%)[g]			
n	150	145	-
0	79 (53%)	84 (58%)	-
1	67 (45%)	56 (39%)	-
2	4 (3%)	5 (3%)	-

a. Participants may have been included in more than 1 category. Only positive results were summarized.
b. Results may not have been collected or reported for all participants.
c. If the participant had at least 1 high-risk abnormality: t(4;14), t(14;16), or 17p13del.
d. If the participant had at least 2 high-risk abnormalities: t(4;14), t(14;16), or 17p13del.
e. If the participant had negative results for all high-risk abnormalities: t(4;14), t(14;16), or 17p13del.
f. Relapse was defined as the time from the start date of the first prior line of the therapy to the date of randomization for participants with 1 prior line or to the start date of the second prior line of the therapy for participants with >1 prior line.
g. Analyzed in the safety population.

Prior anti-myeloma therapy

The types of prior anti-myeloma therapies participants received were generally similar between treatment groups (**Table 25**).

Table 25. Prior Anti-myeloma Therapy and Percentage of Participants Who Were Refractory by Drug Class of Agents-DREAMM 8 Study (ITT Population)

Drug Class, n (%)	Participants with Prior Anti-Myeloma Therapy		Participants Refractory to Prior Anti-Myeloma Therapy	
	BPd (N=155)	PVd (N=147)	BPd (N=155)	PVd (N=147)
Immunomodulator	155 (100%)	147 (100%)	127 (82%)	111 (76%)
Lenalidomide	155 (100%)	147 (100%)	125 (81%)	111 (76%)
Thalidomide	49 (32%)	48 (33%)	9 (6%)	6 (4%)
Pomalidomide	0	1 (<1%)	-	-
Steroids	152 (98%)	146 (>99%)	74 (48%)	62 (42%)
Proteasome inhibitor	140 (90%)	136 (93%)	40 (26%)	35 (24%)
Bortezomib	134 (86%)	130 (88%)	16 (10%)	8 (5%)
Carfilzomib	34 (22%)	37 (25%)	18 (12%)	23 (16%)
Ixazomib	11 (7%)	15 (10%)	8 (5%)	11 (7%)
Chemotherapy	108 (70%)	87 (59%)	15 (10%)	11 (7%)
mAb	42 (27%)	44 (30%)	37 (24%)	36 (24%)
Anti-CD38 antibodies	38 (25%)	42 (29%)	35 (23%)	36 (24%)
Daratumumab	36 (23%)	39 (27%)	33 (21%)	34 (23%)
Isatuximab	2 (1%)	3 (2%)	2 (1%)	2 (1%)
CD38inhibitors	0	1 (<1%)	0	1 (<1%)
Other mAbs	5 (3%)	3 (2%)	3 (2%)	1 (<1%)
Elotuzumab	4 (3%)	3 (2%)	2 (1%)	1 (<1%)
MDX-1097	1 (<1%)	0	1 (<1%)	0
Other	9 (6%)	8 (5%)	3 (2%)	1 (<1%)
Histone deacetylase inhibitor	1 (<1%)	1 (<1%)	0	1 (<1%)
Small molecular kinase inhibitor	1 (<1%)	1 (<1%)	0	1 (<1%)

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

Follow-up anti-myeloma therapy

At the data cut-off, 58% of participants in the BPd group and 78% in the PVd group had discontinued all components of study treatment; this includes participants who died, were never dosed, or had

withdrawn from study. Follow-up anti-myeloma therapy was initiated in 27% and 52% of participants in the BPd and PVd groups, respectively. The median time from study treatment discontinuation to start of subsequent anti-myeloma therapy was longer in the BPd group compared with the PVd group (37.0 days vs. 23.0 days).

For any line of subsequent therapy, a higher percentage of participants in the PVd group vs the BPd group, (**Table 26**).

Table 26. Follow-Up Anti-Myeloma Therapy by Drug Class of Agents-DREAMM 8 Study (ITT Population)

Drug Class, n (%)	Any Subsequent Anti-Myeloma Therapy	
	BPd (N=155)	PVd (N=147)
Steroids	37 (24%)	59 (40%)
mAb	24 (15%)	51 (35%)
Anti-CD38 antibodies	23 (15%)	49 (33%)
Daratumumab	20 (13%)	38 (26%)
Isatuximab	5 (3%)	10 (7%)
Modakafusp alfa	0	1 (<1%)
Other mAb	4 (3%)	2 (1%)
Elotuzumab	4 (3%)	2 (1%)
Proteasome inhibitor	26 (17%)	36 (24%)
Carfilzomib	15 (10%)	23 (16%)
Bortezomib	15 (10%)	10 (7%)
Ixazomib	1 (<1%)	9 (6%)
Immunomodulator	14 (9%)	29 (20%)
Lenalidomide	6 (4%)	16 (11%)
Pomalidomide	5 (3%)	12 (8%)
Thalidomide	3 (2%)	3 (2%)
Iberdomide	1 (<1%)	0
Chemotherapy	16 (10%)	25 (17%)
Bi-specific antibody (BiTE)	6 (4%)	16 (11%)
Teclistamab	1 (<1%)	5 (3%)
Cevostamab	2 (1%)	3 (2%)
Investigational antineoplastic agents	0	4 (3%)
Regn5458	0	3 (2%)
Emb-06	0	1 (<1%)
Talquetamab	2 (1%)	2 (1%)
Elranatamab	0	2 (1%)
Forimtamig	1 (<1%)	0
Other	5 (3%)	7 (5%)
Selinexor	5 (3%)	3 (2%)
Venetoclax	0	3 (2%)
Nirogacestat	0	1 (<1%)
Antibody drug conjugate	0	10 (7%)
Belantamab	0	6 (4%)
Belantamab mafodotin	0	4 (3%)
Stem cell transplant	1 (<1%)	5 (3%)

Note: Multiple categories per participant were possible, total may add to more than 100%.

At a later DCO date of 07 October 2024, more participants remained on study treatment in the BVd group (25%) compared to the DVd group (15%). Hence, with more participants having discontinued study treatment in the DVd group, more had the need to start subsequent therapy, which is reflected in the higher percentage of participants in the DVd group starting subsequent therapy (BVd: 36%; DVd: 52%). For participants who started subsequent therapy, the median time from study treatment discontinuation to the start of subsequent anti-myeloma therapy was 83.0 days in the BVd group and

51.5 days in the DVd group. The patients were often treated with treatment options they had received in earlier lines of treatment. While cross-over between groups was not permitted at the time the study was conducted, both daratumumab and belantamab mafodotin were approved in some countries and available for patients with RRMM. Thus, some participants who progressed on 1 regimen were able to receive these agents either via some other clinical study or through commercial supply.

- **Numbers analysed**

A total of 7 study populations were used in the analyses for this clinical study (**Table 27**). The belantamab mafodotin PK population and the pomalidomide PK population included participants from the BPd treatment group. For the rest of each study population used in analyses, the number of participants was similar between treatment groups.

Table 27. DREAMM 8 Study Populations

Population, n (%)	Screen Failure (N=80)	BPd (N=155)	PVd (N=147)	Total (N=382)
All Screened	80 (100%)	155 (100%)	147 (100%)	382 (100%)
Enrolled	0	155 (100%)	147 (100%)	302 (79%)
ITT	0	155 (100%)	147 (100%)	302 (79%)
Safety	0	150 (97%)	145 (99%)	295 (77%)
Modified ITT	0	149 (96%)	144 (98%)	293 (77%)
Belantamab Mafodotin PK	0	150 (97%)	0	150 (39%)
Pomalidomide PK	0	37 (24%)	0	37 (10%)

Note 1: Treatment columns are based on planned treatment.
Note 2: All randomized participants were included in the ITT Population regardless of whether they received study treatment.
Note 3: Participants were included in the Modified ITT Population if they received at least 1 line of prior therapy including lenalidomide-based therapy, had evidence of measurable disease at baseline and were randomized and received at least 1 dose of their planned study treatment.
Note 4: All participants in the Safety Population from whom at least 1 belantamab mafodotin or pomalidomide PK sample had been obtained, analyzed and was measurable were included in the respective PK population.

- **Outcomes and estimation**

Primary efficacy endpoint

Progression-free survival

PFS primary analysis

The DREAMM-8 study met its primary endpoint of PFS assessed by IRC with a data cut-off 2 October 2023. The median duration of follow-up was 21.782 months with a minimum follow-up of 12.81 months for participants with ongoing follow-up. Results were still in favour of BPd at a later data cut-off date of 7 October 2024 **(Table 28).**

Table 28. Progression-Free Survival Based on IRC-Assessed Response- DREAMM 8 Study (ITT Population)

	IA2 (DCO 29 January 2024)		Post-hoc analysis (DCO 07 October 2024)	
	BPd (N=155)	PVd (N=147)	BPd (N=155)	PVd (N=147)
Number of participants, n (%)				
Progressed or died (event)	62 (40%)	80 (54%)	68 (44%)	89 (61%)
Censored, follow-up ended	25 (16%)	34 (23%)	28 (18%)	37 (25%)
No adequate baseline assessments	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
No adequate post-baseline assessments: randomized, not dosed, withdrawn	4 (3%)	1 (<1%)	4 (3%)	1 (<1%)
No adequate post-baseline assessments before start of new anti-myeloma therapy	0	2 (1%)	0	2 (1%)
With adequate post-baseline assessment and new anti-myeloma treatment started	7 (5%)	17 (12%)	9 (6%)	20 (14%)
Progression after extended loss-to-follow-up	2 (1%)	3 (2%)	3 (2%)	2 (1%)
Death after extended loss-to-follow-up	4 (3%)	4 (3%)	4 (3%)	5 (3%)
Post-baseline assessment but no progression (or death)	7 (5%)	6 (4%)	7 (5%)	6 (4%)
Censored, follow-up ongoing	68 (44%)	33 (22%)	59 (38%)	21 (14%)
Event summary, n (%)				
Disease progression	46 (30%)	66 (45%)	51 (33%)	74 (50%)
Death	16 (10%)	14 (10%)	17 (11%)	15 (10%)
Estimates for time variable (months)[a]				
1st quartile (95% CI)	10.3 (5.6, 14.0)	5.5 (3.7, 6.5)	10.3 (5.6, 14.0)	5.5 (3.7, 6.5)
Median (95% CI)	- (20.6, -)	12.7 (9.1, 18.5)	32.6 (21.1, -)	12.5 (9.1, 17.6)
3rd quartile (95% CI)	- (-, -)	- (20.3, -)	- (-, -)	29.5 (21.2, -)
Hazard ratio[b]				
Estimate (95% CI)	0.52 (0.37, 0.73)		0.49 (0.35,0.68)	
Stratified log-rank[c]				
p-value	<0.001		-	
Progression-free survival rate				
Time-to-event endpoint at 6 months (95% CI)	0.82 (0.75, 0.87)	0.72 (0.64, 0.79)	0.82 (0.75, 0.87)	0.72 (0.64, 0.79)
Time-to-event endpoint at 12 months (95% CI)	0.71 (0.63, 0.78)	0.51 (0.42, 0.60)	0.71 (0.63, 0.78)	0.51 (0.41, 0.59)
Time-to-event endpoint at 18 months (95% CI)	0.62 (0.54, 0.70)	0.43 (0.34, 0.52)	0.63 (0.54, 0.70)	0.41 (0.32, 0.50)

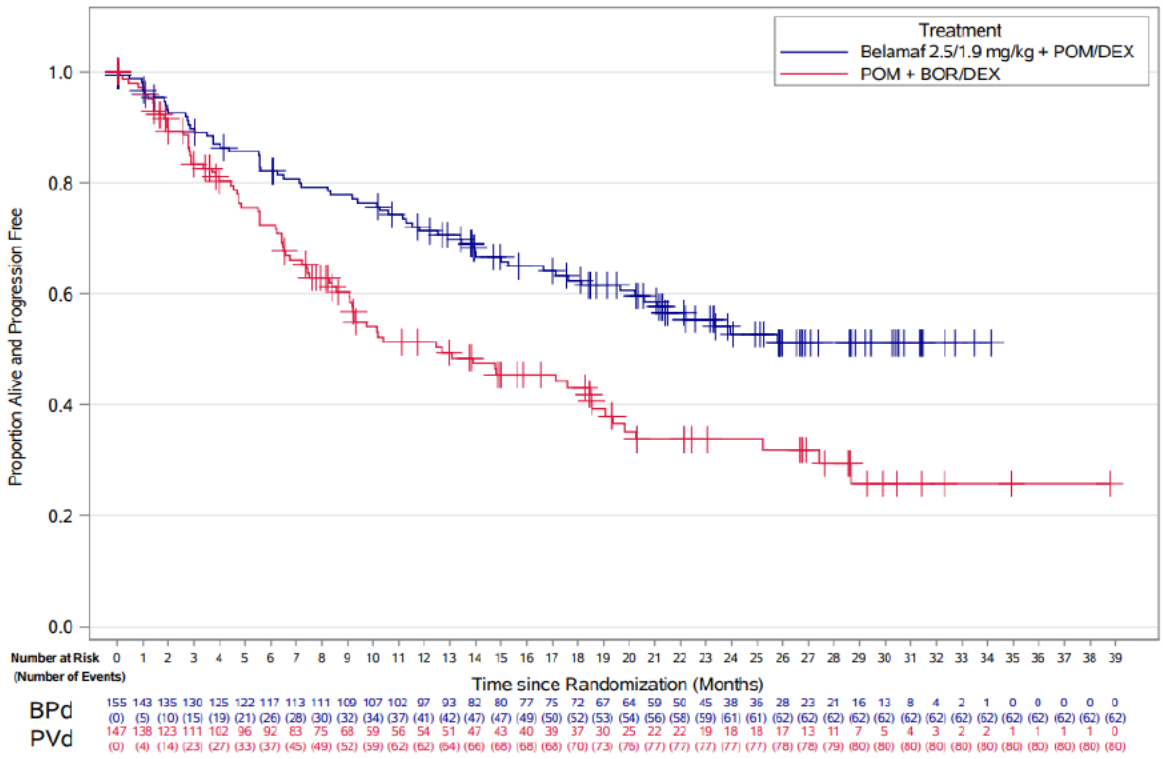
a. CIs were estimated using the Brookmeyer Crowley method.
b. HRs were estimated using a Cox Proportional Hazards model with stratification factors A and B assessed according to the IVRS strata; Covariate: Treatment.
c. p-values from 1-sided stratified log-rank test with stratification factors A and B assessed according to the IVRS strata; Covariate: Treatment.

Note: A: Number of lines of prior therapy; B: Prior bortezomib use.

The KM curves for PFS are shown in (

Figure *18*).

Figure 18. Kaplan-Meier Curves of Progression-Free Survival Based on IRC-Assessed Response-DREAMM 8 Study (ITT Population)



PFS analysis based on investigator-assessed responses was consistent with IRC results (data not shown).

Sensitivity analysis

PFS was analysed using alternate censoring rule 1 where progression documented between scheduled visits and progression documented without extended loss-to-follow-up time was assumed to happen at the date of the next scheduled response assessment.

Using alternate censoring rule 1, the outcome remained the same as the primary analysis, with a median PFS of 11.2 months and 7.0 months in the belantamab mafodotin and pom/dex groups, respectively, and the HR was 1.03.

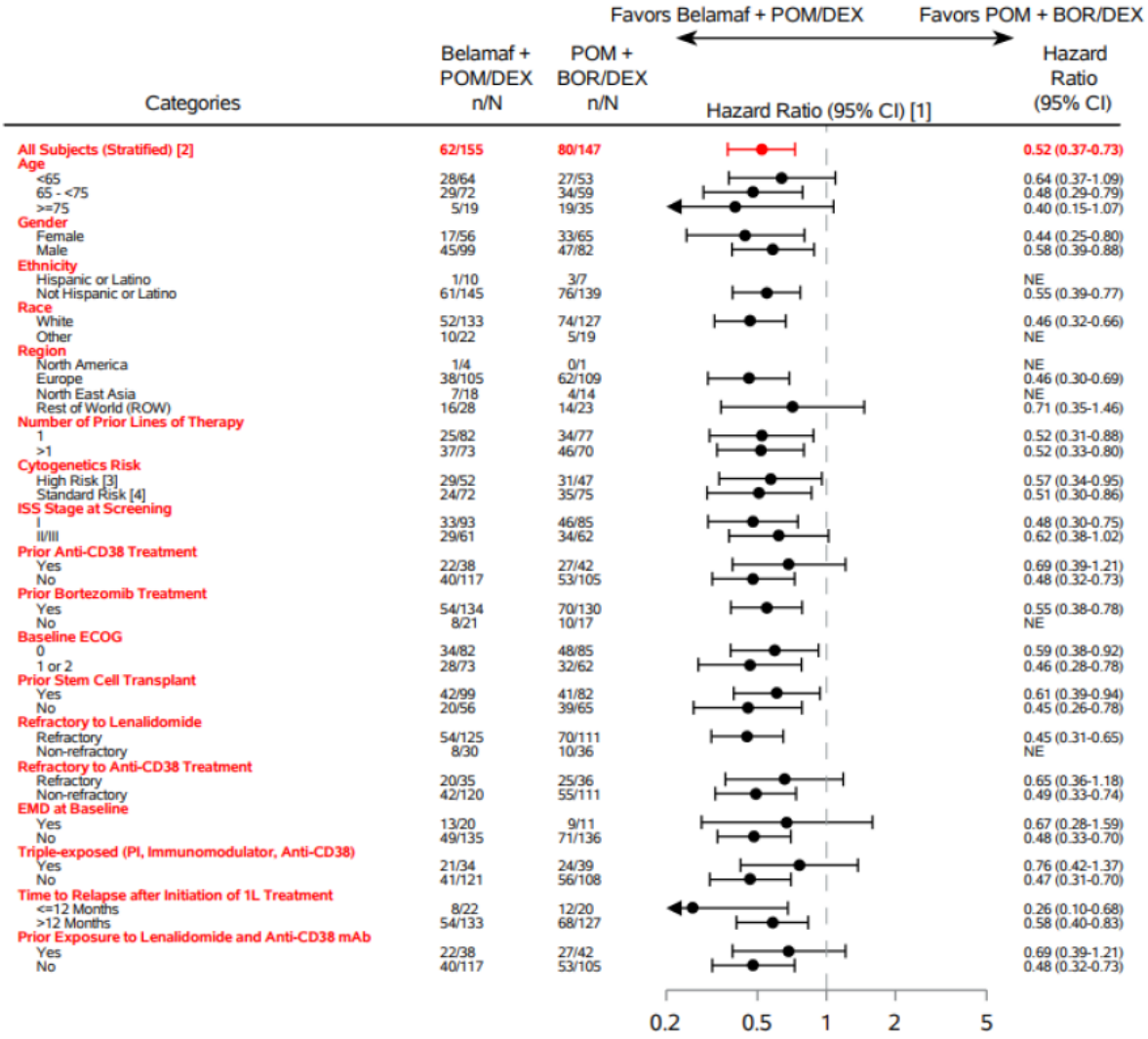
PFS was analysed using alternate censoring rule 2, which considered initiation of new anti-cancer therapy, progression or death after extended loss to follow-up, and treatment discontinuation as events. Analyses using alternate censoring rule 2 (median PFS: 5.6 months in the belantamab mafodotin group and 4.9 months in the pom/dex group), yielded a shorter median PFS in both groups compared with the primary censoring rule, but the HR remained non-significant, albeit slightly favouring belantamab mafodotin (HR=0.90).

Stratification errors were identified for approximately 15% of participants in the study. The outcome remained unchanged following the pre-planned sensitivity analysis using the stratification data based on the clinical database (HR=0.98; 95% CI: 0.69, 1.40).

Subgroup analysis

PFS benefit was consistent across subgroups, including those exposed to or refractory to lenalidomide and those with high-risk cytogenetics with HR point estimates ranging from 0.26 to 0.76 (**Figure 19**).

Figure 19. Forest Plot – Progression-Free Survival Based on IRC-Assessed Response by Subgroup - DREAMM 8 Study (ITT Population)



[1] HRs for subgroups were only plotted if number of events was ≥20 in total across both treatments. HRs for subgroups were estimated using Cox Proportional Hazard models, without adjustment for stratification variables.

[2] Stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≤4), prior bortezomib (no, yes), and according to IVRS strata with a covariate of treatment.

[3] A participant was considered as high risk if the participant had any of the following cytogenetics: t(4;14), t(14;16), or 17p13del.

[4] A participant was considered standard risk if the participant had negative results for all high-risk abnormalities: t(4;14), t(14;16), and 17p13del.

Key secondary efficacy endpoints

OS

At the data cut-off, there was a positive OS trend in favour of the BPd group (**Table 29**).

Table 29. Summary of Overall Survival- DREAMM 8 Study (ITT Population)

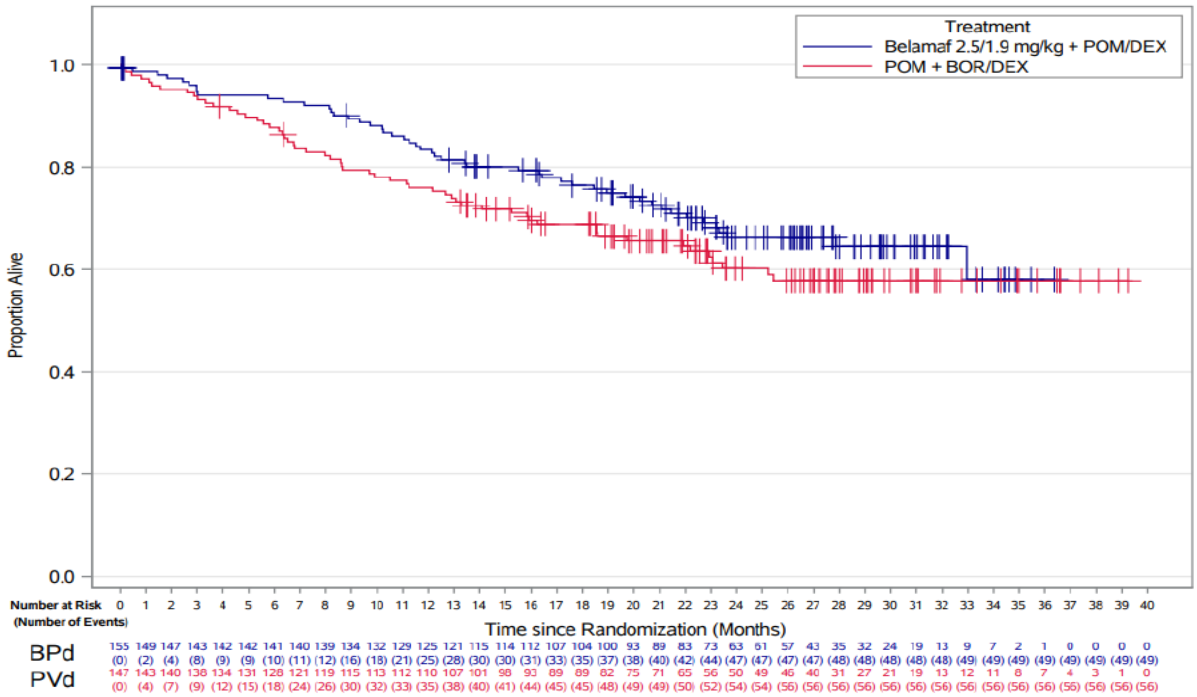
	BPd (N=155)	PVd (N=147)
Number of participants, n (%)		
Died (event)	49 (32%)	56 (38%)
Censored, follow-up ended	12 (8%)	7 (5%)
Censored, follow-up ongoing	94 (61%)	84 (57%)
Event summary, n (%)		
Death	49 (32%)	56 (38%)
Estimates for time variable (months)[a]		
1st quartile	19.0	12.7
95% CI	(12.2, 23.3)	(8.0, 18.5)
Median	-	-
95% CI	(33.0, -)	(25.2, -)
3rd quartile	-	-
95% CI	(-, -)	(-, -)
Hazard ratio[b]		
Estimate[d]	0.77	
95% CI	(0.53, 1.14)	
Estimate[e]	0.78	
95% CI	(0.53, 1.15)	
Stratified log-rank[c]		
P-value[d]	0.095	
P-value[e]	0.102	
OS rate		
Time-to-event endpoint at 6 months	0.93	0.88
95% CI	(0.88, 0.96)	(0.81, 0.92)
Time-to-event endpoint at 12 months	0.83	0.76
95% CI	(0.76, 0.88)	(0.68, 0.82)
Time-to-event endpoint at 18 months	0.76	0.69
95% CI	(0.69, 0.82)	(0.61, 0.76)

a. CIs for time variables estimated using the Brookmeyer Crowley method.
b. Hazard ratios were estimated using a Cox Proportional Hazards model according to the corresponding footnotes.
c. P-Value from 1-sided stratified log-rank test according to the corresponding footnotes.
d. Stratification factors: Number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no) assessed according to IVRS strata; Covariate: Treatment.
e. Stratification factors: Number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no) assessed according to eCRF strata; Covariate: Treatment. Nominal p-value is provided.

Median OS was not reached in either treatment group. OS data reached 34.77% (105/302 participants) overall maturity. The OS p-value (0.095) did not cross the pre-defined OS boundary adjusting for the observed number of events at the time of analysis. Follow up for OS is ongoing and will continue until the next planned IA of OS (IA3) at approximately 60% information fraction. Median OS was not reached in either treatment group. OS data reached 34.77% (105/302 participants) overall maturity and IF equal to 48.39% (105/217), where 217 were the planned deaths for OS analysis according to the SAP. The OS p-value (0.095) did not cross the pre-defined OS boundary adjusting for the observed number of events at the time of analysis.

The KM curves for OS showed an early separation between the treatment groups in favour of BPd (**Figure 20**). Follow up for OS is ongoing and will continue until the next planned IA of OS (IA3) at approximately 60% information fraction.

Figure 20. Kaplan-Meier Curves of Overall Survival- DREAMM 8 Study (ITT Population)



Duration of response

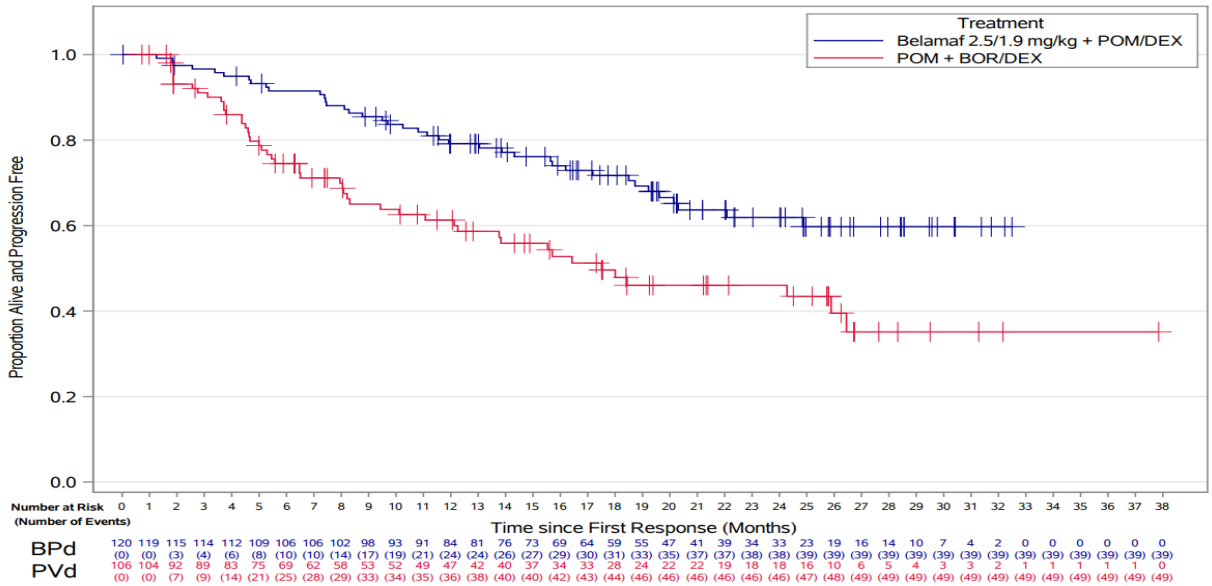
Conventional assessment of duration of response

The median DoR was not reached in the BPd group and 17.5 months in the PVd group. In the BPd group, 55% of participants with response had not progressed or died and had follow-up for PFS ongoing at the data-cut compared with 31% of participants in the PVd group. Sensitivity analysis results of DoR by IRC (considering death due to PD only) were similar to the conventional DoR analysis (death due to any cause) (median DoR not reached in the BPd group vs. 18.4 months in the PVd group).

The KM curves for DoR showed an early separation between the treatment groups in favor of BPd **(**

Figure *21*).

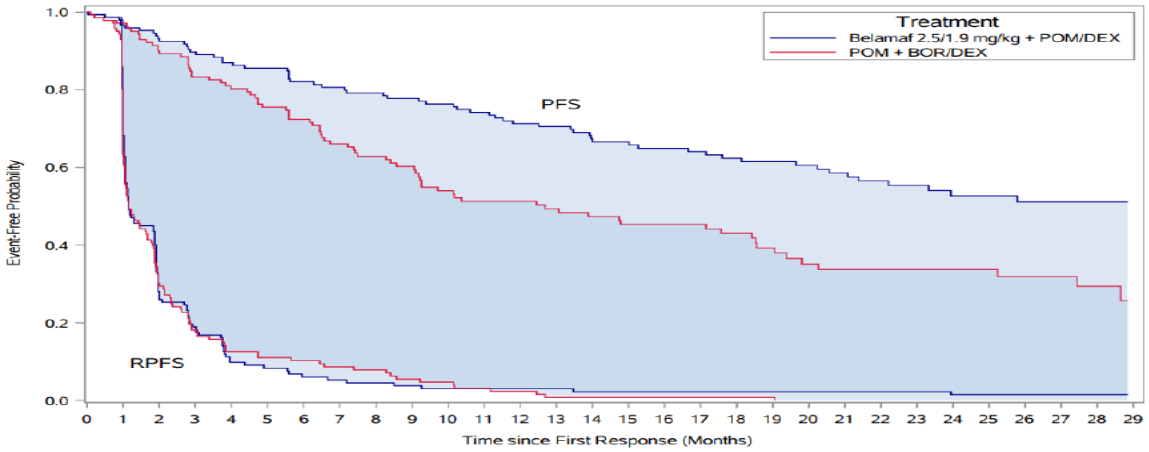
Figure 21. Kaplan-Meier Curves of DoR Based on IRC-Assessed Response- DREAMM 8 (Considering Death Due to Any Cause) (ITT Population)



Restricted mean duration of response

The shaded area between the PFS and RPFS curves within each treatment group up until the common truncation time of 28.8 months is the RMDoR based on IRC assessment for that group; it was larger for the BPd group compared with the PVd group (17.5 months vs. 12.7 months) with a difference of 4.8 months and a ratio of 1.38 (**Figure 22**). RMDoR estimates at the common truncation time of 28.8 months were 17.4 months vs. 12.1 months, ratio 1.44.

Figure 22. Restricted Mean DoR based on IRC-Assessed Response- DREAMM 8 (ITT Population)



Minimal residual disease

The proportion of all participants (ITT population) who achieved MRD negativity was higher in the BPd group compared with the PVd group at the time of primary PFS analysis (23.9% vs. 4.8%) (**Table 30**). OS analysis was not statistically significant at the time of PFS data cut-off, therefore, MRD negativity could not be formally tested at this time. Nominal p-values are provided, but MRD negativity analysis is descriptive only.

Table 30. Summary of MRD Negativity Based on IRC-Assessed Responses-DREAMM 8 Study (ITT Population)

		BPd (N=155)	PVd (N=147)
Best response			
sCR/CR	MRD negativity rate[a]	37 (23.9%)	7 (4.8%)
	95% CI	(17.4%, 31.4%)	(1.9%, 9.6%)
	P-value[b]	<0.001	
	P-value[c]	<0.001	
	P-value[d]	<0.001	
	P-value[e]	<0.001	

a. The percentage of participants achieving MRD negative status (assessed by NGS at 10^{-5} threshold) during confirmed CR+ according to IRC-assessed response based on IMWG. Rates were calculated out of N per treatment group. P-values are 1-sided.
b. Nominal p-value based on CMH test, adjusting for A and B assessed according to IVRS strata.
c. Unadjusted nominal p-value based on Fisher's exact test.
d. Nominal p-value based on CMH test, adjusting for pooling stratification using A, B, C and D.
e. Nominal p-value based on CMH test, adjusting for A and B as per eCRF.

Note: A: Number of lines of prior therapy, B: Prior bortezomib use, C: ISS status, D: Prior Anti-CD38

Results of MRD negativity analysis using investigator-confirmed response or in participants with VGPR or better were consistent with the primary MRD analysis (**Table 31**).

Table 31. MRD Negativity Rate by Best Response Based on IRC-Assessed Response- DREAMM 8 Study (ITT Population)

Best Confirmed Response		BPd (N=155)	PVd (N=147)
Stringent complete response (sCR)	n	14	4
	Number of sCR participants with MRD data	13	4
	MRD negativity rate	8 (57%)	2 (50%)
	95% CI	(28.9%, 82.3%)	(6.8%, 93.2%)
Complete response (CR)	n	48	20
	Number of CR participants with MRD data	41	16
	MRD negativity rate	29 (60%)	5 (25%)
	95% CI	(45.3%, 74.2%)	(8.7%, 49.1%)
Very good partial response (VGPR)	n	37	32
	Number of VGPR participants with MRD data	28	18
	MRD negativity rate	10 (27%)	1 (3%)
	95% CI	(13.8%, 44.1%)	(0.1%, 16.2%)
sCR/CR	n	62	24
	Number of CR+ participants with MRD data	54	20
	MRD negativity rate	37 (60%)	7 (29%)
	95% CI	(46.4%, 71.9%)	(12.6%, 51.1%)
sCR/CR/VGPR	n	99	56
	Number of VGPR+ participants with MRD data	82	38
	MRD negativity rate	50 (51%)	8 (14%)
	95% CI	(40.3%, 60.7%)	(6.4%, 26.2%)

Note 1: CIs are based on the exact method.
Note 2: MRD negativity rate (%) is based on n per best response group and not total ITT population N.

Secondary efficacy endpoints

CRR was higher in the BPd arm compared with the PVd group (40% vs. 16%) as well as VGPR (64% vs. 38%).

Median TTP was not reached in the BPd group (95% CI: 25.8, NR), while the median TTP was 17.1 months in the PVd group.

Median PFS2 was not reached in the BPd arm while the median PFS2 22.4 months in the PVd group (HR=0.61; 95% CI: 0.43, 0.86).

BPd was associated with higher rates of sustained MRD negativity (lasting≥12 months) compared with the PVd group (8.4% vs. 1.4%).

- **Ancillary analyses**

Not applicable.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 32. Summary of efficacy for trial DREAMM-7 (belantamab mafodotin)

Title: A Multicenter, Open-Label, Randomized Phase III Study to Evaluate the Efficacy and Safety of the Combination of Belantamab Mafodotin, Bortezomib, and Dexamethasone (B-Vd) Compared with the Combination of Daratumumab, Bortezomib and Dexamethasone (D-Vd) in Participants with Relapsed/Refractory Multiple Myeloma		
Study identifier	EudraCT 2018-003993-29 EU CT Number: 2023-510537-28-00	
Design	Phase 3, open-label, multicenter, randomized, clinical study to evaluate the efficacy and safety of BVd compared with DVd in participants with RRMM previously treated with at least 1 prior line of therapy.	
	• Duration of main phase:	• Randomisation until PD per IMWG criteria, death, unacceptable toxicity, investigator's discretion, withdrawal of consent, or end of study, whichever occurred first. • not applicable • not applicable
Hypothesis	Superiority. To demonstrate the superiority of B-Vd compared to D-Vd in PFS in participants with relapsed/refractory multiple myeloma. Primary endpoint: PFS, defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause.	

Treatments groups	Arm A: BVd (belentamab mafodotin + Bortezomib + dexamethasone)	Belantamab mafodotin was administered IV at the dose of 2.5 mg/kg on Day 1 of every 21-day cycle. Bortezomib 1.3 mg/m2 was administered SC on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles. Dexamethasone 20 mg (PO or IV) was administered on the day of and the day after bortezomib treatment. Starting dose of dexamethasone was reduced to 10 mg for participants older than 75 years of age, who had a body-mass index of <18.5 kg/m, who had previous unacceptable side effects associated with glucocorticoaid therapy, or who were unable to tolerate the starting dose. 243 participants were enrolled to the BVd	
	Arm B: DVd (daratumumab + bortezomib + dexamethasone)	Daratumumab 16 mg/kg IV was administered according to the approved label schedule in combination with bor/dex weekly for Cycles 1 through 3 (Weeks 1 to 9) (21-day cycles, total of 9 doses), on Day 1 of Cycles 4 through 8 (Weeks 10 to 24) (21-day cycles, total of 5 doses), and then every 4 weeks from Cycle 9 (Week 25) onwards (28-day cycles). Bortezomib and dexamethasone dosing schedule in Arm B was same as that of Arm A.	
Endpoints and definitions	Primary endpoint	Progression Free Survival (PFS)	PFS, defined as the time from the date of randomisation until the earliest date of documented disease progression or death due to any cause
	Key Secondary endpoint	Overall Survival (OS)	OS, defined as the time from the date of randomization until the date of death due to any cause
	Key Secondary endpoint	Duration of response (DoR)	DoR, defined as the time from first documented evidence of PR or better until PD or death due to any cause
	Key Secondary endpoint	Minimal residual disease (MRD) negativity rate	MRD negativity rate, defined as the percentage of participants who are MRD negative by NGS (at 10^{-5} threshold)
	Secondary	Overall Response Rate (ORR)	ORR, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR)
	Secondary	PFS 2	defined as time from randomisation to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier
Database	2 October 2023		

Results and Analysis			
Analysis description	**Primary Analysis - PFS**		
Analysis population and time	Efficacy data based on Intent to treat population, based on Independent Reviewer-Assessed Response Time from randomisation until the earliest date of PD based on IRC-assessment		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BVd	Arm B - DVd
	Number of subjects	243	251
	Progression-free survival (PFS) Number (%) of patients with event	91 (37)	158 (63)
	Median in months (95% CI)[a]	36.6 (28.4, NR)	13.4 (11.1, 17.5)
	Hazard ratio (95% CI)[b]	0.41 (0.31, 0.53)	
	p-value[c]	<0.00001	
	Progression-free survival (PFS) Probability of PFS at 18 months, % (95% CI)	69 (62, 75)	43 (36, 49)
Analysis description	**Secondary analysis – OS (pre-specified IA2 DCO 07Oct2024)**		
Analysis population and time	Efficacy data based on Intent to treat population Time from the date of randomisation until the date of death due to any cause		
Descriptive statistics and estimate	**Treatment group**	Arm A - BVd	Arm B - DVd
	Number of subjects	243	251
	Overall survival (OS) Number (%) of patients with event	68 (28)	103 (41)
	Median in months (95% CI)[a]	NR (NR, NR)	NR (NR, NR)
	Hazard Ratio (95%	0.58 (0.43, 0.79)	
	p-value[c]	0.00023	
	Probability of OS at 18 months, % (95% CI)	84 (79, 88)	73 (67, 78)
Analysis description	**Secondary analysis – DOR (pre-specified)**		

Analysis population and time point description	Efficacy data based on responders in the Intent to treat population, Based on Independent Reviewer-Assessed Response Time from first documented evidence of PR or better until PD or death due to any cause		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BVd	Arm B - DVd
	Number of subjects with response	201	179
	Duration of response (DOR) Number (%) of patients with event	68 (34)	105 (59)
	Median in months (95% CI)[a]	35.6 (30.5, -)	17.8 (13.8, 23.6)
	Probability of OS at 18 months, % (95%	76 (69, 81)	49 (41, 56)
Analysis description	**Secondary analysis – RMDOR (pre-specified)**		
Analysis population and time point	Efficacy data based the Intent to treat population, Based on Independent Reviewer-Assessed Response Time from first documented evidence of PR or better until PD or death due to any cause		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BVd	Arm B - DVd
	Number of subjects	243	251
	Restricted Mean Duration of response (RMDOR) Mean DoR estimated at t* (27.8) (month)	19.0 (17.7, 20.4)	13.2 (11.8, 14.6)
	Difference between mean DoR at t* (27.8) from DVd (months)	5.9 (4.0, 7.8)	
	Hazard Ratio (95%	1.45 (1.28, 1.64)	
	Mean DOR test p-value[e]	<0.00001	
Analysis description	**Secondary analysis – MRD negativity (pre-specified)**		
Analysis population and time point	Efficacy data based the Intent to treat population, Based on Independent Reviewer-Assessed Response During time patients achieve CR/sCR		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BVd	Arm B - DVd
	Number of subjects	243	251
	MRD negativity CR/sCR MRD negativity rate, %	24.7 (19.4, 30.6)	9.6 (6.2, 13.9)

	p-value[g] p-value[h]	<0.00001 <0.00001	
Analysis description	**Secondary analysis – ORR**		
Analysis population and time point	Efficacy data based the Intent to treat population, Based on Independent Reviewer-Assessed Response Time at which subject achieves best response		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BVd	Arm B - DVd
	Number of subjects	243	251
	Overall response rate, n (%) [sCR+CR+VGPR+PR], (95% CI)	82.7 (77.4, 87.3)	71.3 (65.3, 76.8)
Analysis description	**Secondary analysis – PFS2**		
Analysis population and time point description	Efficacy data based the Intent to treat population, Based on investigator-Assessed Response Time from randomisation to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BVd	Arm B - DVd
	Number of subjects	243	251
	Progression-free survival 2 (PFS2) Number (%) of patients with event	70 (29%)	106 (42%)
	Median in months (95% CI)[a]	NR (NR, NR)	34.6 (27.6, NR)
	Hazard ratio (95% CI)[b]	0.56 (0.41, 0.76)	

a. CIs were estimated using the Brookmeyer Crowley method.

b. HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III), with a covariate of treatment

c. P-value from 1-sided stratified log-rank test

d. The common truncation time (t) was calculated using the algorithm defined in Huang and Tian [Huang, 2022].*

e. A ratio of mean DoR >1 implies that the BVd group is favourable.

f. One sided P-value from mean DoR test.

g. MRD negativity rate compared between treatment groups using CMH test, adjusting for stratification factors: number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III).

h. MRD negativity rate compared between treatment groups using unadjusted Fisher's exact test. CIs are based on the exact method. P-values presented are 2-sided 5% and as such significance only declared if MRD negativity Rate is in favour of belantamab mafodotin 2.5 mg/kg (which is equivalent to 1-sided 2.5%).

Table 33. Summary of efficacy for trial DREAMM-8 (belantamab mafodotin)

Title: A Phase III, Multicenter, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone (B-Pd) versus Pomalidomide plus Bortezomib and Dexamethasone (PVd) in Participants with Relapsed/Refractory Multiple Myeloma		
Study identifier	EudraCT 2018-003993-29 EU CT Number: 2023-5066877-37-00	
Design	Phase 3, open-label, multicenter, randomized, clinical study to evaluate the efficacy and safety of BPd compared with PVd in participants with RRMM previously treated with at least 1 prior line of therapy.	
	• Duration of main phase: • Duration of Run-in phase: • Duration of Extension phase:	• Treatment will continue in both arms until progressive disease (PD), death, unacceptable toxicity, start of a new anti-myeloma therapy, withdrawal of consent, or end of the study, whichever occurs first • not applicable • not applicable
Hypothesis	Superiority. To demonstrate the superiority of BPd compared to PVd in PFS in participants with relapsed/refractory multiple myeloma. Primary endpoints: PFS, defined as the time from randomization until the earliest date of PD based on IRC-assessment per IMWG criteria, or death due to any cause.	
Treatments groups	Arm A: BPd (belantamab mafodotin + pomalidomide + dexamethasone)	Belantamab mafodotin was administered intravenously (IV) at the dose of 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2 onwards in each 28-day cycle. Pomalidomide was taken orally 4 mg per day on Days 1 to 21 of each 28-day cycle. Dexamethasone was administered orally at a dose of 40 mg per day on Days 1, 8, 15, and 22 of each 28-day cycle. For participants who were >75 years old or had comorbidities or were intolerant to 40 mg, dexamethasone could be administered at the lower dose of 20 mg in Arm A at the discretion of the investigator.

	Arm B: PVd (pomalidomide + botezomib + dexamethasone)		Pomalidomide was administered orally at 4 mg daily on Days 1 to 14 of each 21-day cycle, with bortezomib injected SC at 1.3 mg/m2 on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1 through 8, and on Days 1 and 8 of each 21-day cycle for Cycles 9+. Dexamethasone was administered orally at a dose of 20 mg on the day of and day after bortezomib of each 21-day cycle or on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for Cycles 1 through 8, and then on Days 1, 2, 8, 9, and Q3W for Cycles 9+. For participants who were >75 years old or had comorbidities or were intolerant to 20 mg, dexamethasone could be administered at the lower dose of 10 mg on the day of and day after bortezomib in Arm B at the discretion of the investigator.
Endpoints and definitions	Primary endpoint	Progression-free survival	PFS, defined as the time from randomisation until the earliest date of PD based on IRC-assessment per IMWG criteria, or death due to any cause
	Key Secondary endpoint	Overall Survival	OS, defined as the interval of time from randomization to the date of death due to any cause
	Key Secondary endpoint	Duration of Response	DoR, defined as the time from first documented evidence of PR or better until PD or death due to any cause. Response will be based on IRC-assessment per IMWG criteria
	Key Secondary endpoint	Minimal residual disease negativity rate	MRD negativity rate, defined as the percentage of participants who achieve MRD negative status (as assessed by NGS at 10^{-5} threshold) at least once during the time of confirmed CR or better response based on IRC-assessment
	Secondary	Overall response rate	ORR, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR) based on IRC-assessment per IMWG criteria
	Secondary	PFS2	Defined as time from randomisation to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier
Database lock	29 January 2024		
Results and Analysis			
Analysis description	**Primary Analysis - PFS**		

Analysis population and time point description	Efficacy data based on Intent to treat population Time from randomization until the earliest date of PD based on IRC-assessment per IMWG criteria, or death due to any cause		
Descriptive statistics and estimate variability	Treatment group	Arm A - BPd	Arm B - PVd
	Number of subjects	155	147
	Progression-free survival (PFS) Number (%) of patients with event	62 (40)	80 (54)
	Median in months (95% CI)[a]	NR (20.6, NR)	12.7 (9.1, 18.5)
	Hazard ratio (95% CI)[b]	0.52 (0.37, 0.73)	
	p-value[c]	<0.001	
	Probability of PFS at 12 months, % (95% CI)	71 (63, 78)	51 (42, 60)
Analysis description	**Secondary analysis – OS (pre-specified)**		
Analysis population and time point description	Efficacy data based on Intent to treat population Time from the date of randomization until the date of death due to any cause		
Descriptive statistics and estimate	**Treatment group**	Arm A - BPd	Arm B - PVd
	Number of subjects	155	147
	Overall survival (OS) Number (%) of patients with event	49 (32)	56 (38)
	Median in months (95% CI)[a]	NR (33.0, NR)	NR (25.2, NR)
	Hazard Ratio (95% CI)[b]	0.77 (0.53, 1.14)	
	p-value[c]	0.095	
	Probability of OS at 12 months, % (95% CI)	76 (69, 82)	69 (61, 76)
Analysis description	**Secondary analysis – DOR (pre-specified)**		
Analysis population and time point description	Efficacy data based on responders in the Intent to treat population, Based on Independent Reviewer-Assessed Response Time from first documented evidence of PR or better until PD or death due to any cause		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BPd	Arm B - PVd
	Number of subjects with response	120	106
	Duration of response (DOR) Number (%) of patients with event	39 (33)	49 (46)
	Median in months (95% CI)[a]	NR (24.9, NR)	17.5 (12.1, 26.4)
	Probability of OS at 12 months, % (95% CI)	72 (62, 79)	50 (38, 60)

Analysis description	**Secondary analysis – RMDOR (pre-specified)**		
Analysis population and time point description	Efficacy data based the Intent to treat population, Based on Independent Reviewer-Assessed Response Time from first documented evidence of PR or better until PD or death due to any cause		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BPd	Arm B - PVd
	Number of subjects	155	147
	Restricted Mean Duration of response (RMDOR) Mean DoR estimated at t* (28.8) (month) (95% CI)[d]	17.5 (15.7, 19.3)	12.7 (10.7, 14.7)
	Difference between mean DoR at t* (28.8) from DVd (months)	4.8 (2.1, 7.5)	
	Hazard ratio (95% CI)[b]	1.38 (1.14, 1.66)	
	Mean DOR test p-value[e]	<0.001	
Analysis description	**Secondary analysis – MRD negativity (pre-specified)**		
Analysis population and time point description	Efficacy data based the Intent to treat population, Based on Independent Reviewer-Assessed Response During time patients achieve CR/sCR		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BPd	Arm B - PVd
	Number of subjects	155	147
	MRD negativity CR/sCR MRD negativity rate, % (95% CI)	23.9 (17.4, 31.4)	4.8 (1.9, 9.6)
	p-value[g] p-value[h]	<0.001 <0.001	
Analysis description	**Secondary analysis – ORR**		
Analysis population and time point description	Efficacy data based the Intent to treat population, Based on Independent Reviewer-Assessed Response Time at which subject achieves ORR		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BPd	Arm B - PVd
	Number of subjects	155	147
	Overall response rate, n (%) [sCR+CR+VGPR+PR], (95% CI)	77 (70.0, 83.7)	72, (64.1, 79.2)
Analysis description	**Secondary analysis – PFS2**		

Analysis population and time point description	Efficacy data based the Intent to treat population, Based on investigator-Assessed Response Time from randomization to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier		
Descriptive statistics and estimate variability	**Treatment group**	Arm A - BPd	Arm B - PVd
	Number of subjects	155	147
	Progression-free survival 2 (PFS2) Number (%) of patients with event	56 (36)	73 (50)
	Median in months (95% CI)[a]	NR (33.0, NR)	22.4 (13.8, NR)
	Hazard ratio (95% CI)[b]	0.61 (0.42, 0.86)	

a. CIs were estimated using the Brookmeyer Crowley method.

b. HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy and prior bortezomib (no, yes), with a covariate of treatment

c. P-value from 1-sided stratified log-rank test

d. The common truncation time (t) was calculated using the algorithm defined in Huang and Tian [Huang, 2022].*

e. A ratio of mean DoR >1 implies that the BVd group is favorable.

f. One sided P-value from mean DoR test.

g. MRD negativity rate compared between treatment groups using CMH test, adjusting for stratification factors: number of lines of prior therapy, prior bortezomib (no, yes).

h. MRD negativity rate compared between treatment groups using unadjusted Fisher's exact test. CIs are based on the exact method. P-values presented are 2-sided 5%

2.6.5.3. Clinical studies in special populations

Table 34. Summary of studies in special populations

	Controlled Studies			**Non-controlled Studies[a]**	
	DREAMM-7 BVd (N=243)	**DREAMM-8 BPd (N=155)**	**DREAMM-3 Belantamab mafodotin (N=218)**	**DREAMM-2 2.5 mg/kg (N=97)**	**DREAMM-6[c] Arm A and Arm B (1.9 and 2.5 mg/kg dose levels) (N=124)**

Baseline renal impairment status per eGFR (mL/min/1.73 m^2)					
n	243	155	217	97	124
Normal (≥90)	59/243	37/155	54/217	19/97	37/124
Mild (≥60 to <90)	123/243	88/155	98/217	48/97	58/124
Moderate (≥30 to <60)	53/243	29/155	61/217	24/97	29/124
Severe (≥15 to <30)	0	1/155	4/217	2/97	0
Missing	8/243	0	0	4/97	0
Baseline hepatic impairment status defined using NCI-ODWG classification[b]					
n	243	155	217	95	124
Normal	217/243	138/155	177/217	83/95	103/124
Mild dysfunction	22/243	16/155	28/217	10/95	20/124
Moderate dysfunction	0	1/155	1/217	2/95	0
Severe dysfunction	0	0	0	0	0
Missing	4/243	0	11/217	0	1/124
Age (participants number/total number)					
65 to <75	85/243	72/155	90/218	39/97	57/124
Age ≥75	37/243	19/155	47/218	13/97	24/124
Age ≥85	3/243	0/155	3/218	2/97	0

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.6.5.6. Supportive studies

DREAMM-6

DREAMM-6 is an ongoing Phase 1/2, open-label, dose escalation and expansion clinical study to assess different doses (1.9 mg/kg, 2.5 mg/kg, and 3.4 mg/kg) and dosing schedules of belantamab mafodotin when given in combination with Vd (Arm B) on a 21-day cycle, and to evaluate safety and clinical activity of the combination treatment in participants with RRMM.

Participants had to have at least 1 prior line of MM therapy and must have documented PD during or after their most recent therapy.

The primary efficacy endpoint for Part 2 in DREAMM-6 was ORR and was based on the responses assessed by the investigator. The ITT population included 107 participants.

In Arm B, ORR ranged from 50% to 92%. The ORR was numerically highest in the 2.5 mg/kg Q6W Step-down Stretch treatment group (92% [95% CI: 61.5, 99.8]) compared with other treatment groups. A lower VGPR or better rate was observed in cohorts with a starting dose of 1.9 mg/kg. However, these results should be interpreted with caution due to the small sample size of the treatment groups (N=12 to N=18), leading to larger ORR CIs.

ALGONQUIN

The ALGONQUIN study is an ongoing Phase 1/2, multicentre single-arm, open-label, dose-escalation and expansion study evaluating the safety and efficacy of BPd in participants with RRMM [Trudel, 2024]. This study consisted of a Part 1 dose-exploration phase and a Part 2 dose-expansion phase. Participants in Part 1 received doses of 1.92 mg/kg, 2.5 mg/kg, and 3.4 mg/kg belantamab mafodotin at different dosing schedules in combination with Pd. In Part 2, all participants received BPd 2.5 mg/kg Q8W on a 28-day cycle.

A total of 87 participants with RRMM were enrolled and treated in the ALGONQUIN study between 04 January 2019 and 17 May 2022. Participants were previously treated with 1 or more prior lines of MM therapy including a lenalidomide-containing regimen and a PI (in separate regimens or in combination), and who were refractory to their last line of therapy.

The primary endpoints of the ALGONQUIN study included evaluating dose-limiting toxicities, establishing the RP2D, and ORR for participants treated at the RP2D.

The results indicated that the clinical efficacy for 2.5 mg/kg Q4W (ORR: 100%; VGPR or better rate: 100%, median PFS: 25.3 [95% CI: 11.8, NYR], N=7) was greater than for 1.92 mg/kg Q4W (ORR: 66.7%; VGPR or better rate: 63.7%, median PFS: 16.9 [95% CI: 5.3, 19.7], N=11). The Part 2 dose expansion regimen was 2.5 mg/kg Q8W (ORR: 85.3%; VGPR or better rate; 75.7%; median PFS: NR [95% CI: 13.7, NYR], N=34). Limited data were obtained with the regimen of 2.5 mg/kg in Cycle 1 followed by 1.92 mg/kg Q4W from Cycle 2 onwards used in the DREAMM-8 study (ORR: 100%; VGPR or better rate: 40%; median PFS: 9 months [95% CI: 5.3, NYR], N=5) [Trudel, 2024]).

DREAMM-2

DREAMM-2 is an ongoing Phase 2, open-label, 2-arm, randomised, multicentre clinical study to investigate the efficacy and safety of single-agent belantamab mafodotin at a dose of 2.5 mg/kg or 3.4 mg/kg Q3W in participants with RRMM who had 3 or more prior lines of treatment, were refractory to a PI and an immunomodulatory agent, and for whom treatment with an anti-CD38 antibody had failed.

This clinical study evaluated the 2.5 mg/kg and 3.4 mg/kg doses of the frozen liquid presentation of belantamab mafodotin, and a 3.4 mg/kg dose as a lyophilized presentation in a separate cohort of participants (total of 196 participants). The primary endpoint of Part 2 of the DREAMM-2 study was ORR.

The ORR was 32% in the 2.5 mg/kg cohort and 35% in the 3.4 mg/kg cohort. The median PFS was 2.8 months and 3.9 months, respectively, and the median OS was 15.3 months and 14.0 months.

DREAMM-3

DREAMM-3 is an ongoing Phase 3, open-label, randomised, multicentre clinical study to evaluate the efficacy and safety of single-agent belantamab mafodotin compared with Pd in participants with RRMM. Participants were centrally randomised in a 2:1 ratio to either Group 1 (belantamab mafodotin 2.5 mg/kg on Day 1 of each 21-day cycle) or Group 2 (SoC Pd). Participants in both groups were treated until PD, death, unacceptable toxicity, withdrawal of consent, loss to follow-up, or end of OS follow-up, whichever occurred first.

The study enrolled a total of 325 participants with RRMM who had undergone AutoSCT or were transplant ineligible and received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and a PI. Participants must have had documented disease progression on or within 60 days of completion of the last treatment or been non-responsive.

The primary endpoint of the DREAMM-3 study was PFS. OS was a key secondary endpoint.

The primary analysis of the Phase 3 DREAMM-3 study (data cut-off date: 12 September 2022) did not meet its primary endpoint for investigator-assessed PFS.

There was no statistically significant difference in PFS between the 2 treatment groups, as demonstrated by an HR of 1.03 (95%CI:0.72,1.47), based on the stratified Cox model (p=0.558).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The claimed indications for Blenrep are for the treatment multiple myeloma of adult patients, in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; and in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide.

DREAMM-7

The purpose of the pivotal phase 3 study DREAMM-7 was to evaluate the efficacy and safety of the combination of belantamab mafodotin, bortezomib, and dexamethasone (BVd) compared with the combination of daratumumab, bortezomib and dexamethasone (DVd) in participants with relapsed/refractory multiple myeloma with at least 1 prior line of therapy. Treatment was continued in both arms until PD per IMWG criteria, death, unacceptable toxicity, investigator's discretion, withdrawal of consent, or end of study, whichever occurred first.

Belantamab mafodotin was administered IV at the dose of 2.5 mg/kg on Day 1 of every 21-day cycle in combination with Vd for the first 8 cycles. From Cycle 9 onwards, belantamab mafodotin was administered as monotherapy. Dosing was selected based on previously approved monotherapy dosing, and limited data from small clinical studies exploring belantamab mafodotin in combination with other medicinal products.

Subjects were randomised 1:1 to BVd or DVd. Randomisation was stratified by number of lines of prior therapy, prior bortezomib use and R-ISS stage. The study was open-label. No cross-over was allowed and no more than 50% of participants with ≥2 prior lines of treatment were enrolled. PFS was the primary endpoint and the primary assessment of responses for PFS analysis was conducted by an IRC per IMWG2016 criteria to avoid bias given the open-label nature of the design (ITT population).

In study DREAMM-7, 6 major amendments were made during an ongoing study. Changes to the study design during the course of this open-label pivotal study were based on external factors, including regulatory feedback, and the applicant remained blinded to the aggregate results throughout the study. The applicant took measures to control the type I error rate by keeping the sponsor blinded to any aggregate outcome data. It is also noted, that the addition of the IA1 in the latest protocol amendment allowed the applicant to test for early efficacy with approximately the same number of events as originally planned, but with a more stringent efficacy boundary to cross.

DREAMM-8

The purpose of the pivotal phase 3 study DREAMM-8 was to evaluate the efficacy and safety of the combination belantamab mafodotin, pomalidomide and dexamethasone (BPd) compared with pomalidomide, bortezomib and dexamethasone (PVd) in participants with RRMM previously treated with at least 1 prior line of therapy including a lenalidomide-containing regimen. Treatment was continued in both arms until PD per IMWG criteria, death, unacceptable toxicity, investigator's discretion, withdrawal of consent, or end of study, whichever occurred first.

Belantamab mafodotin was administered IV at a single dose of 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2 onwards in each 28-day cycle. The dosing schedule of Q4W was chosen to match the 28-day cycle required for Pd dosing. Dose reduction to 1.9 mg/kg Q8W or 1.4 mg/kg Q8W was allowed. Dose selection was based on very limited clinical data from clinical study ALGONQUIN exploring different belantamab mafodotin dose levels in combination with Pd. Therefore, the acceptability of the selected dosing relies on B/R assessment of DREAMM-8 study.

Subjects were randomised 1:1 to BPd or PVd. Subjects were stratified based on the number of prior lines of therapy, prior bortezomib use; initially ISS stage at screening (I vs. II/III) was a third stratification factor, which was replaced by prior anti-CD38 treatment. No cross-over was allowed, and at least 50% of the participants were required to have had no more than 1 prior line of therapy. PFS was the primary endpoint and the primary assessment of responses for PFS analysis was conducted by an IRC per IMWG2016 criteria to avoid bias given the open-label nature of the design (ITT population).

A major limitation of the study DREAMM-8, potentially hampering the efficacy results, is the modification of the study design with several amendments during the ongoing study. Sample size was greatly reduced from 450 to 300, while capping for patients with one prior line of treatment was maintained. This resulted in enrolment of only 2L patients after the protocol amendment, in fact during the last recruitment year, and therefore the data for this key subgroup is more immature. The primary PFS analysis was delayed for a longer duration of follow-up and increase of OS data maturity and the targeted number of PFS events were increased from approximately 139 to approximately 173 events. The primary efficacy endpoint analysis (data cut-off 29 January 2024) is based on an additional IA2 for PFS, added in Protocol amendment 4 dated 28 Sep 2023 implemented when enrolment was already completed (late 2022). In addition, several other changes were implemented during the ongoing study. The applicant has provided scientific justification and reasons for the performed multiple protocol changes. Importantly, the applicant remained blinded to the aggregate data (including unblinded safety data as well as the efficacy data for the primary endpoint of the study) until the decision was made to unblind the study following IA2. The results were consistent across different key subgroups and all sensitivity analyses, suggesting that these changes did not have a meaningful impact to the study results. By reducing the overall sample size of the study and completing enrollment in December 2022, it ensured that all participants had a robust follow-up of >1 year.

Efficacy data and additional analyses

DREAMM-7

A total of 494 participants with RRMM were randomised to either BVd or DVd. While considerably more subjects discontinued due to disease progression in the DVd arm, more patients discontinued due to AEs (19% vs. 9%), and physician's decision (14% vs. 4%) in the BVd arm. At the time of primary data cut-off, more subjects continued treatment in the BVd arm (34% vs. 22%). This is also seen at the latest DCO date of 07 October 2024 (IA2), with more participants remaining on study treatment in the BVd group (25%) compared to the DVd group (15%) and reflected in the higher percentage of participants in the DVd group starting subsequent therapy (BVd: 36%; DVd: 52%). For participants who started subsequent therapy, the median time from study treatment discontinuation to the start of subsequent anti-myeloma therapy was 83.0 days in the BVd group and 51.5 days in the DVd group. Patients were often treated with treatment options they had received in earlier lines of treatment. While cross-over between groups was not permitted at the time the study was conducted, both daratumumab and belantamab mafodotin were approved in some countries and were available for patients with RRMM. Thus, some participants who progressed on a particular regimen were able to receive these agents either via some other clinical study or through commercial supply.

The baseline patient and disease characteristics were well balanced between the 2 treatment groups, without major differences. Patients were young and fit and the majority of the patients were < 65 years of age, despite the fact that the median time from diagnosis was approximately 4 years. Subjects ≥75 years of age accounted for 15% and 12% of study subjects in the BVd and DVd groups, partly addressing the need for targeting the most vulnerable and "real-world" patient population. Most participants had an ECOG performance status of either 0 (50% and 46% in the BVd and DVd groups, respectively) or 1 (46% and 50%) at baseline.

The types of prior therapies for MM were consistent with standard of care for the population enrolled in the study and comparable between treatment groups. Median prior lines of therapy were calculated as 1.0 (BVd) and 2.0 (DVd) but distribution by lines of therapy was very similar between groups. Mean prior lines of therapy was similar in the BVd (2.0) and DVd (1.9) groups. Importantly, approximately 50% of the patients had one previous line of treatment, which is in line with the proposed second-line indication.

Most of the subjects were pretreated with immunomodulators (81% in the BVd arm and 86% in the DVd arm) and proteasome inhibitors and (90% in the BVd arm and 86% in the DVd arm) reflecting the use of these therapies also as part of the authorised first-line treatment regimens, but not specifically requiring these products to be used as part of the first (or subsequent) lines of therapy. The most notable difference to current second-line patient population is a lack of prior daratumumab treatment. However, this is acceptable as this was due to the selected comparator in the study. In addition, prior daratumumab treatment is not likely to have a relevant impact on BVd treatment effect.

The majority of patients had either relapsed MM (54%) or refractory disease (43%). To better reflect the study population, the CHMP requested that the indication should be revised to: "Belantamab mafodotin is indicated in adults for the treatment of relapsed or refractory multiple myeloma, in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy; and in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide", and this was accepted by the applicant.

Primary endpoint

The study met its primary endpoint for PFS assessed by IRC. The median PFS was 36.6 months for the BVd treatment arm and 13.4 months for the DVd treatment arm (95% CI: 0.31, 0.53; p <0.00001), which is considered clinically relevant particularly in a population that had received a mean of 2 prior treatments. Most PFS events were attributed to disease progression (28% in the BVd treatment arm and 55% in the DVd treatment arm). Results of all sensitivity analyses were consistent with the primary PFS analysis. The applicant provided information on the reasons for early censoring in the primary PFS analysis and there appears to be no clear imbalance in the reasons for censoring between the two treatment groups.

A PFS analysis assessed by IRC, where all intercurrent events were handled with a treatment policy strategy, was requested. This could not be provided, since IRC assessment of disease progression after initiation of subsequent anti-myeloma therapy is not available for participants that discontinued study drug without documented disease progression prior to start of subsequent therapy. However, since the number of participants who were censored for starting subsequent anti-myeloma therapy is similar in both arms, and the provided results using different censoring rules were consistent with the primary PFS analysis as per the primary estimand, it is unlikely that the treatment policy strategy for intercurrent events would impact the results meaningfully.

The 95% CI of HR crossed 1 in the subgroups of age (>75 years), race ('other'), and region (North-East Asia). However, these subgroups had small sample size to allow any conclusions to be drawn. This could be of relevance for patients >75 as the real-world median age at the time of diagnosis for MM is much higher than in DREAMM-7. Tolerability of the treatment could be lower in this population, and more extensive treatment breaks and dose reductions could also reduce the efficacy. However, this issue is often encountered in clinical trials. In clinical practice treatment decisions need to be made individually based patient and disease characteristics, especially for elderly / frail patients.

Secondary endpoints

The results of all key secondary endpoints were in favour of BVd treatment arm.

Both the restricted mean DoR (RMDoR; 19.0 months vs. 13.2 months) and the conventional assessment of duration of response (DoR; median, 35.6 months vs. 17.8 months) displayed a longer response in the BVd treatment arm. The used RMDoR method is unconventional, and the results are difficult to interpret.

OS also displayed a statistically significant result (HR=0.58; 95% CI: 0.43, 0.79, p = 0.00023) in favour of BVd treatment arm (IA2 DCO date 07 October 2024). OS data has reached 35% (171/494 participants) maturity, and IF was equal to 48.2% (171/355). Median OS was not reached in either treatment group.

Finally, a statistically significant increase of MRD negativity rate was observed in favour of the BVd group at the time of primary PFS analysis (24.7% vs. 9.6%).

Demonstration of efficacy based on PFS, OS, and MRD is considered to be clear. Clinically relevant differences were observed in all primary and key secondary endpoints, and the results were consistent across relevant subgroups.

DREAMM-8

A total of 302 participants with RRMM were randomised to either BPd or PVd. More subjects discontinued due to disease progression in the PVd arm, while the number of patients who discontinued due to AEs or due to physician's decision were roughly at a similar percentage. More subjects continued treatment at the time of the primary data cut-off in the BVd arm than in the PVd arm (42% vs. 22%). This was also observed at the time of a later DCO (07 October 2024), with a higher percentage of participants remaining on study treatment in the BPd group (35%) compared with the PVd group (14%) and reflected in the higher percentage of participants in the PVd group starting subsequent therapy (BPd: 30%; PVd: 58%). 26 participants were censored due to start with new treatment, without progression. The median time from study treatment discontinuation to start of subsequent anti-cancer therapy was similar between treatment groups (30.0 days and 31.0 days). Patients received mostly therapies they had received in prior lines of treatment. While cross-over between groups was not permitted, at the time the study was conducted, both daratumumab and belantamab mafodotin were approved in some countries and available for patients with RRMM. Thus, some participants who progressed on 1 regimen were able to receive these agents either via some other clinical study or through commercial supply. This seems to be the reason that 10 participants in the PVd group received subsequent belantamab mafodotin. However, the number of patients receiving targeted therapies, such as bispecific antibodies and/or CAR t-cell therapies is surprisingly low.

The baseline patient and disease characteristics are consistent with second-line patient population and well balanced between the 2 treatment groups, without major differences. The median age of the subjects were 67.0 years and 68.0 years in the BPd and PVd arms, representing a relatively young patient population. The median time from diagnosis was approximately 3.6 years. Subjects ≥75 years of age accounted only for 12% and 24% of study participants in the BPd and PVd arms, providing limited data from the most vulnerable and "real-world" patient population. The median number of prior treatments received was calculated as 1.0 and approximately 50% of the patients had one previous line of treatment, which is in line with the proposed second-line indication.

In DREAMM-8, all subjects were pretreated with lenalidomide and majority were also refractory to an immunomodulator (app. 80% in both arms). In addition, most subjects were pretreated with proteasome inhibitors (90% in the BPd arm and 93% in the PVd arm) and some with anti-CD 38 antibodies (25% in the BPd arm and 29% in the PVd arm) reflecting the current use of these therapies also as part of the authorized first-line treatment regimens. The median number of prior treatments received was calculated as 1.0 and about 50% of the patients had one previous line of treatment, which is in line with the proposed second-line indication. In the BPd group of DREAMM-8, 83% of

participants had refractory MM, while in the PVd group, 78% had refractory MM. The remaining participants (17% in the BPd group and 22% in the PVd group) had relapsed disease that was not refractory. Since patients in DREAMM-8 were either relapsed or refractory, the proposed indication wording has been amended to adequately reflect the study population.

Primary endpoint

The study met its primary endpoint for PFS assessed by IRC. The median PFS was not reached in the BPd treatment arm and was 12.7 months in the PVd treatment arm (95% CI: 9.1, 18.5), with a HR of 0.52 (95% CI: 0.37, 0.73; p-value <0.001), which is considered clinically relevant in the studied RRMM patients population that had received a median of 1 prior treatments. Most PFS events were attributed to disease progression (30% in the BPd treatment arm and 45% in the PVd treatment arm). Results of all sensitivity analyses were consistent with the primary PFS analysis. No new concerns were observed based on the requested and provided unplanned PFS update (DCO 07 October 2024).

More participants in the PVd group started new anti-myeloma therapy prior to a PFS event than in the BPd group. It is noted that 6 of the 8 participants censored in the PVd group during >3 to 9 months had an unconfirmed PD as assessed by the IRC at the time of censoring. For 5 of these participants, the investigators have also reported the reason for discontinuing study treatment as either 'progressive disease' or 'clinical relapse'. This suggests that these participants had worsening disease and would have experienced an event had the investigators waited for confirmation of the PD before starting new anti-myeloma therapy. It is possible therefore that higher censoring in the PVd group could have led to over-estimation of PFS in the PVd group.

Similar to DREAMM 7, analysis where all ICEs were handled with a treatment policy strategy was not provided, because for participants who discontinued study drug without documented disease progression prior to start of subsequent therapy, IRC assessment of disease progression after initiation of subsequent anti-myeloma therapy was not available. However, results using different censoring rules were consistent with the primary PFS analysis as per the primary estimand.

The 95% CI of HR crossed 1 in the subgroups of age (<65 and >75 years), region (ROW), prior anti-CD38 treatment (refractory), EMD at baseline (Yes), triple exposed (Yes), prior exposure to lenalidomide and anti-CD38 antibody (Yes). These subgroups had small sample sizes to draw any conclusions.

Secondary endpoints

The results of all key secondary endpoints were also consistent and in favour of BPd treatment arm.

There was a positive OS trend in favor of the BPd arm, taking into consideration the fact that the median OS was not reached in either treatment group and that the OS data have reached 34.77% overall maturity (105 events reported). As the IA2 was statistically significant for PFS, the next interim analysis (IA3) is planned when approximately 130 OS events have occurred. The CHMP requested that the updated OS results of the planned interim analyses and final analysis should be provided when available.

The restricted mean DoR (RMDoR; 17.5 months vs. 12.7 months) displayed a longer response in the BPd treatment arm. The conventional median DoR was not reached in the BPd group and the median DoR was 17.5 months in the PVd group. DoR (neither RMDoR nor conventional DoR) were a part of the testing hierarchy.

An increase of MRD negativity rate was also observed in favour of the BVd group at the time of primary PFS analysis (23.9% vs. 4.9%). This was not formally tested, as the OS result was not significant.

Given that OS and MRD negativity rate have not reached formal statistical significance yet, the change in multiplicity adjustment procedure does not currently impact their interpretation – however, it might do so in future data updates.

2.6.7. Conclusions on the clinical efficacy

The addition of belantamab mafodotin to the combination of either bortezomib and dexamethasone or pomalidomide and dexamethasone translates into a significant delay in the progression of the disease in the targeted patient population, i.e. patients with multiple myeloma who have received at least one prior line of therapy.

This benefit in terms of PFS is supported by several secondary endpoints. Importantly, despite the immaturity of the OS data, no evidence of detrimental effects on survival has been observed so far.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Table 35. Overview of Clinical Studies Contributing to Safety Information and Number of Participants Exposed to Belantamab Mafodotin (Monotherapy and in Combination with Standard of Care Treatments)

Study; Phase	**Design and Objectives**	**Study Population/Study Analysis Set**	**Participants Exposed (Safety Population)**	**Exposure Profile (ITT Population)**
Registrational studies on triplet combination therapy				
207503 (DREAMM-7); Phase 3	Randomized, open-label; Efficacy and safety	Participants had to have at least 1 prior line of MM therapy	Study Group A (BVd): 242 participants Study Group B (DVd): 246 participants	Median time on treatment for the BVd group was 15.90 months Median duration of follow-up was 29.18 months in the BVd group with a minimum follow-up of 0.16 months
207499 (DREAMM-8); Phase 3	Randomized, open-label; Efficacy and safety	Participants had to have at least 1 prior line of MM therapy including lenalidomide	Study Group A (BPd): 150 participants Study Group B (PVd): 145 participants	Median time on treatment for the BPd group was 16.542 months Median duration of follow-up was 22.439 months in the BPd group with a minimum follow-up of 0.03 months
Supportive studies on triplet combination therapy				
207497 (DREAMM-6); Phase 1/2	Non-randomized, open-label, dose escalation and dose expansion; Safety, tolerability, and clinical activity	Participants had to have at least 1 prior line of MM therapy	Study Arm A (BRd): 45 participants (All Treated Population) Study Arm B (BVd): 79 participants (All Treated Population) (Total number of participants: 124, except 3.4 mg/kg groups), of which 18 participants (Arm B) were dosed with 2.5 mg/kg Q3W as in DREAMM-7 study	Median time on treatment ranged from 9.00 weeks (2.5 mg/kg Q3W Split group) to 49.00 weeks (2.5 mg/kg Q6W Step-down Stretch group) Median duration of follow-up was 17.38 months, with a minimum duration of follow-up of 0.8 months

Study; Phase	Design and Objectives	Study Population/Study Analysis Set	Participants Exposed (Safety Population)	Exposure Profile (ITT Population)
209418 (ALGONQUIN) https://clinicaltrials.gov/study/NCT03715478; Phase 1/2	Open-label, dose expansion; Recommended Part 2 dose, safety and efficacy	Participants had to have at least 1 prior line of MM therapy	Single arm (BPd): 87 participants (All Treated Population) Part 1 dose-exploration phase: 61 participants Part 2 dose-expansion phase: 38 participants (BPd 2.5 mg/kg Q8W)	In Part 1 exposure was not reported; median follow-up was 17.1 months. In Part 2: patients received a median of 15 cycles of treatment. Median follow-up was 13.9 months; minimum follow-up was not reported
Supportive studies on monotherapy				
207495 (DREAMM-3); Phase 3	Randomized, open-label; Safety and efficacy	Participants had to have at least 2 prior lines of MM therapy	Study Group A (Belantamab mafodotin 2.5 mg/kg): 217 participants Study Group B (Pomalidomide/dexamethasone): not relevant for this submission	Median time on treatment for the belantamab mafodotin group was 4.14. months (5.0 treatment cycles). Median follow-up was 10.78 months with a minimum follow-up of 0.00 months.
205678 (DREAMM-2); Phase 2	Randomized, 2-arm, open-label; Safety and efficacy	Participants had to have at least 3 prior lines of MM therapy	Study Group A (Belantamab mafodotin 2.5 mg/kg): 95 participants Study Group B (Belantamab mafodotin 3.4 mg/kg): not relevant for this submission	The median time on treatment was 9.3 weeks in the 2.5 mg/kg cohort and 12 weeks in the 3.4 mg/kg cohort. The median duration of follow-up was 12.5 months for the 2.5 mg/kg cohort and 13.8 months in the 3.4 mg/kg cohort. The minimum duration of follow-up was 0.1 month for both 2.5 mg/kg and 3.4 mg/kg cohorts.
209626 (DREAMM-12); Phase 1	Open-label, single arm; Safety, tolerability, PK, immunogenicity, and clinical activity	Participants who have normal to impaired renal function, had at least 3 prior lines of MM therapy (or at least 2 lines of prior treatment if ineligible for AutoSCT)	Single arm (Belantamab mafodotin 2.5 mg/kg): 23 participants Study Group 1 (normal/mildly impaired renal function): 8 participants Study Group 2 (severely impaired renal function): 8 participants	Median time on treatment was 2 treatment cycles Median duration of follow-up was 5.29 months with minimum follow-up of 0.3 months

Pooling:

Two sets of pooled safety data were generated to support the safety profile of belantamab mafodotin:

- Pooled ocular safety data from the triplet combination studies (DREAMM-6, DREAMM-7, and DREAMM-8) ('pooled combination therapy data').
- Pooled safety data from belantamab mafodotin monotherapy studies (DREAMM-2 and DREAMM-3) ('pooled monotherapy data').

Data on the triplet combination therapies from the ongoing DREAMM-6, DREAMM-7, and DREAMM-8 studies were pooled for study population (demographics and baseline disease characteristics) and ocular safety. Unlike for ocular safety, which has a very specific safety pattern related specifically to belantamab mafodotin, other safety data (exposure, general safety, and clinical laboratory data) were analysed on a by-study basis. No pooling of general safety and exposure data was conducted for the triplet combination studies since each combination regimen had a slightly different safety profile based

on the specific combination partners used. Combining other safety data would add complexity to data interpretation and would not add value in terms of defining the safety profile for belantamab mafodotin.

Only relevant belantamab mafodotin 1.9 mg/kg or 2.5 mg/kg dose groups were included in the pooled combination therapy analysis, irrespective of dose or dosing schedule, unless otherwise specified.

To further evaluate the safety of belantamab mafodotin in the absence of the combination partners, the pooled set of data from monotherapy studies, DREAMM-2 and DREAMM-3, was generated and analysed for study population, overall exposure, and general safety, including AEs, ocular safety and other AESIs, and clinical laboratory/vital signs. The similarities in study population, data collection, and analyses across these 2 studies allow for evaluation of safety concerns associated with belantamab mafodotin alone and provide a reference for combination treatments.

2.6.8.2. Adverse events

Table 36. Adverse event overview for belantamab mafodotin studies (combination and monotherapy)

	DREAMM-7		DREAMM-8		DREAMM-2 + DREAMM-3
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)	Belantamab mafodotin (N=312)
Any AE, (n%)	242 (100%)	246 (100%)	149 (>99%)	139 (96%)	304 (97%)
AEs related to any study treatment[a]	242 (100%)	234 (95%)	143 (95%)	118 (81%)	265 (85%)
Grade 3 or 4 AEs	229 (95%)	187 (76%)	136 (91%)	106 (73%)	244 (78%)
Grade 3 or 4 AEs related to any study treatment[a]	219 (90%)	164 (67%)	120 (80%)	85 (59%)	178 (57%)
AEs leading to permanent discontinuation of any study treatment	75 (31%)	46 (19%)	22 (15%)	18 (12%)	43 (14%)
AEs related to any study treatment and leading to permanent discontinuation of any study treatment[a]	64 (26%)	36 (15%)	19 (13%)	9 (6%)	18 (6%)
AEs leading to dose reduction	182 (75%)	146 (59%)	92 (61%)	88 (61%)	113 (36%)
AEs leading to dose interruption/delay	228 (94%)	185 (75%)	136 (91%)	109 (75%)	185 (59%)
Any SAE, n (%)	121 (50%)	90 (37%)	95 (63%)	65 (45%)	137 (44%)
SAEs related to any study treatment[a]	47 (19%)	30 (12%)	45 (30%)	21 (14%)	39 (13%)
Fatal SAEs[b]	23 (10%)	19 (8%)	17 (11%)	16 (11%)	21 (7%)
Fatal SAEs related to any study treatment[a,b]	7 (3%)	2 (<1%)	3 (2%)	0	2 (<1%)

a. 'Related to any study treatment' included responses of 'Yes' and missing responses to the following question: 'Is there a reasonable possibility that the AE may have been caused by the study treatment?'. Study treatments included dexamethasone, bortezomib, daratumumab, and belantamab mafodotin for DREAMM-7; and dexamethasone, bortezomib, pomalidomide, and belantamab mafodotin for DREAMM-8.

b. If a fatal SAE occurred but no active decision to discontinue study treatment before death occurred, then the fatal SAE was not reported as leading to study treatment discontinuation. If an AE led to decision to discontinue treatment prior to a fatal outcome, then the AE was reported as leading to study treatment discontinuation.

In DREAMM-7, the most commonly reported AEs (>20% of participants) in the BVd group by CTCAE were thrombocytopenia AESI (87%), ocular AESIs (79%), diarrhoea (32%), peripheral sensory neuropathy (25%), COVID-19 (24%), and neuropathy peripheral (21%).

In DREAMM-8, the most commonly reported AEs (>20% of participants) in the BPd group by CTCAE were ocular AESI (89%), neutropenia/neutrophil count decreased/febrile neutropenia (63%),

thrombocytopenia AESI (55%), COVID-19 (37%), cataract (27%), fatigue (27%), upper respiratory tract infection (27%), pneumonia (24%), anaemia (23%), and diarrhoea (23%).

Most common AEs by SOC and PT

Table 37. Summary of all treatment-emergent adverse events by System Organ Class and Preferred Term, in ≥20% of participants in either treatment group (Safety population, ordered alphabetically by SOC and within SOC by descending frequency in the BVd group) (DREAMM-7 & DREAMM-8)

System Organ Class, n (%)/ Preferred Term, n (%)	DREAMM-7 BVd (N=242)	DREAMM-7 DVd (N=246)	DREAMM-8 BPd (N=150)	DREAMM-8 PVd (N=145)
ANY EVENT	**242 (100%)**	**246 (100%)**	**149 (>99%)**	**139 (96%)**
Blood and lymphatic system disorders	**185 (76%)**	**158 (64%)**	**96 (64%)**	**83 (57%)**
Thrombocytopenia	167 (69%)	122 (50%)	54 (36%)	44 (30%)
Anaemia	46 (19%)	65 (26%)	35 (23%)	38 (26%)
Neutropenia	34 (14%)	27 (11%)	72 (48%)	50 (34%)
Eye disorders	**194 (80%)**	**93 (38%)**	**136 (91%)**	**54 (37%)**
Vision blurred	160 (66%)	26 (11%)	119 (79%)	22 (15%)
Dry eye	123 (51%)	17 (7%)	91 (61%)	14 (10%)
Photophobia	114 (47%)	6 (2%)	66 (44%)	6 (4%)
Foreign body sensation in eyes	106 (44%)	10 (4%)	91 (61%)	9 (6%)
Eye irritation	103 (43%)	13 (5%)	75 (50%)	13 (9%)
Eye pain	77 (32%)	8 (3%)	49 (33%)	7 (5%)
Cataract	49 (20%)	25 (10%)	40 (27%)	15 (10%)
Visual acuity reduced	14 (6%)	5 (2%)	34 (23%)	8 (6%)
Corneal epithelial microcysts	1 (<1%)	0	34 (23%)	0
Punctate keratitis	2 (<1%)	1 (<1%)	34 (23%)	1 (<1%)
Gastrointestinal disorders	**147 (61%)**	**149 (61%)**	**69 (46%)**	**71 (49%)**
Diarrhoea	78 (32%)	77 (31%)	35 (23%)	33 (23%)
Constipation	46 (19%)	56 (23%)	23 (15%)	33 (23%)
General disorders and administration site conditions	**129 (53%)**	**127 (52%)**	**82 (55%)**	**82 (57%)**
Fatigue	47 (19%)	48 (20%)	40 (27%)	32 (22%)
Infections and infestations	**170 (70%)**	**166 (67%)**	**123 (82%)**	**99 (68%)**
COVID-19	58 (24%)	49 (20%)	56 (37%)	31 (21%)
Upper respiratory tract infection	48 (20%)	49 (20%)	40 (27%)	25 (17%)
Pneumonia	44 (18%)	22 (9%)	36 (24%)	17 (12%)
Investigations	**142 (59%)**	**100 (41%)**	**79 (53%)**	**54 (37%)**
Platelet count decreased	51 (21%)	40 (16%)	30 (20%)	22 (15%)
Neutrophil count decreased	9 (4%)	14 (6%)	31 (21%)	19 (13%)
Nervous system disorders	**164 (68%)**	**160 (65%)**	**53 (35%)**	**80 (55%)**
Peripheral sensory neuropathy	61 (25%)	51 (21%)	5 (3%)	15 (10%)
Neuropathy peripheral	50 (21%)	55 (22%)	11 (7%)	34 (23%)

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, the most frequently reported AEs (≥20% of participants) were ocular AEs (70%), thrombocytopenia (31%), and anaemia (28%).

Grade 3 or higher AEs by SOC and PT

Table 38. Summary of all treatment-emergent adverse events of Grade 3 or higher, by System Organ Class and Preferred Term, in ≥5% of participants in either treatment group (Safety population, ordered alphabetically by SOC and within SOC by descending frequency in the BVd group) (DREAMM-7 and DREAMM-8)

System Organ Class, n (%)/ Preferred Term, n (%)	DREAMM-7 BVd (N=242)	DREAMM-7 DVd (N=246)	DREAMM-8 BPd (N=150)	DREAMM-8 PVd (N=145)
ANY EVENT	**230 (95%)**	**192 (78%)**	**141 (94%)**	**110 (76%)**
Blood and lymphatic system disorders	**151 (62%)**	**109 (44%)**	**77 (51%)**	**61 (42%)**
Thrombocytopenia	134 (55%)	87 (35%)	36 (24%)	29 (20%)
Neutropenia	30 (12%)	15 (6%)	63 (42%)	41 (28%)
Anemia	20 (8%)	25 (10%)	15 (10%)	19 (13%)
Lymphopenia	13 (5%)	17 (7%)	4 (3%)	2 (1%)
Eye disorders	**92 (38%)**	**14 (6%)**	**72 (48%)**	**9 (6%)**
Vision blurred	53 (22%)	2 (<1%)	26 (17%)	0
Cataract	17 (7%)	6 (2%)	9 (6%)	6 (4%)
Dry eye	17 (7%)	0	12 (8%)	0
Visual impairment	13 (5%)	1 (<1%)	15 (10%)	1 (<1%)
Eye irritation	12 (5%)	0	6 (4%)	0
Foreign body sensation in eyes	8 (3%)	0	9 (6%)	0
Photophobia	5 (2%)	0	5 (3%)	0
Visual acuity reduced	4 (2%)	1 (<1%)	20 (13%)	1 (<1%)
Corneal epithelial microcysts	1 (<1%)	0	12 (8%)	0
Punctate keratitis	1 (<1%)	0	9 (6%)	1 (<1%)
Gastrointestinal Disorders	**29 (12%)**	**20 (8%)**	**13 (9%)**	**16 (11%)**
Diarrhoea	9 (4%)	10 (4%)	2 (1%)	10 (7%)
General disorders and administration site conditions	**19 (8%)**	**20 (8%)**	**19 (13%)**	**23 (16%)**
Fatigue	9 (4%)	6 (2%)	9 (6%)	7 (5%)
Asthenia	5 (2%)	4 (2%)	3 (2%)	7 (5%)
Infections and infestations	**75 (31%)**	**49 (20%)**	**73 (49%)**	**38 (26%)**
Pneumonia	28 (12%)	10 (4%)	26 (17%)	11 (8%)
COVID-19	14 (6%)	11 (4%)	10 (7%)	3 (2%)
COVID-19 pneumonia	8 (3%)	9 (4%)	16 (11%)	6 (4%)
Investigations	**79 (33%)**	**43 (17%)**	**52 (35%)**	**37 (26%)**
Platelet count decreased	44 (18%)	26 (11%)	22 (15%)	18 (12%)
Gamma-glutamyltransferase increased	22 (9%)	4 (2%)	2 (1%)	1 (<1%)
Alanine aminotransferase increased	14 (6%)	3 (1%)	2 (1%)	5 (3%)
Neutrophil count decreased	4 (2%)	6 (2%)	31 (21%)	18 (12%)
Vascular disorders	**20 (8%)**	**13 (5%)**	**3 (2%)**	**5 (3%)**
Hypertension	13 (5%)	6 (2%)	1 (<1%)	2 (1%)

In DREAMM-7, the exposure-adjusted rates of grade ≥3 AEs were balanced between the BVd and DVd groups: 68.771 vs. 62.424 per 100 PY, respectively. In DREAMM-8, the exposure-adjusted rates of grade ≥3 AEs in the BPd group compared with the PVd group were 65.655 vs. 78.068 per 100 PY, respectively.

In the DREAMM-2 and DREAMM-3 pooled data, Grade 3/4 AEs (in ≥5% of participants) were reported in the majority of participants (79%). The most frequently reported Grade 3/4 AEs in the belantamab mafodotin monotherapy group were thrombocytopenia (21%) and anemia (17%).

Treatment-related AEs by SOC and PT

Table 39. Summary of all treatment-related adverse events by System Organ Class and Preferred Term, in ≥20% of participants in either treatment group (Safety Population, ordered alphabetically by SOC and within SOC by descending frequency in the BVd group) (DREAMM-7 and DREAMM-8)

System Organ Class, n (%)/ Preferred Term, n (%)	DREAMM-7 BVd (N=242)	DREAMM-7 DVd (N=246)	DREAMM-8 BPd (N=150)	DREAMM-8 PVd (N=145)
ANY EVENT	**242 (100%)**	**234 (95%)**	**143 (95%)**	**118 (81%)**
Blood and lymphatic system disorders	**172 (71%)**	**146 (59%)**	**NC**	**NC**
Thrombocytopenia	160 (66%)	118 (48%)	47 (31%)	37 (26%)
Neutropenia	28 (12%)	24 (10%)	60 (40%)	43 (30%)
Eye disorders	**189 (78%)**	**39 (16%)**	**NC**	**NC**
Vision blurred	156 (64%)	11 (4%)	114 (76%)	3 (2%)
Dry eye	119 (49%)	4 (2%)	86 (57%)	4 (3%)
Photophobia	110 (45%)	0	64 (43%)	1 (<1%)
Foreign body sensation in eyes	100 (41%)	0	89 (59%)	0
Eye irritation	96 (40%)	1 (<1%)	71 (47%)	0
Eye pain	71 (29%)	2 (<1%)	48 (32%)	0
Visual acuity reduced	12 (5%)	1 (<1%)	33 (22%)	1 (<1%)
Punctate keratitis	2 (<1%)	0	30 (20%)	0
Investigations	**120 (50%)**	**71 (29%)**	**NC**	**NC**
Platelet count decreased	50 (21%)	38 (15%)	27 (18%)	20 (14%)
Nervous system disorders	**146 (60%)**	**144 (59%)**	**NC**	**NC**
Peripheral sensory neuropathy	60 (25%)	49 (20%)	3 (2%)	15 (10%)
Neuropathy peripheral	48 (20%)	55 (22%)	8 (5%)	32 (22%)

NC = not calculated

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, treatment-related AEs were reported in almost all participants (85%). The most frequently reported treatment-related AEs (≥20%) were ocular AEs (vision blurred 32%, keratopathy 29%, dry eye 22%) and thrombocytopenia (22%).

Grade 3 or higher treatment related AEs

Table 40. Summary of all treatment-related adverse events of grade 3 or higher, by System Organ Class and Preferred Term, in ≥1% of participants in either treatment Group (Safety population, ordered alphabetically by SOC and within SOC by descending frequency in the BVd group) (DREAMM-7 and DREAMM-8)

System Organ Class, n (%)/ Preferred Term, n (%)	DREAMM-7 BVd (N=242)	DREAMM-7 DVd (N=246)	DREAMM-8 BPd (N=150)	DREAMM-8 PVd (N=145)
ANY EVENT	**220 (91%)**	**166 (67%)**	**120 (80%)**	**85 (59%)**
Blood and lymphatic system disorders	**139 (57%)**	**104 (42%)**	**NC**	**NC**
Thrombocytopenia	128 (53%)	87 (35%)	28 (19%)	22 (15%)
Neutropenia	24 (10%)	14 (6%)	54 (36%)	37 (26%)
Anemia	11 (5%)	17 (7%)	7 (5%)	9 (6%)
Lymphopenia	11 (5%)	13 (5%)	1 (<1%)	1 (<1%)
Leukopenia	5 (2%)	6 (2%)	3 (2%)	1 (<1%)
Febrile neutropenia	0	0	4 (3%)	3 (2%)
Endocrine disorders	**0**	**0**	**NC**	**NC**
Cushingoid	0	0	0	2 (1%)
Eye disorders	**88 (36%)**	**9 (4%)**	**NC**	**NC**
Vision blurred	51 (21%)	1 (<1%)	26 (17%)	0
Dry eye	17 (7%)	0	12 (8%)	0
Cataract	13 (5%)	4 (2%)	2 (1%)	1 (<1%)
Visual impairment	13 (5%)	1 (<1%)	14 (9%)	0
Eye irritation	12 (5%)	0	6 (4%)	0
Foreign body sensation in eyes	8 (3%)	0	9 (6%)	0
Photophobia	5 (2%)	0	5 (3%)	0
Keratitis	5 (2%)	0	4 (3%)	0
Visual acuity reduced	4 (2%)	1 (<1%)	20 (13%)	0
Keratopathy	4 (2%)	0	4 (3%)	0
Eye pain	2 (<1%)	1 (<1%)	3 (2%)	0
Punctate keratitis	1 (<1%)	0	9 (6%)	0
Corneal epithelial microcysts	1 (<1%)	0	12 (8%)	0
Corneal opacity	0	0	2 (1%)	0
Conjunctivitis	0	0	2 (1%)	0
Gastrointestinal disorders	**15 (6%)**	**14 (6%)**	**NC**	**NC**
Diarrhoea	5 (2%)	9 (4%)	1 (<1%)	8 (6%)
Constipation	1 (<1%)	0	1 (<1%)	2 (1%)
General disorders and administration site conditions	**16 (7%)**	**10 (4%)**	**NC**	**NC**
Fatigue	9 (4%)	6 (2%)	7 (5%)	7 (5%)
Asthenia	4 (2%)	2 (<1%)	3 (2%)	7 (5%)
Face oedema	0	0	2 (1%)	0
Oedema peripheral	0	0	1 (<1%)	3 (2%)
Infections and infestations	**37 (15%)**	**26 (11%)**	**NC**	**NC**
Pneumonia	14 (6%)	6 (2%)	17 (11%)	4 (3%)
COVID-19	9 (4%)	8 (4%)	0	0
COVID-19 pneumonia	4 (2%)	5 (2%)	0	1 (<1%)
Lower respiratory tract infection	3 (1%)	0	0	0
Atypical pneumonia	1 (<1%)	0	2 (1%)	0
Bronchitis	0	2 (<1%)	2 (1%)	1 (<1%)
Pneumocystis jirovecii pneumonia	0	0	3 (2%)	0
Neutropenic sepsis	0	0	2 (1%)	2 (1%)
Bronchiolitis	0	0	0	2 (1%)
Injury, poisoning and procedural complications	**3 (1%)**	**5 (2%)**	**NC**	**NC**

System Organ Class, n (%)/ Preferred Term, n (%)	DREAMM-7 BVd (N=242)	DREAMM-7 DVd (N=246)	DREAMM-8 BPd (N=150)	DREAMM-8 PVd (N=145)
Infusion related reaction	1 (<1%)	4 (2%)	0	0
Investigations	**74 (31%)**	**40 (16%)**	**NC**	**NC**
Platelet count decreased	44 (18%)	25 (10%)	19 (13%)	16 (11%)
Alanine aminotransferase increased	13 (5%)	3 (1%)	1 (<1%)	3 (2%)
Gamma-glutamyltransferase increased	19 (8%)	3 (1%)	1 (<1%)	0
Lymphocyte count decreased	7 (3%)	8 (3%)	3 (2%)	4 (3%)
White blood cell count decreased	4 (2%)	5 (2%)	2 (1%)	4 (3%)
Aspartate aminotransferase increased	3 (1%)	0	2 (1%)	1 (<1%)
Neutrophil count decreased	3 (1%)	5 (2%)	27 (18%)	16 (11%)
Blood creatine phosphokinase increased	3 (1%)	0	0	0
Blood alkaline phosphatase increased	1 (<1%)	0	2 (1%)	1 (<1%)
Metabolism and nutrition disorders	**9 (4%)**	**18 (7%)**	**NC**	**NC**
Hyperglycaemia	3 (1%)	4 (2%)	1 (<1%)	0
Hypokalaemia	2 (<1%)	6 (2%)	0	0
Hyponatraemia	0	0	0	2 (1%)
Musculoskeletal and connective tissue disorders	**5 (2%)**	**6 (2%)**	**NC**	**NC**
Muscular weakness	0	0	0	2 (1%)
Nervous system disorders	**16 (7%)**	**20 (8%)**	**NC**	**NC**
Neuropathy peripheral	3 (1%)	10 (4%)	0	3 (2%)
Polyneuropathy	3 (1%)	3 (1%)	0	0
Dizziness	1 (<1%)	0	0	2 (1%)
Syncope	2 (<1%)	2 (<1%)	0	2 (1%)
Psychiatric disorders	**5 (2%)**	**4 (2%)**	**NC**	**NC**
Insomnia	3 (1%)	2 (<1%)	2 (1%)	1 (<1%)
Agitation	0	0	3 (2%)	0
Renal and urinary disorders	**6 (2%)**	**2 (<1%)**	**NC**	**NC**
Proteinuria	3 (1%)	0	0	0
Respiratory, thoracic and mediastinal disorders	**6 (2%)**	**6 (2%)**	**NC**	**NC**
Pulmonary embolism	2 (<1%)	2 (<1%)	0	2 (1%)
Vascular disorders	**12 (5%)**	**7 (3%)**	**NC**	**NC**
Hypertension	7 (3%)	3 (1%)	1 (<1%)	2 (1%)
Orthostatic hypotension	6 (2%)	3 (1%)	0	0

NC = not calculated
Source: DREAMM-7 Table 3.0008; DREAMM-8 Table 3.0500

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, grade ≥3 treatment-related AEs (in ≥1% of participants) were reported in 57% of participants. The most frequently reported were eye disorders (30%) and blood and lymphatic system disorders (21%).

Adverse drug reactions for SmPC

Pooled data from the DREAMM-6/7/8 combination studies is considered to be the most representative of the patient experience, in terms of ADR frequency and severity for the proposed indications, without the inclusion of monotherapy data.

The adverse reaction frequencies are based on all-cause adverse event frequencies, from 516 clinical trial patients with multiple myeloma exposed to belantamab mafodotin, for which a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.

Table 41. Adverse reactions in multiple myeloma patients treated with belantamab mafodotin

System organ class (SOC)	Adverse reaction	Frequency	Incidence (%)	
			Any grade	Grade 3-4
Infections and infestations	COVID-19	Very common	18	3
	Upper respiratory tract infection	Very common	15	<1
	Pneumonia	Very common	13	7
	Urinary tract infection	Common	9	2
	Bronchitis	Common	5	<1
	COVID-19 pneumonia	Common	3	2
	Hepatitis B reactivation	Uncommon	<1	<1
Blood and lymphatic system disorders	Thrombocytopenia[a]	Very common	62	47
	Neutropenia[b]	Very common	27	22
	Anaemia	Very common	23	12
	Lymphopenia[c]	Very common	10	7
	Leukopenia[d]	Common	9	4
	Febrile neutropenia	Common	1	1
Immune system disorders	Hypogammaglobulinemia	Common	2	<1
Metabolism and nutrition disorders	Decreased appetite	Common	8	<1
Psychiatric disorders	Insomnia	Very Common	13	1
Nervous system disorders	Neuropathies[e]	Very common	23	2
Eye disorders	Corneal examination findings (including keratopathy)[f,g]	Very common	84	62
	Visual acuity reduced[f]	Very common	81	50
	Vision blurred	Very common	52	13
	Dry eye	Very common	36	5
	Foreign body sensation in eyes	Very common	32	2
	Photophobia	Very common	30	1
	Eye irritation	Very common	28	3
	Eye pain	Very common	21	<1
	Cataract	Very common	13	4
	Visual impairment	Common	8	5
	Lacrimation increased	Common	5	<1
	Diplopia	Common	3	<1
	Eye pruritus	Common	2	<1
	Ocular discomfort	Common	1	<1
	Corneal ulcer[h]	Common	1	<1
	Corneal hypoesthesia	Not known	-	-
Respiratory, thoracic and mediastinal disorders	Cough	Very common	11	<1
	Dyspnoea	Common	9	1
	Pneumonitis	Uncommon	<1	<1
Gastrointestinal disorders	Diarrhoea	Very common	23	2
	Nausea	Very common	17	<1

System organ class (SOC)	Adverse reaction	Frequency	Incidence (%)	
			Any grade	Grade 3-4
	Constipation	Very common	15	<1
	Vomiting	Common	7	<1
Hepatobiliary Disorders	Increased aspartate aminotransferase	Very common	15	2
	Increased alanine aminotransferase	Very common	13	3
	Increased gamma glutamyltransferase	Very common	11	5
	Porto-sinusoidal vascular disorder[i]	Uncommon	<1	<1
Skin and subcutaneous tissue disorders	Rash	Common	4	<1
Musculoskeletal and connective tissue disorders	Arthralgia	Very common	11	<1
	Back pain	Very common	11	1
	Increased creatine phosphokinase	Common	3	1
Renal and urinary disorders	Albuminuria[j]	Common	3	<1
General disorders and administration site conditions	Fatigue	Very common	19	3
	Pyrexia	Very common	18	<1
	Asthenia	Common	6	1
Injury, poisoning and procedural complications	Infusion-related reactions[k]	Very Common	11	<1

[a] Includes thrombocytopenia and platelet count decreased.
[b] Includes neutropenia and neutrophil count decreased.
[c] Includes lymphopenia and lymphocyte count decreased.
[d] Includes leukopenia and white blood cell count decreased.
[e] Includes peripheral sensory neuropathy, neuropathy peripheral, neuralgia, polyneuropathy, peripheral motor neuropathy, sensory loss, peripheral sensorimotor neuropathy.
[f] Based on ophthalmic examination findings.
[g] Includes superficial punctate keratopathy, microcyst-like epithelial changes, stippled vortex staining pattern, sub-epithelial haze, corneal epithelial defects, and stromal opacity with or without changes in visual acuity.
[h] Includes infective keratitis and ulcerative keratitis.
[i] Signs or symptoms may include abnormal liver function tests, portal hypertension, varices, and ascites.
[j] Includes albuminuria, albumin urine present, urine albumin/creatinine ratio increased, and microalbuminuria.
[k] Includes adverse reactions determined to be related to infusion. Infusion reactions may include, but are not limited to, pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, and tachycardia.

[a] Includes thrombocytopenia and platelet count decreased
[b] Includes neutropenia and neutrophil count decreased
[c] Includes lymphopenia and lymphocyte count decreased.
[d] Includes leukopenia and white blood cell count decreased.
[e] Based on ophthalmic examination findings.
[f] Includes infective keratitis and ulcerative keratitis.
[g] Includes albuminuria, albumin urine present, urine albumin/creatinine ratio increased, and microalbuminuria.
[h] Includes adverse reactions determined to be related to infusion. Infusion reactions may include, but are not limited to, pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, and tachycardia.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

In DREAMM-7, SAEs were reported in 50% of participants in the BVd group. The most frequently reported SAEs in the BVd group were pneumonia (11%), COVID-19 and pyrexia (5% each), and thrombocytopenia and COVID-19 pneumonia (3% each). In DREAMM-8, SAEs were reported in 63% of participants in the BPd group. The most frequently reported SAEs in the BPd group were pneumonia (18%), COVID-19 pneumonia and COVID-19 (11% each), neutropenia (7%), and febrile neutropenia and urinary tract infection (3% each).

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, the incidence of SAEs was 44%. The most frequent SAEs (≥3%) were pyrexia (4%), pneumonia (4%), and thrombocytopenia (3%).

Treatment related serious adverse events

Treatment-related SAEs were reported in 19% of participants in the BVd group in DREAMM-7. The most frequently reported treatment-related SAEs in the BVd group were pneumonia (4%) and thrombocytopenia (3%); other treatment-related SAEs were reported in ≤1% of participants.

Treatment-related SAEs were reported for 30% of participants in the BPd group in DREAMM-8. The most frequently reported treatment-related SAE in the BPd group was pneumonia (11%), neutropenia (5%), and febrile neutropenia (3%).

Deaths

Table 42. Summary of deaths for DREAMM-7 and DREAMM-8 studies

	DREAMM-7 BVd (N=242)	DREAMM-8 BPd (N=150)
Participant status, n (%)		
Dead	50 (21%)	47 (31%)
Alive at last contact, follow-up ended	23 (10%)	9 (6%)
Death date retrieved	5 (2%)	1 (<1%)
Alive at last contact, follow-up ongoing	169 (70%)	94 (63%)
Primary cause of death, n (%)		
Cancer	18 (7%)	25 (17%)
Equivocally due to disease under study	2 (<1%)	6 (4%)
Unequivocally due to disease under study	16 (7%)	16 (11%)
Other cancer	0	3 (2%)
Haemorrhage	4 (2%)	0
Heart failure	0	1 (<1%)
Myocardial infarction	1 (<1%)	1 (<1%)
Other cardiovascular diagnosis	1 (<1%)	0
Other non-cardiovascular cause	19 (8%)	17 (11%)
Related to COVID-19	-	7 (5%)
Sepsis	6 (2%)	1 (<1%)
Stroke	0	1 (<1%)
Trauma	0	1 (<1%)
Time to death from last dose, n (%)		
≤30 Days	17 (7%)	14 (9%)
>30 Days	32 (13%)	34 (23%)
Unknown	1 (<1%)	0

Across all monotherapy and combination therapy studies, disease under study (multiple myeloma) was the most common cause of death. In DREAMM-7, fatal SAEs were reported in 10% of participants in the BVd group, in which pneumonia and COVID-related illness (with or without pneumonia) were the most common fatal SAEs. In DREAMM-8, fatal SAEs were reported in 11% of participants in BPd group, in which pneumonia and COVID-related illness (with or without pneumonia) were the most common fatal SAEs.

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, the incidence of fatal SAEs was 7%; various individual fatal events were reported in <1% of the participants.

Deaths causally related to the medicinal product

In DREAMM-7, seven participants (3%) in the BVd group experienced treatment-related fatal SAEs, with pneumonia being the most common treatment-related fatal SAE (4 participants). The other patients in the BVd group experienced gastrointestinal hemorrhage, subdural hemorrhage, and thrombosis mesenteric vessel. In DREAMM-8, 3 participants (2%) in the BPd group experienced treatment related fatal SAEs (gastrointestinal cancer metastatic, meningoencephalitis herpetic, and pneumonia). In DREAMM-2 and DREAMM-3 pooled data (n=312) two patients died due to a treatment related fatal SAE.

2.6.8.3.1. Adverse events of special interest

Thrombocytopenia is associated with multiple myeloma, a frequently observed adverse event in RRMM patients and is a known class effect of MMAF. It is identified as a risk for belantamab mafodotin. Infusion-related reactions (IRRs) are expected for biologic agents administered as infusions. Ocular AEs related to keratopathy, including visual impairment, are a class effect of MMAF-containing ADCs.

Thrombocytopenia

Table 43. Summary of characteristics of thrombocytopenia for DREAMM-7 and DREAMM-8 Studies (Safety Population)

Thrombocytopenia AESIs/ Characteristics, n (%)	DREAMM-7		DREAMM-8	
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)
Number of participants with event	211 (87%)	160 (65%)	82 (55%)	60 (41%)
Number of events	604	357	171	146
Event characteristics (% based on participants with an event)[a,b]				
Serious	11/211 (5%)	4/160 (3%)	2/82 (2%)	6/60 (10%)
Related to study treatment	203/211 (96%)	154/160 (96%)	72/82 (88%)	53/60 (88%)
Number of events (% based on participants with an event)				
One	84/211 (40%)	77/160 (48%)	46/82 (56%)	32/60 (53%)
Two	44/211 (21%)	34/160 (21%)	19/82 (23%)	8/60 (13%)
Three or more	83/211 (39%)	49/160 (31%)	17/82 (21%)	20/60 (33%)
Maximum grade (% based on participants with an event)				
Grade 1	11/211 (5%)	15/160 (9%)	9/82 (11%)	8/60 (13%)
Grade 2	24/211 (11%)	32/160 (20%)	16/82 (20%)	10/60 (17%)
Grade 3	63/211 (30%)	60/160 (38%)	39/82 (48%)	23/60 (38%)
Grade 4	113/211 (54%)	53/160 (33%)	18/82 (22%)	19/60 (32%)
Action taken (% based on participants with an event)[a,c]				
Dose not changed	158/211 (75%)	123/160 (77%)	82/82 (100%)	54/60 (90%)
Dose interrupted/delayed or reduced	121/211 (57%)	67/160 (42%)	24/82 (29%)	21/60 (35%)
Dose interrupted/delayed	113/211 (54%)	63/160 (39%)	18/82 (22%)	16/60 (27%)
Dose reduced	89/211 (42%)	32/160 (20%)	12/82 (15%)	10/60 (17%)
Study treatment withdrawn	7/211 (3%)	2/160 (1%)	0/82	0/60
Dose increased	3/211 (1%)	0/160	0/82	0/60
Not applicable	9/211 (4%)	8/160 (5%)	9/82 (11%)	9/60 (15%)
Worst outcome (% based on participants with an event)[d]				
Recovered/resolved	136/211 (64%)	117/160 (73%)	65/82 (79%)	40/60 (67%)
Recovered/resolved with sequalae	14/211 (7%)	10/160 (6%)	0/82	0/60
Recovering/resolving	13/211 (6%)	5/160 (3%)	4/82 (5%)	2/60 (3%)
Not Recovered/not resolved	48/211 (23%)	24/160 (15%)	13/82 (16%)	18/60 (30%)

Note 1: Thrombocytopenia is based on a hybrid of terms identified in the eCRF, and the terms thrombocytopenia and platelet count decreased.
Note 2: In DREAMM-8, an AE of 'Thrombocytosis' was also flagged as a Thrombocytopenia AESI in error by the investigator. The event has been updated and is no longer flagged as an AESI in the database following interim analysis database lock.
a. Participants may be included in more than 1 category for 'Event Characteristics' and 'Action Taken'.
b. 'Study treatment related' includes responses of 'Yes' and missing responses to the question 'Is there a reasonable possibility that the AE may have been caused by the study treatment?'.
c. 'Action Taken' counts actions related to any of the study treatments.
d. Outcome worst case hierarchy: fatal >not recovered/not resolved >recovering/resolving >recovered/resolved with sequelae >recovered/resolved. Participants were counted once in worst outcome experienced.

Table 44. Summary of thrombocytopenia and bleeding events for DREAMM-7 and DREAMM-8 Studies (Safety Population)

	DREAMM-7		DREAMM-8	
Thrombocytopenia and Bleeding Events, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Any Grade 3/4 platelet count decreased[a]	178 (74%)	118 (48%)	60 (40%)	43 (30%)
Any Grade 2 or above bleeding event[b]	31 (13%)	20 (8%)	15 (10%)	8 (6%)
Concomitant Grade 3/4 platelet count decreased and Grade 2 or above bleeding event[c]	16 (7%)	14 (6%)	4 (3%)	5 (3%)

Note: Thrombocytopenia is based on a hybrid of terms identified in the eCRF, and the terms thrombocytopenia and platelet count decreased.

a. In DREAMM-7 and DREAMM-8, platelet count decreased event is identified based on the platelet count decreased laboratory assessments with an increase to Grade 3 or 4.
b. In DREAMM-7, bleeding events included bleeding AEs (investigator-reported) or minor/major bleeding associated with thrombocytopenia AEs. In DREAMM-8, bleeding events included a hybrid of terms identified in the eCRF (investigator reported thrombocytopenia AESI with associated minor/major bleeding), and a list of terms identified by GSK internal review (Hemorrhage terms).
c. In DREAMM-7 and DREAMM-8, a Grade 2 or above bleeding event was considered as concomitant if the start date was within 3 days of a Grade 3/ 4 platelet count decreased laboratory assessment.

In the pooled monotherapy group (n=312), thrombocytopenic AESIs were reported in 44%, with 28% having a grade ≥3 event.

Infusion-related reactions

In DREAMM-7, IRRs occurred in 5 (2%) participants in the BVd group, with no grade ≥3 IRR. IRRs were managed by dose interruption, and resolution was documented for 4 of the 5 participants. Data are missing for 1 participant. In DREAMM-8, IRRs occurred in 11 (7%) participants in the BPd group, with grade 3 IRRs in 2 (1%) participants, none of grade 4-5. In the majority, IRRs were managed by dose interruption and resolution was documented. Of the 11 participants, 2 reported events of tremors and nausea, which were identified as IRRs, were resolving and ongoing respectively at data cut-off.

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, IRRs were reported in 19% of the participants. Of participants with an event by maximum grade, 2% had Grade 3 events, no participant had Grade 4 events, and 1 participant had a Grade 5 event. This participant had tolerated 3 infusions without incident; after the last infusion, the participant died of a cardiac arrest the following day. The investigator did not consider the event to be related to belantamab mafodotin. 95% of participants had recovered or were recovering at the time of the data cut-off.

Ocular AEs

Patients with current corneal epithelial disease except for mild punctate keratopathy were excluded from the DREAMM-7 and DRAMM-8 studies. In the registrational studies, DREAMM-7 and DREAMM-8, preservative-free artificial tears were administered in each eye at least 4 to 8 times daily beginning on cycle 1 day 1 until end-of-treatment. Corticosteroid eye drops were not required as prophylaxis in DREAMM-7 and DREAMM-8.

In DREAMM-7 and DREAMM-8 with belantamab mafodotin, 79% and 89%, respectively, developed ocular symptoms (by CTCAE) and most events were Grade 2 or Grade 3, with few Grade 4 events (2% and 1%). The frequency and severity of ocular AEs (by CTCAE) by PT in ≥ 5% of patients are shown in **Table 45**.

Table 45. Summary of any grade and grade 3 and 4 ocular symptoms (by CTCAE) in ≥5% of total participants in pooled belantamab mafodotin-containing group, and ocular AESI (by CTCAE) in DREAMM-7 BVd Group and DREAMM-8 BPd Groups, by PT and maximum grade (Safety Population)

PT, n (%)	DREAMM-7 (BVd) (N=242)		DREAMM-8 (BPd) (N=150)		Pooled Belantamab Mafodotin-Containing Group (N=516)	
	Grade 3+4	Total	Grade 3+4	Total	Grade 3+4	Total
Any event	82 (34%)	191 (79%)	65 (43%)	133 (89%)	215 (42%)	428 (83%)
Vision blurred	53 (22%)	160 (66%)	26 (17%)	119 (79%)	89 (17%)	321 (62%)
Dry eye	17 (7%)	123 (51%)	12 (8%)	91 (61%)	31 (6%)	225 (44%)
Foreign body sensation in eyes	8 (3%)	106 (44%)	9 (6%)	91 (61%)	17 (3%)	205 (40%)
Photophobia	5 (2%)	114 (47%)	5 (3%)	66 (44%)	11 (2%)	192 (37%)
Eye irritation	12 (5%)	103 (43%)	6 (4%)	75 (50%)	19 (4%)	179 (35%)
Eye pain	2 (<1%)	77 (32%)	3 (2%)	49 (33%)	5 (<1%)	139 (27%)
Keratopathy[a]	4 (2%)	6 (2%)	4 (3%)	11 (7%)	74 (14%)	120 (23%)
Visual acuity reduced[a]	4 (2%)	14 (6%)	20 (13%)	34 (23%)	40 (8%)	81 (16%)
Visual impairment[a]	13 (5%)	26 (11%)	15 (10%)	23 (15%)	30 (6%)	52 (10%)
Punctate keratitis[a]	1 (<1%)	2 (<1%)	9 (6%)	34 (23%)	12 (2%)	39 (8%)
Corneal epithelial microcysts[a]	1 (<1%)	1 (<1%)	12 (8%)	34 (23%)	13 (3%)	35 (7%)

Note 1: Includes all treatment-emergent AEs.
Note 2: PTs are presented by descending order by the number of total participants in the pooled group.
Note 3: Ocular Symptoms include PTs under group terms 'keratopathy/keratitis', and symptoms 'vision blurred', 'dry eye', 'photophobia', 'eye pain', 'eye irritation' and 'foreign body sensation' identified by GSK internal medical review.

a. In DREAMM-6 all corneal exam findings were reported as AEs, whereas in DREAMM-7 and DREAMM-8, corneal exam findings were only reported as AEs by CTCAE prior to Protocol Amendment 1 (refer to Section 1.1.3). For a

The median time to first onset for ocular symptoms (by CTCAE) was 41.0 and 29.0 days, respectively. The majority of ocular AEs (by CTCAE) resolved with adequate follow-up, with a median resolution time of 86.5 days in the pooled belantamab mafodotin group (n=516). Of the participants in the pooled belantamab mafodotin containing group with an event, the first occurrence resolved in 57% of participants, and a further 22% are still in follow-up. For the remaining participants (21%), the follow-up ended before resolution. For participants with more than one occurrence, the median duration of the last occurrence was similar to the first occurrence. 61% experienced their first occurrence of ocular symptoms within the first 2 cycles, and 77% experienced their first ocular event within 4 cycles.

In DREAMM-7 and -8 with belantamab mafodotin, 34% and 34% had worsening of BCVA to bilateral 20/50 or worse. Duration of first occurrence was in median 64.0 and 57.0 days. It did not resolve (ongoing at last follow-up) in 5 (6%) and 8 (16%) of participants in DREAMM-7 and DREAMM-8, respectively. For participants with normal baseline, bilateral worsening of Snellen scores to ≤20/200 was reported in 5 participants in DREAMM-7 and 2 participants in DREAMM-8 with belantamab mafodotin.

Corneal events by overall GSK/KVA scale (including both corneal examination findings and BCVA events) occurred in 92% and 93% of patients in DREAMM-7 and DREAMM-8, respectively. 77% and 78%, respectively, had a severe (grade ≥3) corneal event and 21% and 9%, respectively, grade 4 events (i.e. corneal ulcer or BCVA worse than 20/200). The effects resulted in one corneal ulcer in DREAMM-7 and DREAMM-8 studies. The time to first occurrence of corneal event was in median 42 days in the pooled group (n=516). Regarding other ophthalmic examination findings than corneal ones, the PT of cataract was reported more frequently in the belantamab mafodotin groups in the combination therapy studies than in the monotherapy studies (20%-27% versus 4%).

The median time from onset of a corneal event (by GSK/KVA scale) to the onset of an ocular symptom was 1 day. Of the 91% of participants in the combination pool (n=516), who experienced a GSK/KVA event, 88% had experienced their first event within 4 cycles. 49% of participants in the combination

pool had ≥3 occurrences (overall KVA grade ≥2, i.e. BCVA decline of 2 or 3 lines from baseline and/or following corneal examination findings: any or a combination of moderate superficial punctate keratopathy, patchy microcyst-like deposits, sub-epithelial haze peripheral, or a new peripheral stromal opacity). 80% of participants had their first occurrence resolve. For 80% (67/88) of the participants with unresolved corneal events, no further follow-up data was available.

Of those who had a normal corneal epithelium at baseline versus those who had an abnormal corneal epithelium at baseline (15% in the DREAMM-7 and 16% in the DREAMM-8 with belantamab mafodotin), a similar percentage of participants in both studies developed an abnormal finding, 89% and 87%, respectively.

Patient-Reported Outcomes (PROs) relevant to ocular safety and presented by the Applicant were OSDI (Ocular Surface Disease Index), PRO-CTCAE, FACT-GP5, and impact on reading and driving. Regarding OSDI in DREAMM-7 and DREAMM-8, participants who experienced minimally important deteriorations in Vision-related Functioning of the OSDI, typically saw improvement or resolution within 6 to 8 weeks in both the BVd and BPd groups. Levels of minimally important deterioration in Vision-related Functioning appeared to peak at Week 10 and 9, respectively, with 74% and 51% of participants, respectively, experiencing deterioration. Regarding PRO-CTCAE in DREAMM-7 and DREAMM-8, blurred vision was reported by 59% and 47% of participants, respectively, as '3-quite a bit' or '4-very much' interference. Regarding FACT-GP5 in DREAMM-7 and DREAMM-8, 54% and 36% of participants, respectively, reported feeling 'quite a bit' or 'very much' bothered due to overall treatment side effects. Of the participants in DREAMM-7 and DREAMM-8 who were able to read with little or no difficulty at baseline, 27% and 24%, respectively, stopped reading mainly due to eyesight issues at least at one visit during the study. Of the participants in DREAMM-7 and DREAMM-8 who were able to drive with little or no difficulty at baseline, 40% and 24%, respectively, stopped driving due to eyesight issues at least at one visit during the study.

Adverse events of special interest by age range

Table 46. Poled summary of AESIs by age range from DREAMM-7 and DREAMM-8

	Active (BVd and BPd)			**Comparator (DVd and PVd)**		
AE Type	**Age <65 (N=185) n (%)**	**Age 65 to <75 (N=154) n (%)**	**Age ≥75 (N=53) n (%)**	**Age <65 (N=176) n (%)**	**Age 65 to <75 (N=153) n (%)**	**Age ≥75 (N=62) n (%)**
Ocular AEs	156 (84%)	127 (82%)	41 (77%)	50 (28%)	46 (30%)	20 (32%)
Thrombocytopenia	141 (76%)	116 (75%)	36 (68%)	91 (52%)	98 (64%)	31 (50%)
Infusion related reaction event	10 (5%)	6 (4%)	0	27 (15%)	17 (11%)	4 (6%)

Note: Includes all TEAEs. Participants with missing subgroup category information were not included

Other significant events

Hypogammaglobulinemia and immunoglobulin (IVIG) replacement therapy

In DREAMM-7 INV-assessed hypogammaglobulinemia events were reported in 2% in the BVd group. 20 (8%) participants in the BVd group received IVIG replacement therapy during the study. In DREAMM-8 INV-assessed hypogammaglobulinemia events were reported in 5% in the BPd group. 27 (18%) participants in the BPd group received IVIG replacement therapy during the study.

2.6.8.4. Laboratory findings

Clinical chemistry and haematology: In DREAMM-7 and DREAMM-8, shifts to grade 3-4 in clinical chemistry assessments were rare (ranging from 1% to 4%) and consistent with pooled data from monotherapy. There were no clinically relevant changes from baseline in any of the clinical chemistry parameters assessed. Hematology results are consistent with thrombocytopenia and neutropenia discussed elsewhere.

Liver function tests: The incidence of hepatobiliary disorders AEs in belantamab mafodotin arms was low across monotherapy and combination therapy studies. In DREAMM-7 increases to grade 3-4 in liver parameters were not frequent but while very rare in DVd arm, were seen more often in BVd arm. In BVd arm the most frequent grade 3 increase was seen with GGT (n=32, 13%), while in ALT, ALP, AST and bilirubin grade 3 increases were more rare (<1%-5%). For all liver parameters grade 4 increases concerned only single patients. In DREAMM-8 a similar trend is seen in liver parameters, with grade 3-4 increases only rarely. Based on available information from all combination and monotherapy studies, ALT, AST, GGT increases are considered as adverse reactions for belantamab mafodotin. Biochemical/potential Hy's Law cases in both registrational studies were balanced between treatment groups and were confounded with respect to causality (in DREAMM-7, 2 potential Hy's law cases were reported in BVd arm). In DREAMM-8 possible Hy's law event was recorded in 1 patient in the BPd arm and had confounding factors. There were no Hy's Law cases in the monotherapy studies.

Renal parameters: The risk for renal toxicity in participants treated with BVd or BPd is low and consistent with what is observed in the pooled monotherapy data. AE of albuminuria was reported in 5% and 3% in BVd and BPd groups, respectively, and in 1% in the combined monotherapy studies.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Age

Table 47. Pooled analysis for AEs in DREAMM-7 and DREAMM-8 by age range

	Active (BVd and BPd)				**Comparator (DVd and PVd)**			
MedDRA Terms	**Age <65 (N=185) n (%)**	**Age 65-74 (N=154) n (%)**	**Age 75-84 (N=50) n (%)**	**Age 85+ (N=3) n (%)**	**Age <65 (N=176) n (%)**	**Age 65-74 (N=153) n (%)**	**Age 75-84 (N=58) n (%)**	**Age 85+ (N=4) n (%)**
Total AEs	184 (>99%)	154 (100%)	50 (100%)	3 (100%)	173 (98%)	152 (>99%)	56 (97%)	4 (100%)
Serious AEs – Total	89 (48%)	94 (61%)	32 (64%)	1 (33%)	66 (38%)	62 (41%)	24 (41%)	3 (75%)
Fatal	11 (6%)	23 (15%)	6 (12%)	0	13 (7%)	17 (11%)	4 (7%)	1 (25%)
Hospitalization/prolong existing hospitalization	83 (45%)	87 (56%)	30 (60%)	1 (33%)	57 (32%)	59 (39%)	23 (40%)	3 (75%)
Life-threatening	16 (9%)	18 (12%)	5 (10%)	0	10 (6%)	5 (3%)	1 (2%)	1 (25%)
Disability/incapacity	1 (<1%)	2 (1%)	0	0	2 (1%)	2 (1%)	0	0
Other (medically significant)	7 (4%)	9 (6%)	7 (14%)	0	6 (3%)	5 (3%)	1 (2%)	0
AE leading to treatment withdrawal[a]	35 (19%)	44 (29%)	18 (36%)	0	24 (14%)	28 (18%)	9 (16%)	1 (25%)

	Active (BVd and BPd)				Comparator (DVd and PVd)			
MedDRA Terms	**Age <65 (N=185) n (%)**	**Age 65-74 (N=154) n (%)**	**Age 75-84 (N=50) n (%)**	**Age 85+ (N=3) n (%)**	**Age <65 (N=176) n (%)**	**Age 65-74 (N=153) n (%)**	**Age 75-84 (N=58) n (%)**	**Age 85+ (N=4) n (%)**
Psychiatric disorders	51 (28%)	34 (22%)	11 (22%)	2 (67%)	45 (26%)	30 (20%)	13 (22%)	0
Nervous system disorders	93 (50%)	91 (59%)	30 (60%)	3 (100%)	108 (61%)	89 (58%)	40 (69%)	3 (75%)
Injury, poisoning and procedural complications	25 (14%)	30 (19%)	9 (18%)	1 (33%)	41 (23%)	39 (25%)	11 (19%)	1 (25%)
Cardiac disorders	18 (10%)	14 (9%)	8 (16%)	3 (100%)	14 (8%)	12 (8%)	7 (12%)	0
Vascular disorders	30 (16%)	24 (16%)	10 (20%)	1 (33%)	22 (13%)	23 (15%)	11 (19%)	1 (25%)
Infections and infestations	141 (76%)	118 (77%)	33 (66%)	1 (33%)	118 (67%)	102 (67%)	42 (72%)	3 (75%)
Postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	18 (10%)	24 (16%)	12 (24%)	1 (33%)	21 (12%)	28 (18%)	14 (24%)	2 (50%)

Note: Includes all TEAEs. Participants with missing subgroup category information were not included.
a. Participants with ≥1 AE where 'drug withdrawn' was reported as action taken for any treatment component.

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, no meaningful or discernible differences were found between the different age subgroups for general safety.

Ocular medical history

In the pooled combination therapy data, no meaningful or discernible differences were found between the different ocular medical history subgroups for the following ocular safety evaluations: ocular AEs (CTCAE) overview (including treatment discontinuations due to ocular AEs), grade ≥2 ocular AEs (CTCAE) by PT, grade ≥2 ocular symptoms (CTCAE) by PT, and worst post-baseline grade ≥2 BCVA (calculated CTCAE). In addition, there were no meaningful or discernible differences between the ocular medical history subgroups for the corneal events (GSK/KVA scale) overview and worst post-baseline visual acuity (GSK/KVA scale). No monotherapy pooled data are available for ocular safety across ocular medical history subgroups.

Geographic region

In DREAMM-7, no meaningful or discernible differences were found between the different region subgroups. In DREAMM-8, the incidence of SAEs, fatal SAEs, and pneumonia was higher in some regions (e.g., North East Asia) compared with others (e.g., Europe, n=209). However, the number of participants from North America (n=5) and Asia (n=30) are small; thus, this difference was not considered clinically meaningful by the applicant. No other meaningful or discernible differences were found between the different prior region subgroups. In the DREAMM-2 and DREAMM-3 pooled monotherapy data, no meaningful or discernible differences were found between different region subgroups for general safety.

Sex

In DREAMM-7 nor DREAMM-8, meaningful or discernible differences were not found between males and females. In the DREAMM-2 and DREAMM-3 pooled monotherapy data, no meaningful or discernible differences were found between males and females for general safety.

Race

In DREAMM-7, there were too few (n=8) participants in the Black subgroup to make meaningful conclusions, and there were no meaningful or discernible differences found between the other race subgroups (includes Asian and Mixed race). In DREAMM-8, the number of participants in Other race was small (n=20) and no Black participant enrolled on the study, so no meaningful conclusion can be drawn from the data. In the DREAMM-2 and DREAMM-3 pooled monotherapy data, no meaningful or discernible differences were found between different race subgroups for general safety (White n=236, Black n=18, Other n=50).

Extramedullary disease

In DREAMM-7 and DREAMM-8, numbers with extramedullary disease were small (in DREAMM-7 in BVd group n=13, in DREAMM-8 in BPd group n=20); therefore, meaningful conclusions cannot be made. In the DREAMM-2 and DREAMM-3 pooled monotherapy data, no meaningful or discernible differences were found between the different baseline extramedullary subgroups for general safety.

Prior anti-myeloma therapy

In DREAMM-7, no meaningful or discernible differences were found between the different prior anti-myeloma therapy subgroups. In DREAMM-8, the incidence of AEs that lead to permanent treatment discontinuation was higher in participants who had 2 or more prior lines of therapy than those who had 1 prior line of therapy (15 (21%) and 7 (9%), respectively, in the BPd arm). However, the rates of AEs that led to permanent treatment discontinuation were balanced between the treatment arms in the same prior anti-myeloma therapy subgroups. The incidence of grade 3 and 4 ocular AEs in the belantamab mafodotin group was also higher in participants who had 2 or more prior lines of therapy than those who had one prior line of therapy (51% vs. 36%). There were no other meaningful or discernible differences in the AE profiles between the different prior anti-myeloma therapy subgroups. No monotherapy pooled data are available for prior anti-myeloma therapy subgroups.

Hepatically and renally impaired patients

Table 48. Pooled analysis of AES in hepatically or renally impaired patients in DREAMM-7 and DREAMM-8

	Active (BVd and BPd)		**Comparator (DVd and PVd)**	
MedDRA Terms	**Hepatically impaired[a] (N=38) n (%)**	**Renally impaired[b] (N=288) n (%)**	**Hepatically impaired[a] (N=62) n (%)**	**Renally impaired[b] (N=294) n (%)**
Total AEs	38 (100%)	288 (100%)	61 (98%)	289 (98%)
Serious AEs – Total	21 (55%)	154 (53%)	22 (35%)	116 (39%)
Fatal	2 (5%)	31 (11%)	3 (5%)	27 (9%)
Hospitalization/prolong existing hospitalization	20 (53%)	140 (49%)	20 (32%)	109 (37%)
Life-threatening	4 (11%)	32 (11%)	1 (2%)	13 (4%)
Disability/incapacity	1 (3%)	3 (1%)	0	2 (<1%)
Other (medically significant)	3 (8%)	19 (7%)	2 (3%)	6 (2%)
AE leading to treatment withdrawal[c]	10 (26%)	73 (25%)	9 (15%)	48 (16%)
Psychiatric disorders	8 (21%)	75 (26%)	12 (19%)	64 (22%)
Nervous system disorders	19 (50%)	165 (57%)	35 (56%)	181 (62%)

Injury, poisoning and procedural complications	6 (16%)	52 (18%)	14 (23%)	61 (21%)
Cardiac disorders	7 (18%)	29 (10%)	9 (15%)	25 (9%)
Vascular disorders	7 (18%)	47 (16%)	12 (19%)	41 (14%)
Infections and infestations	25 (66%)	210 (73%)	37 (60%)	193 (66%)
Postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	6 (16%)	46 (16%)	12 (19%)	44 (15%)

Note: Includes all TEAEs. Participants with missing subgroup category information are not included.

b. Level of hepatic impairment at baseline is defined using NCI-ODWG classification. Normal – total bilirubin and AST ≤ULN; Mild – total bilirubin ≤ULN and AST >ULN OR total bilirubin >1–1.5x ULN and any AST; Moderate – total bilirubin >1.5-3x ULN and any AST; Severe – total bilirubin >3x ULN and any AST.

c. Baseline renal impairment status per eGFR (mL/min/1.73 m^2).

d. Participants with ≥1 AE where "drug withdrawn" was reported as action taken for any treatment component.

2.6.8.7. Immunological events

In pooled analysis of combination therapy studies DREAMM-6, DREAMM-7, and DREAMM-8, the total incidence of treatment-emergent anti-drug antibodies (ADA) was 15/515 (3%). A total of 2/515 (<1%) of study participants had treatment-emergent neutralizing ADA (NAb).

2.6.8.8. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with belantamab mafodotin.

2.6.8.9. Discontinuation due to adverse events

Adverse events leading to permanent discontinuation of study intervention

Discontinuation of belantamab mafodotin due to AEs across the combination and monotherapy studies was 19% in the BVd group, 16% in the BPd group, and 14% in the monotherapy pooled data, respectively.

In DREAMM-7, the incidence of AEs leading to discontinuation of any study treatment (including belantamab mafodotin, daratumumab, bortezomib, and dexamethasone) was higher in the BVd group than in the DVd group (31% vs. 19%, respectively). Peripheral neuropathy is a known AE of bortezomib. Neuropathic AEs were the most common AEs leading to treatment discontinuation in the BVd group. By PT, the AEs leading to withdrawal were peripheral sensory neuropathy (5%), polyneuropathy (3%), and neuropathy peripheral (2%).

In DREAMM-8, the incidence of AEs leading to discontinuation of any study treatment (including belantamab mafodotin, bortezomib, pomalidomide, and dexamethasone) was similar between the BPd group and the PVd group (15% vs. 12%, respectively;suggesting that addition of belantamab mafodotin to pomalidomide/dexamethasone vs. bortezomib to pomalidomide/dexamethasone did not alter the tolerability of pomalidomide/dexamethasone. The most common AEs leading to treatment discontinuation in the BPd group were fatigue, keratopathy, muscular weakness, and neuralgia (1% each); the remaining PTs were reported in single participants (<1%).

In both DREAMM-7 and DREAMM-8, 9% percent of participants discontinued belantamab mafodotin due to KVA or CTCAE event. There were no discontinuations due to KVA or CTCAE events in the comparator treatment arms.

In the DREAMM-2 and DREAMM-3 pooled data, the incidence of AEs leading to discontinuation in the belantamab mafodotin monotherapy group was 14%. Individual AEs by PT were reported in ≤1% of the participants. Ocular toxicity led to drug discontinuation in 3% of monotherapy participants.

Adverse events leading to dose reduction

The incidence of dose reduction of any study intervention was higher in the combination studies compared with the pooled monotherapy studies, as multiple agents could be dose reduced in the combination studies.

The incidence of AEs leading to dose reduction of belantamab mafodotin was higher in the combination therapy studies (69% in BVd group and 58% in BPd group) than in the pooled monotherapy studies (36%). Differences in the dose modification guidelines for each protocol may also have led to some differences between the studies. Ocular toxicity was a common cause of belantamab mafodotin dose reduction, but toxicity related to other combination components could also lead to dose reduction in the belantamab mafodotin groups.

In DREAMM-7, the incidence of AEs leading to dose reductions of any study treatment (including belantamab mafodotin, daratumumab, bortezomib, and dexamethasone) was higher in the BVd group than in the DVd group (75% vs. 59%, respectively). By PT, the most frequently reported AEs (≥5% of participants) leading to dose reductions in the BVd group were thrombocytopenia (28%), peripheral sensory neuropathy (14%), vision blurred (11%), neuropathy peripheral (10%), platelet count decreased (9%), and insomnia (5%).

In DREAMM-8, the incidence of AEs leading to dose reductions of any study treatment (including belantamab mafodotin, bortezomib, pomalidomide, and dexamethasone) was similar between the BPd group and the PVd group (61% in both groups). By PT, the most common AEs (≥5% of participants) leading to dose reductions in the BPd group were neutropenia (14%), neutrophil count decreased (10%), fatigue (7%), muscular weakness (7%), and insomnia (6%).

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, the incidence of AEs leading to dose reductions was 36%. By PT, the most frequent AEs (≥5% of participants) leading to dose reduction include keratopathy (13%), visual acuity reduced (5%) and vision blurred (5%).

Adverse events leading to dose interruptions / delays

The incidence of dose interruption/delay of any study intervention was higher in the combination studies, compared with the pooled monotherapy studies. The incidence of AEs leading to dose interruption/delay of belantamab mafodotin was 94% in the BVd group, 91% in the BPd group, and 59% in the pooled monotherapy studies. Across the studies, ocular toxicity was a common cause of dose delay in belantamab mafodotin groups, but the backbone therapy also commonly led to dose delays for the combination studies.

In DREAMM-7, the incidence of AEs leading to dose interruptions/delays of any study treatment (including belantamab mafodotin, daratumumab, bortezomib, and dexamethasone) was higher in the BVd group compared with the DVd group (94% vs. 75%, respectively). The most frequently reported AEs (≥15% of participants) leading to dose interruptions/delays in the BVd group were thrombocytopenia (35%), vision blurred (33%), and COVID-19 (15%).

In DREAMM-8, the incidence of AEs leading to dose interruptions/delays of any study treatment (including belantamab mafodotin, bortezomib, pomalidomide, and dexamethasone) was higher in the BPd group compared with the PVd group (91% vs. 75%, respectively). By PT, the most frequently reported AEs (≥15% of participants) leading to dose interruptions/delays in the BPd group were vision blurred (37%), COVID-19 (28%), neutropenia (23%), dry eye (21%), visual acuity reduced (17%), foreign body sensation in eyes (17%), pneumonia (17%), eye irritation (16%), and photophobia (15%).

In DREAMM-7, ocular AEs (CTCAE) or corneal events (KVA) led to dose delays in 78% of participants and in DREAMM-8, 83% of participants and resulted in a mean time between doses of 7.2 weeks (mean dose 2.2 mg/kg) and 9.5 weeks (mean dose 2 mg mg/kg), respectively.

The frequencies of dose delays, reductions and withdrawals due to corneal events (GSK/KVA Scale) are tabulated in **Table 49**.

Table 49. Summary of all dose modifications due to corneal events (GSK/KVA Scale) by study.

	GSK916 Study 207497 (N=124)	GSK916 Study 207503 (N=242)	GSK916 Study 207499 (N=150)
Total Number of Dose Modifications due to Corneal Events (GSK/KVA Scale)	49	371	428
Summary of Action Taken with Study Treatment			
Dose Interrupted/Delayed	11 (22%)	293 (79%)	329 (77%)
Dose Reduced	32 (65%)	63 (17%)	87 (20%)
Drug Withdrawn	6 (12%)	15 (4%)	12 (3%)
Duration of Dose Delay (days)			
Number of Events	11	293	308
Mean	53.4	77.2	64.2
SD	38.78	45.77	36.56
Median	42.0	81.0	57.0
Min.	7	10	26
Max.	113	349	248

Note: Dose delays due to corneal events (GSK/KVA scale) are identified by linking reports of 'dose interrupted/delayed' from the ocular grading corneal event page with treatment exposure. The onset of a dose delay is determined using date of previous dose and expected cycle length.
Dose modification is defined as dose delay, dose reduction or drug withdrawal.

Study 207497 = DREAMM-6, 207503 = DREAMM-7, and 207499 = DREAMM-8

In the DREAMM-2 and DREAMM-3 pooled monotherapy data, the incidence of AEs leading to dose interruption/delay was 59%. By PT, the most frequent AEs (≥5% of participants) leading to dose interruptions/delay in the BPd group include keratopathy (19%), vision blurred (10%), visual acuity reduced (9%) and dry eye (5%). It should be noted that corneal examination findings were only collected as AEs until protocol amendment 1 in DREAMM-3.

An overview of all dose modifications (of any component of the triplet regimen), separated out by the reason for modification (any, ocular, or non-ocular toxicity) is presented in **Table 50**.

Table 50. Summary of events leading to dose modification for DREAMM-7 and DREAMM-8 Studies

	DREAMM-7		DREAMM-8	
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)
Any modification due to AE or KVA scale event, n (%)	**237 (98%)**	**220 (89%)**	**143 (95%)**	**124 (86%)**
Study treatment withdrawn	84 (35%)	46 (19%)	29 (19%)	18 (12%)
Dose reduced	197 (81%)	146 (59%)	116 (77%)	88 (61%)
Drug interrupted/delayed	231 (95%)	185 (75%)	143 (95%)	109 (75%)
Any modification due to non-ocular AE, n (%)	**233 (96%)**	**219 (89%)**	**127 (85%)**	**124 (86%)**
Study treatment withdrawn	72 (30%)	46 (19%)	18 (12%)	18 (12%)
Dose reduced	169 (70%)	145 (59%)	88 (59%)	88 (61%)
Drug interrupted/delayed	216 (89%)	183 (74%)	124 (83%)	109 (75%)
Any modification due to ocular AE or KVA scale event, n (%)	**200 (83%)**	**4 (2%)**	**126 (84%)**	**2 (1%)**
Study treatment withdrawn	22 (9%)	0	14 (9%)	0
Dose reduced	106 (44%)	2 (<1%)	88 (59%)	0
Drug interrupted/delayed	189 (78%)	3 (1%)	124 (83%)	2 (1%)

Note 1: Ocular AEs were based on a hybrid of terms identified in the eCRF, and a list of terms identified by GSK internal review. For the complete list of PTs used to analyze ocular AEs (CTCAE grade) in the individual studies, refer
Note 2: Any modification includes study treatment withdrawal, dose reduced, and drug interrupted/delayed only. Modifications are summarized if at least one component of study treatment was modified.
Note 3: In DREAMM-8, per original protocol, dose reductions were not recommended for belantamab mafodotin. After Protocol Amendment 1, dose reductions were allowed after recovery from Grade ≥2 corneal events (KVA scale).
Note 4: In DREAMM-8, corneal examination findings (e.g., corneal epithelial microcysts, corneal opacity, punctate keratitis, keratopathy) were reported as ocular AEs and graded per CTCAE under the original protocol. After Protocol Amendment 1, corneal examination findings were not required to be reported as AEs and they were assessed by the KVA scale

2.6.8.10. Post marketing experience

The applicant received its first approval of belantamab mafodotin 100 mg powder for concentrate for solution for infusion on 05 August 2020 in the United States for multiple myeloma at dose(s) of 2.5 mg/kg once every 3 weeks. Belantamab mafodotin 100 mg powder for concentrate for solution for infusion was approved in all European Economic Area countries on 25 August 2020. On 15 December 2023, the Committee for Medicinal Products for Human Use (CHMP) did not grant the renewal of the conditional Marketing Authorization for Blenrep. Healthcare professionals with patients already prescribed Blenrep could have the option to decide to enrol their patient in an Expanded Access Program (EAP) or Named Patient Program (NPP) to continue to access treatment

There have been 7987 patients exposed to belantamab mafodotin including 1731 patients in clinical trials (data as of 02 January 2025), 3211 patients in expanded access/compassionate use programs (data as of 27 February 2025) and 3045 patients in the Blenrep REMS program prior to its closure in February 2023. Additionally, cumulative post-marketing experience is estimated to be 2506 patient months of treatment up to 31 December 2024.

2.6.9. Discussion on clinical safety

Patient exposure

The safety of belantamab mafodotin has been evaluated in 516 patients treated with triplet combinations (DREAMM-6 & BRd and BVd, DREAMM-7 & BVd, DREAMM-8 & BPd) with supportive information from the ALGONQUIN study (investigator-initiated single arm trial with BPd). Further information is available from monotherapy studies (DREAMM-2, DREAMM-3; 312 patients), the DREAMM-12 study (normal/mildly/severely impaired renal function), and earlier post-marketing data.

In general, the population in the combination therapy safety pool is suitable for the safety evaluation of belantamab mafodotin in MM in the EU, as the median age of the patients was 66 years, 85% were white and 49% were from Europe.

The monotherapy pool helps to identify risks specific to belantamab mafodotin. The most relevant safety data is derived from DREAMM-7 and DREAMM-8, considering the sought indications for triplet combinations in a relatively early treatment setting. It is not always possible to disentangle the role of belantamab mafodotin in all ADRs from a triplet combination. The combination partners cause AEs and can aggravate some toxicities from belantamab mafodotin. Belantamab mafodotin could also aggravate toxicities of standard medicines in the combinations. Further, some manifestations of multiple myeloma overlap with AEs (e.g., infections).

In DREAMM-7 and DREAMM-8 the median total duration of exposure with experimental triplets was longer than with comparator arms (15.9 months with BVd vs 12.9 months with DVd, 16.5 months with BPd vs 8.5 months with PVd, respectively). In both experimental arms the relative dose intensity (RDI) for belantamab mafodotin was low, decreasing through time (median RDI with BVd 50.9%, 77% up to 6 months, 68% during 6-12 months and 28% from month 13 onwards, and median RDI with BPd 52.6% and 100% for cycle 1, 56.6% for cycles 2-8, and 33.3% from cycle 9 onwards). Thus, it is possible, that the doses and dosing intervals of belantamab mafodotin in these triplets are not optimal for the target population (elderly, burdened with comorbidities).

At DCO of 2 October 2023 in DREAMM-7, 27% of patients in the BVd arm had new or ongoing AEs beyond treatment discontinuation. In DREAMM-8 at DCO of 29 January 2024, 55% of patients in the BPd arm had new or ongoing AEs beyond treatment discontinuation. In DREAMM-7 49% of events were not resolved and in DREAMM-8 43%, while 4% and 3%, respectively, were fatal. AEs beyond treatment discontinuation affected the same SOCs as those reported during treatment (typically ocular toxicity, blood and lymphatic system disorders, infections & infestations, and nervous system disorders). In DREAMM-7, of AEs beyond treatment discontinuation, the proportion of fatal events was 7% (n=18) and of these 17 patients were affected by infections and infestations. In DREAMM-8 beyond treatment discontinuation, the proportion of fatal events was 12% (n=18), the majority of them infections.

The difference between BPd and BVd in persistent AEs (55% vs. 27%) could be due to differences in the lengths of treatment with pomalidomide and bortezomib, to patients mandated to have prior lenalidomide-treatment in DREAMM-8, to other unknown reasons or due to a combination of factors. The sought indication is for early treatment setting and the patients are most likely to receive subsequent therapies. Persistent AEs of grade ≥3 beyond treatment discontinuation can have significant effects to the patients' QoL and subsequent systemic therapies. The median time for new AEs or new SAEs beyond discontinuation from last belantamab mafodotin dose was 23 days and 25 with BVd and 56 days and 65 days with BPd. For ongoing AEs beyond treatment discontinuation the median time to resolution was 92 days with BVd and 101 days with BPd. Such persistent toxicity highlights the need for diligent follow-up and care of the patients beyond treatment discontinuation.

Adverse events

Comparison to SoC in DREAMM-7 and DREAMM-8 illustrates the risks of belantamab mafodotin combinations. Grade ≥3 AEs and grade ≥3 related AEs were more frequent with belantamab mafodotin containing triplets. AEs and related AEs leading to permanent discontinuation were also more frequent in experimental arms, as were SAEs and SAEs related to any study treatment. Similarly, AEs leading to dose interruption/delay were more frequent in experimental arms. Fatal SAEs were nearly as frequent across study arms.

While AEs leading to dose reduction were more frequent in belantamab mafodotin arm in DREAMM-7, they were equal between arms in DREAMM-8. This could be related to the dose and dosing schedule in DREAMM-8, albeit also other factors could contribute to this finding. DREAMM-7 and DREAMM-8 show that toxicity in general is high in all treatment arms (AEs 100% with BVd and DVd, >99% with BPd and 96% with PVd) and these are mostly related to study treatment (100% with BVd, 95% with Dd, 95% with BPd and 81% with PVd).

The applicant pointed out possible causes for the increase in toxicity: the longer overall exposure time, longer follow-up duration, triplet regimen's added toxicity, and possible influence of COVID-19 pandemic. Exposure-adjusted rates for AEs were provided to show that the longer exposure to belantamab mafodotin based treatment leads to longer periods for AE collection. This approach is in principle understood. However, non-adjusted data for AEs is more relevant for treatment decisions. In DREAMM-7 COVID-19 AE was reported in 24% in BVd and in 20% in DVd, while in DREAMM-8 in 37% in BPd and 21% in PVd. The reasons for these differences are not fully known. This could be related to slightly different timeframes of these studies and to chance, especially given the smaller size of DREAMM-8.

In DREAMM-7, the most commonly reported AEs (>20% of participants) in the BVd group by CTCAE were thrombocytopenia AESI (87%), ocular AESIs (79%), diarrhoea (32%), peripheral sensory neuropathy (25%), COVID-19 (24%) and neuropathy peripheral (21%).

In DREAMM-8, the most commonly reported AEs (>20% of participants) in the BPd group by CTCAE were ocular AESI (89%), neutropenia/neutrophil count decreased/febrile neutropenia (63%), thrombocytopenia AESI (55%), COVID-19 (37%), cataract (27%), fatigue (27%), upper respiratory tract infection (27%), pneumonia (24%), anaemia (23%), and diarrhoea (23%).

For treatment emergent AEs by SOC and PT in DREAMM-7 and DREAMM-8, the major difference between experimental arms and SoC arms is the frequent ocular toxicity with belantamab mafodotin based treatment (80% vs 38% in DREAMM-7, 91% vs 37% in DREAMM-8). In many AEs there are no relevant differences whether the patient was treated with experimental therapy or with SoC. Slight differences in AE profiles of BVd or BPd can aid the clinician in choosing between these 2 triplets: e.g., for a patient with pre-existing neuropathy BPd would be preferred over BVd. Further, BPd combination led to neutropenia in 21% while BVd in 4%.

When belantamab mafodotin is used as monotherapy, the frequencies of all AEs (with the exception of IRRs) are lower, despite that patients were more heavily pretreated in DREAMM-2 and DREAMM-3. In the monotherapy pooled data, the most frequently reported AEs (>20% of participants) were ocular AEs (66%), thrombocytopenia (31%), and anaemia (28%).

The frequencies of grade ≥3 AEs were higher in the experimental arms (95% with BVd in DREAMM-7, 91% with BPd in DREAMM-8) compared to the control arms (76% in DREAMM-7, 73% in DREAMM-8). For some grade ≥3 AEs there were no relevant differences, whether the patient received experimental therapy or SoC (e.g., GI disorders were equal between arms in DREAMM-7 and DREAMM-8). Some differences in DREAMM-8 between treatment arms could be also due to chance, due to the smaller size of this study. For ocular grade ≥3 AEs the differences between experimental arms and SoC arms are notable. The effects on haematology parameters differ: in DREAMM-7 thrombocytopenia grade ≥3 affected more than half of the experimental arm patients and 35% in DVd arm, while this was equally reported in both treatment arms (24% and 20%) in DREAMM-8. Grade ≥3 anaemia was as frequent in all arms, while grade ≥3 neutropenia was reported especially in DREAMM-8 and with higher frequency in BPd (42%) than in PVd (28%). Also for grade ≥3 infections and infestations the highest frequencies were reported in DREAMM-8 and more predominantly in BPd arm (49%) than PVd arm (26%). In everyday clinical praxis these frequencies could be even higher, as potential future patients differ from carefully selected trial patients.

Most of all AEs were considered related to the medicines used. To disentangle which treatment related AEs were specifically caused by belantamab mafodotin is more challenging. The effect of belantamab mafodotin on related ocular AEs is however clear (e.g., vision blurred in 64% with BVd and 76% with BPd, while 4% with DVd and 2% in PVd). Other risks, such as thrombocytopenia are also clearly higher in patients treated with belantamab mafodotin e.g., based on DREAMM-7, BVd is associated to treatment-related thrombocytopenia in 66% of patients and in 48% in DVd treated patients. Comparing treatment related AEs between arms in DREAMM-7 with the 20% cut-off, it is evident, that replacing daratumumab with belantamab mafodotin does not decrease the risk for these AEs in any SOC. In DREAMM-8 the only alleviation for treatment related AEs with experimental therapy concerns nervous system disorders: when bortezomib is replaced with belantamab mafodotin, the risks for peripheral (sensory) neuropathy are lower.

Treatment related grade ≥3 AEs were also frequent and especially in the experimental arms (91% in DREAMM-7 with BVd, 80% in DREAMM-8 with BPd). Some treatment related AEs grade ≥3 were reported with the same frequency in the control and experimental arms (e.g., fatigue). Ocular toxicity of grade ≥3, however, was a treatment related AE characteristic to belantamab mafodotin. A notable difference was also seen in treatment related grade ≥3 thrombocytopenia, reported in 53% of patients in the BVd arm and 35% in the DVd arm. This treatment related grade ≥3 AE was also reported in DREAMM-8 but with a lower frequency and without relevant differences across arms (19% with BPd, 15% with PVd).

Adverse events of special interest

Thrombocytopenia AESIs

Thrombocytopenia was more frequent in DREAMM-7 (87%, grade ≥3 73%) and in DREAMM-8 (55%, grade ≥3 38%) than in the monotherapy pool (44%, grade ≥3 28%), in which patients were more heavily pretreated. This reflects the additive effects from bortezomib and pomalidomide and the longer duration of exposure with belantamab mafodotin. In DREAMM-7 thrombocytopenia was more frequent in the BVd arm than in the DVd arm (65%), as also in DREAMM-8 in BPd arm than in PVd arm (41%). These differences provide further evidence for the role of belantamab mafodotin in this ADR. Comparison across experimental arms illustrates, that with BVd thrombocytopenia was more frequent than with BPd (87% vs 55%) and more often of grade ≥3 (73% vs 38%). The majority of thrombocytopenia events had resolved, with or without sequelae. While there were no fatal events, this ADR can be of clinical importance, considering that 7% of patients in DREAMM-7 BVd arm had a concomitant grade ≥3 thrombocytopenia and grade ≥2 bleeding event, and 3% in DREAMM-8 BPd arm, respectively.

In DREAMM-7, 49% of patients in the BVd arm were treated with antithrombotic agents, illustrating patient characteristics and clinical praxis. Of these patients, 31% had grade 3-4 thrombocytopenia, 8% grade ≥2 bleeding event and 3% concomitant grade 3-4 thrombocytopenia and grade ≥2 bleeding event. These rates are higher than in the DVd arm (18%, 4%, and 2%, respectively).

In DREAMM-8, 93% of patients in the BPd arm were treated with antithrombotic agents. This is in line with recommendations for treatment with pomalidomide. Of these patients, 39% had grade 3-4 thrombocytopenia, 10% grade ≥2 bleeding event and 3% concomitant grade 3-4 thrombocytopenia and grade ≥2 bleeding event. These rates are higher than those seen in PVd-arm (29%, 4%, and 2%, respectively).

As reflected in SmPC section 4.4, complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment. Patients experiencing Grade 3 or 4 thrombocytopenia or those on concomitant anticoagulant treatments may require more frequent

monitoring and may be managed with a dose delay or dose reduction. Supportive therapy (e.g., platelet transfusions) may be provided according to standard medical practice.

Infusion-related reactions

IRRs were more frequent in the monotherapy pool (19%) than in DREAMM-7 (2%) or DREAMM-8 (7%). Grade ≥3 IRRs were very rare (none in DREAMM-7, 1% in DREAMM-8). The lower incidence could be related to the use of dexamethasone in triplet combinations, while no premedication was mandated in the monotherapy studies. Prescribers are advised that if a Grade 2 or higher infusion-related reaction occurs during administration, the infusion rate should be reduced or stopped depending on the severity of the symptoms. In that case, appropriate medical treatment should be instituted and the infusion restarted at a slower rate if the patient's condition is stable. If Grade 2 or higher IRR occurs, premedication for subsequent infusions should be considered.

Ocular AESIs

Ocular AEs related to keratopathy, including visual impairment, are a class effect of MMAF-containing ADCs. While the exact mechanism for these corneal events is unknown, it is believed that there is a certain degree of uptake of the ADCs in the epithelial cells.

Ocular toxicity of belantamab mafodotin was very frequent in DREAMM-7 and DREAMM-8 while the incidence and severity of ocular AEs in the comparator treatment arms was substantially lower. Toxicity to the ocular surface is of concern and can largely impact the QoL of the patients. Moreover, further complications could lead to corneal ulceration and threaten the vision. However, the majority of ocular AEs (by CTCAE) resolved with adequate follow-up, with a median resolution time of approximately 3 months.

In DREAMM-7 and DREAMM-8 with belantamab mafodotin, 79% and 89%, respectively, developed ocular symptoms (by CTCAE) and most events were grade 2 or grade 3, with few grade 4 events. The most commonly reported symptoms were vision blurred (66% in DREAMM-7 and 79% in DREAMM-8), dry eye (51%, 61%), foreign body sensation (44%, 61%), and photophobia (47%, 44%). In the monotherapy pooled data, the incidence of ocular symptoms was 66%.

In both DREAMM-7 and DREAMM-8, 34% of patients with belantamab mafodotin based treatment experienced worsening of BCVA to bilateral 20/50 or worse, which is clinically meaningful. Of the participants in DREAMM-7 and DREAMM-8 who were able to read with little or no difficulty at baseline, 27% and 24%, respectively, stopped reading mainly due to eyesight issues, translating the change of BCVA into an impact on everyday life. Bilateral worsening to ≤20/200 was rare (5 participants in DREAMM-7 and 2 in the DREAMM-8). BCVA ≤20/200 is the limit of legal blindness in the U.S.

The biomicroscopy findings, namely corneal epithelial microcysts and punctate keratitis, were seen at comparable rates in both DREAMM-7 and DREAMM-8 studies with belantamab mafodotin (superficial punctate keratopathy: DREAMM-7: 86% vs DREAMM-8: 82%; microcyst-like deposits: DREAMM-7: 68% vs DREAMM-8: 70%), regardless of the differences in prior treatments or combination partners between the two studies.

In DREAMM-7 and DREAMM-8, 92% and 93%, respectively, had corneal events by GSK/KVA scale which includes both corneal examination findings and BCVA events. 56% and 69%, respectively, had grade 3 corneal events and 21% and 9%, respectively, grade 4 events (i.e. corneal ulcer or BCVA worse than 20/200). GSK/KVA scale was developed by the Applicant in response to regulatory guidance with FDA and it is not used outside the GSK trials. There is no 'gold-standard' scale for assessing corneal AEs and the scale is not validated. However, it is acknowledged that although the scale is not validated, it enhanced the efficiency and consistency in grading corneal events by eye care professionals in the DREAMM studies, and it also facilitated better communication with hematologists

regarding recommendations for managing corneal events and modifying dose and eventually, also improved patient safety.

In DREAMM-7, 6 participants were reported to have developed evidence of corneal ulcers post-baseline; only 1 of them met a formal definition for a corneal ulcer. In DREAMM-8, 3 participants were reported to have developed evidence of corneal ulcers post-baseline, including 1 event of grade 3 ulcerative keratitis in the BPd group; none of them met the formal definition of a corneal ulcer. In DREAMM-2, one case of corneal ulcer was confirmed. Foremost, there were no perforations in DREAMM-7 and DREAMM-8 studies.

Cataract was reported more frequently in the belantamab mafodotin groups in the combination therapy studies than in the monotherapy studies (20%–27% vs. 4%). The Applicant has provided several possible influencing factors: longer on-treatment time, systemic dexamethasone use, and change in data collection. Cataract was reported in more than twice as many participants in the belantamab mafodotin groups compared with the control groups, which could be attributed to several factors specific to the control groups: less frequent eye exams, not requiring re-baselining of BCVA, and having shorter time on study treatment. Although no plausible mechanism by which belantamab mafodotin might cause cataracts is yet known, the applicant has agreed to add cataract as an ADR because a causal relationship is at least a reasonable possibility.

The median time to first onset for ocular symptoms (by CTCAE) was 41.0 and 29.0 days, in DREAMM-7 and DREAMM-8, respectively and 88% had experienced their first event within 4 cycles in the combination pool (n=516) and approximately half of the participants had grade ≥3 occurrences (GSK/KVA grade). Consequently, in the SmPC Section 4.4, ophthalmic examinations, including assessment of visual acuity and slit lamp examination, are recommended to be performed before each of the first 4 doses of belantamab mafodotin and during treatment as clinically indicated. This approach is supported by the finding that a total 88% (455/516) of the first corneal events occurred within the first 4 belantamab mafodotin doses. After the 4th dose there is a lower likelihood of corneal events developing for the first time. With 2 further ophthalmic exams (i.e. total of 6), only 8 additional participants had experienced their first corneal event, giving a total of 90% (463/516) participants with corneal events.

In terms of BCVA, worsening of BCVA was transient with most participants returning to baseline within 2 months. However, follow-up data is not available for all participants.

In terms of CTCAE grade, in the pooled analysis ocular symptoms resolved (with or without sequelae) in 48% of participants; 45% had not recovered, and 7% were recovering at the time of study report (data cut-off for DREAMM-6 28 February 2023, for DREAMM-7 02 October 2023, and for DREAMM-8 29 January 2024). Regarding individual studies, in the initial submission for DREAMM-7 and DREAMM-8, 52% and 56% of participants had their ocular symptoms resolve (with or without sequalae), 41% and 37% had not recovered; and 7% and 8% were recovering at the data cut-offs, respectively. An updated analysis was not possible for DREAMM-6. In the updated analysis for DREAMM-7 and DREAMM-8, 56% and 57% of participants had their ocular symptoms resolve (with or without sequalae), 36% and 32% had not recovered; and 7% and 11% were recovering at the data cut-off 07 October 2024. The resolution rates are numerically (but not statistically) higher compared to ones reported previously (41% and 37%).

In terms of GSK/KVA grade, in the pooled analysis of the initial submission with DREAMM-6, DREAMM-7, and DREAMM-8, the last occurrences of corneal events had resolved for 39% of participants, with 31% of participants remaining on study treatment or in follow-up. No updated data was available from DREAMM-6. With additional follow-up, 43% of participants from DREAMM-7 and 55% of participants from DREAMM-8 had their last Grade ≥2 corneal event resolve. 34% and 27% of participants remained on study treatment or in follow-up in DREAMM-7 and DREAMM-8, respectively. It is important to note

that not all the events reported as 'unresolved' at the updated data cut are the same as those that were 'unresolved' at the initial data cut. To overcome this reporting caveat, the most insightful analysis of the outcome of Grade ≥2 corneal events was the additional post-hoc analysis provided by the applicant which showed that 84% of corneal Grade ≥2 occurrences (GSK/KVA scale) with a minimum follow-up of 90 days, had resolved (Grade 1 or better in both eyes). Regarding the 16% (n=76 out of 485) of cases with > 90 days of follow-up that had not resolved at the data-cut-off, the applicant claims that there is no evidence these occurrences are permanent/irreversible. CTCAE measures symptoms but GSK/KVA scale is dependent on measured BCVA and biomicroscopy findings and according to this analysis, symptoms tended to be more persistent. Of note, the background rate of reported dry eye symptoms (vision blurred, dry eye, photophobia, eye pain, eye irritation, foreign body sensation) is substantial in this age group and among individuals with multiple myeloma.

In addition to the required ophthalmic examinations, patients should be advised to administer preservative-free artificial tears at least 4 times a day during treatment and avoid using contact lenses until the end of treatment. Bandage contact lenses may be used under the direction of an ophthalmologist.

Educational materials for healthcare professionals and patients as well as a patient card will also be available, with detailed information on the ocular effects of belantamab mafodotin, the description of required ocular exams for patients receiving belantamab mafodotin and instructions on how to manage ocular adverse reactions.

Pneumonitis

Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin. Evaluation of patients with new or worsening unexplained pulmonary symptoms (e.g., cough, dyspnoea) must be performed to exclude possible pneumonitis. In case of suspected or confirmed Grade 3 or higher pneumonitis, it is recommended that belantamab mafodotin is discontinued and appropriate treatment initiated. This information is provided in SmPC section 4.4.

Hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation can occur in patients treated with medicinal products directed against B cells, including belantamab mafodotin, and in some cases, may result in fulminant hepatitis, hepatic failure, and death. Patients with evidence of positive HBV serology must be monitored for clinical and laboratory signs of HBV reactivation as per clinical guidelines. In patients who develop reactivation of HBV while on belantamab mafodotin, treatment must be withheld and patients must be treated according to clinical guidelines. This information is provided in SmPC section 4.4.

Deaths

50 patients (21%) in DREAMM-7 treated with BVd and 47 patients (31%) in DREAMM-8 treated with BPd died. In both studies a higher number of these patients had >30 days from the last treatment dose until death (32 and 34 patients, respectively). The number of patients dying from cancer, either equivocally or unequivocally due to MM, is lower in DREAMM-7 (18, 7%) than in DREAMM-8 (25, 17%). Fatal SAEs were (nearly) equal between arms (in DREAMM-7 10% vs. 8%, in DREAMM-8 11% vs. 11%, respectively) and comparable to monotherapy pool (7%). The most common fatal SAEs were pneumonia and COVID-related illness in DREAMM-7. In DREAMM-8, pneumonia and COVID-related illness (with or without pneumonia) were the most common fatal SAEs in the BPd group.

Fatal SAEs related to any study treatment were rare (in DREAMM-7 3% vs. <1%, in DREAMM-8 2% vs. 0). Seven participants in the BVd group experienced treatment-related fatal SAEs, including 4 events of pneumonia. The remaining participants in the BVd arm experienced gastrointestinal hemorrhage,

subdural hemorrhage, and thrombosis mesenteric vessel. Of these, the fatal subdural hemorrhage and mesenteric vessel thrombosis were associated with thrombocytopenia. The three patients in the BPd arm experiencing treatment related fatal SAE had gastrointestinal cancer metastatic, meningoencephalitis herpetic, and pneumonia.

In DREAMM-7, fatal outcomes with pneumonia were reported in 18%, 3% with COVID-19 pneumonia and <1% with Coronavirus pneumonia in the BVd arm. In DREAMM-8 fatal outcomes with pneumonia were reported in 24% and 12% with COVID-19 pneumonia in the BPd arm. The risk of infections including pneumonia is a well-known complication of MM. Pneumonia is also an ADR for belantamab with the frequency "very common" in the PI. No new safety concerns were identified with the fatal treatment-related pneumonia cases.

Laboratory findings

Clinically relevant observations were rare and largely consistent e.g. with thrombocytopenia and neutropenia events discussed among AEs. Possible Hy's law events were very rare (2 patients in BVd arm, one in BPd arm) and all had confounding factors. Therefore, increases in liver enzyme, albuminuria, and cytopenias are added as ADRs in the SmPC.

Safety in special populations

Despite pooling BVd and BPd data from DREAMM-7 and DREAMM-8, only 3 patients represent the ≥85 years of age population. Thus, pooled data from DREAMM-7 and DREAMM-8 can be used for 65-84 years old patients. Toxicity in elderly patients is generally higher compared to younger patients treated with experimental therapy e.g., in patients treated with BVd or BPd, SAEs were reported in 48% in <65 years of age but in 61% in 65-74 years and 64% in 75-84 years of age. However, for AESIs (including ocular events) there were no overall differences between patients 65 years of age and older and younger adult patients. No dose adjustment is recommended for patients who are aged 65 years or over.

After pooling of BVd and BPd data from DREAMM-7 and DREAMM-8, the hepatically impaired patient population is limited (38 patients) and the renally impaired patient population considerable (288 patients). Based on observed results, no dose adjustment is recommended in patients with mild (eGFR 60-89 mL/min), moderate (eGFR 30-59 mL/min), severe renal impairment (eGFR < 30 mL/min not requiring dialysis), or end-stage renal disease. No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin greater than upper limit of normal [ULN] to ≤ 1.5 × ULN and any aspartate transaminase [AST] or total bilirubin ≤ ULN with AST > ULN). There are limited data in patients with moderate hepatic impairment (total bilirubin greater than 1.5 × ULN to ≤ 3.0 × ULN and any AST level), or in patients with severe hepatic impairment (total bilirubin greater than > 3.0 × ULN and any AST level) to support a dose recommendation; Belantamab mafodotin should only be used in these patients if the potential benefits outweigh any potential risks.

Patients with prior ASCT were more prone to need dose reductions than patients without prior ASCT, both with BVd (79% vs 67%) and BPd (67% vs. 51%). With BVd, patients with prior ASCT had more frequently grade 3-4 related AEs (90% vs 79%) while with BPd the difference was less (82% vs. 75%).

It is agreed with the applicant, that sex, race, extramedullary disease, number of prior lines, geographic region, or ocular history does not appear to have an impact on safety. However, these conclusions are deducted from very limited numbers.

Immunological events

In pooled analysis of combination therapy studies DREAMM-6, DREAMM-7, and DREAMM-8, the total incidence of treatment-emergent anti-drug antibodies (ADA) was 15/515 (3%). A total of 2/515 (<1%) of study participants had treatment-emergent neutralizing ADA (NAb). Thus, belantamab mafodotin

has a low propensity for inducing immune responses in patients with RRMM. ADA formation is not expected to have an impact on pharmacokinetics, efficacy or safety.

Dose modifications and discontinuations due to AEs

AEs leading to dose modifications (of any agent) were more frequent in the belantamab mafodotin-containing groups than in the control groups (98% vs. 89% for DREAMM-7 and 95% vs. 86% for DREAMM-8).

Regarding permanent discontinuation of any study treatment, the highest frequency was reported in BVd arm of DREAMM-7 (31%), compared to 15% in BPd arm and 14% in pooled monotherapy data. Discontinuation of belantamab mafodotin due to AEs was reported in 19% in the BVd group, 16% in the BPd group, and 14% in the monotherapy pooled data, respectively.

Discontinuation

In DREAMM-7 the most common non-ocular AEs leading to any study treatment discontinuation in the BVd group were related to peripheral neuropathy (peripheral sensory neuropathy 5%, neuropathy peripheral 2%, polyneuropathy 3%), pneumonia (4%), and other infections (COVID-19, COVID-19 pneumonia, sepsis <1%-1%). In DREAMM-8 the most common non-ocular AEs leading to any study treatment discontinuation in the BPd group were fatigue, muscular weakness, and neuralgia (1% each).

The permanent treatment discontinuations due to corneal events were rare. In both DREAMM-7 and DREAMM-8, 9% of participants discontinued belantamab mafodotin due to KVA or CTCAE event. Ocular toxicity led to drug discontinuation in 3% of monotherapy participants.

AEs leading to dose reduction or dose delays

The incidence of AEs leading to dose reduction of belantamab mafodotin was higher in the combination therapy studies (69% in BVd group and 58% in BPd group) than in the pooled monotherapy studies (36%), as was the incidence of dose interruption / delay.

In DREAMM-7 in BVd arm, by PT the most frequently reported non-ocular AEs leading to dose reductions of any study treatment in the BVd group were thrombocytopenia (28%), peripheral sensory neuropathy (14%), neuropathy peripheral (10%), platelet count decreased (9%), and insomnia (5%). In DREAMM-8 in BPd arm these were neutropenia (14%), neutrophil count decreased (10%), fatigue (7%), muscular weakness (7%), and insomnia (6%).

In DREAMM-7 the most frequently reported non-ocular AEs leading to dose interruptions/delays of any study treatment in the BVd group were thrombocytopenia (35%), COVID-19 (15%) and upper respiratory tract infection (11%). In DREAMM-8 these were COVID-19 (28%), neutropenia (23%), pneumonia (17%), and upper respiratory tract infection (13%).

Dose delays and modifications because of corneal events (GSK/KVA) or symptoms (CTCAE) were common. The incidence of dose modifications because of ocular toxicity was higher in the belantamab mafodotin-containing regimens. After experiencing the first occurrence of a KVA grade ≥2, 91% and 92% of participants continued treatment. Dose reductions due to an ocular symptom (CTCAE grade) were reported in 17% of pooled participants, and dose interruptions/delays in 58% of participants. Ocular symptoms (CTCAE grade) resolved in 48% of participants with an event.

When treatment is withheld, normal renewal of the corneal epithelium allows for regression of the lesions. Consequently, a change in the dosing frequency can be used as a strategy for the management of ocular toxic effects associated with belantamab mafodotin. The applicant’s view, that dose modification as recommended in the study protocols (delay and/or reduction), based on the participant’s tolerability of belantamab mafodotin, appears to be the most effective approach to

optimise belantamab mafodotin therapy, is supported. These are reflected accordingly in section 4.2 of the SmPC.

2.6.10. Conclusions on the clinical safety

Belantamab mafodotin containing triplet therapies are impacted by AEs which are notably higher compared to belantamab mafodotin monotherapy. Ocular events were the most frequently reported safety events in the belantamab mafodotin groups and were mostly managed with dose modifications and treatment delays. Warnings for this risk are included in the SmPC and together with the prescribers' guidance and educational material for patients it is expected that this risk can be adequately managed.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 51. Summary of safety concerns

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

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 52. Summary table of risk minimisation measures by safety concern

Safety concern	**Risk Minimisation Measures**

Corneal examination findings (including keratopathy), potentially resulting in vision changes	**Routine risk minimisation measures**: The following SmPC sections include guidance for ocular adverse reactions: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects PIL sections: 2. What you need to know before you take Belantamab Mafodotin 4. Possible side effects Prescription only medicine Use restricted to physicians experienced in the use of anticancer medicinal products. **Additional risk minimisation measures:** Educational Materials for Healthcare Professionals and Patients

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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 IBD is 17 April 2025. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

2.9.2. 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 is a biological product.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is submitting a Marketing Authorization Application of belantamab mafodotin, for the treatment of adults with relapsed or refractory multiple myeloma:

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

and

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

3.1.2. Available therapies and unmet medical need

Much progress has been made over the past decade in the understanding of myeloma disease biology and individualised treatment approaches. Several new classes of drugs have been added to the traditional armamentarium (corticosteroids, alkylating agents and anthracyclines) and, along with high-dose therapy and autologous haemopoietic stem cell transplantation, have led to deeper and durable clinical responses. Furthermore, CAR-T therapies are now approved at second and third lines. In addition, several bispecifics are currently approved for patients who have received 4 or more lines of therapy.

There are several treatment options available for initial treatment of MM, as well as for treatment of relapsed disease. A number of different combination regimens have been studied in clinical trials in these settings. Despite this, there remains a need for expanding the therapeutic armamentarium with more treatment options, especially for the increasing number of patients who have received 1 or more prior line/s of therapy and are exposed or refractory to standard agents like PIs, lenalidomide, and anti-CD38 antibodies.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is derived from two phase 3 studies: DREAMM-7 and DREAMM-8.

DREAMM-7

A total of 494 participants with RRMM with at least 1 prior line of therapy, were randomized to evaluate the efficacy and safety of the combination of belantamab mafodotin, bortezomib, and dexamethasone (BVd) compared with the combination of daratumumab, bortezomib and dexamethasone (DVd).

Belantamab mafodotin was administered IV at the dose of 2.5 mg/kg on Day 1 of every 21-day cycle in combination with Vd for the first 8 cycles. From Cycle 9 onwards, belantamab mafodotin was administered as monotherapy. Subjects were randomized 1:1 to BVd or DVd. Randomization was stratified by number of lines of prior therapy, prior bortezomib use and R-ISS stage. PFS was the primary endpoint.

DREAMM-8

A total of 302 participants with RRMM, previously treated with at least 1 prior line of therapy including a lenalidomide-containing regimen, were randomized to evaluate the efficacy and safety of the combination belantamab mafodotin, pomalidomide and dexamethasone (BPd) compared with pomalidomide, bortezomib and dexamethasone (PVd) in participants.

Belantamab mafodotin was administered IV at a single dose of 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2 onwards in each 28-day cycle. Subjects were randomized 1:1 to BPd or PVd. Subjects were stratified based on the number of prior lines of therapy, prior bortezomib use; initially ISS stage at screening (I vs. II/III) was a third stratification factor, which was replaced by prior anti-CD38 treatment. PFS was the primary endpoint.

3.2. Favourable effects

DREAMM-7

The PFS assessed by IRC showed a statistically significant benefit of BVd compared to DVd, as demonstrated by an HR of 0.41 (95% CI: 0.31, 0.53; p <0.00001). The median PFS was longer in the BVd group at 36.6 months (95% CI: 28.4, NR) vs. 13.4 months (95% CI: 11.1, 17.5) in the DVd group.

A statistically significant OS benefit continued to favour the BVd group vs. the DVd group with an HR of 0.58 (95% CI: 0.43, 0.79; p-value=0.00023). This is based on updated OS data with DCO date of 07 October 2024 (IA2).

A statistically significant increase of MRD negativity rate was observed in favour of the BVd group at the time of the primary PFS analysis (24.7% vs. 9.6%, p-value < 0.00001).

DREAMM-8

The PFS assessed by IRC showed a statistically significant benefit of BPd compared to PVd. The median PFS was not reached in the BPd treatment arm and was 12.7 months in the PVd treatment arm (95% CI: 9.1, 18.5), with a HR of 0.52 (95% CI: 0.37, 0.73; p-value <0.001).

A positive trend in OS in favour of the BPd group was observed at the time of the PFS the data cut-off (HR 0.77; 95% CI 0.53, 1.14). Median OS was not reached in either treatment group. OS data have reached 34.77% (105/302 participants) overall maturity and IF equal to 48.39% (105/217).

The proportion of all participants who achieved MRD negativity was higher in the BPd group compared with the PVd group at the time of primary PFS analysis (23.9% vs. 4.8%).

3.3. Uncertainties and limitations about favourable effects

A major limitation in this application is the modification of the study design of both pivotal studies with several amendments after study initiation. This raise concerns related to the internal validity of the study and the potential compromise of the integrity of the data of both open label, pivotal studies.

However, the provided scientific justification and reasons for the performed multiple protocol changes in both studies are considered to be acceptable.

The subgroup of elderly patients (>75 years) is very limited in both clinical studies, and consistency of the treatment effect in this relevant subgroup cannot be confirmed. In clinical practice treatment decisions need to be made individually based patient and disease characteristics, especially for elderly / frail patients.

Dose selection was based on very limited clinical data. The treatment was poorly tolerated. Dose delays of Blenrep occurred in 88% of patients in DREAMM-7 and in 93% of patients in DREAMM-8. Of those patients, approximately 2/3 experienced ≥ 3 dose delays with a median duration of delay of nearly 8 weeks. The impact of recommended extensive dose reductions on efficacy is difficult to assess due to limited data. Importantly, the tolerability may be even lower in clinical practice, as the target population (elderly, burdened with co-morbidities) was underrepresented in the clinical trials.

DREAMM-8 (BPd)

PFS is currently the only formally positive efficacy endpoint supporting the efficacy of BPd compared to PVd.

OS-data is currently immature. Follow up for OS is ongoing and the CHMP recommended that data updates from this study should be submitted when available.

3.4. Unfavourable effects

AEs were reported in all patients in DREAMM-7 treated with BVd or DVd and in DREAMM-8 in 99.3% of patients in BPd arm and 96% in PVd arm. In BVd arm 95% of AEs were of grade ≥3 and in BPd arm 91%, respectively. These frequencies are higher than grade ≥3 AEs in comparator arms: 76% in DVd arm in DREAMM-7 and 73% in PVd arm in DREAMM-8.

The most frequent adverse reactions (≥20%) in BVd arm (DREAMM-7) were reduced visual acuity (89%), thrombocytopenia (87%), corneal examination findings (86%), blurred vision (66%), dry eye (51%), photophobia (47%), foreign body sensation in eyes (44%), eye irritation (43%), eye pain (32%), diarrhoea (32%), and upper respiratory tract infection (20%).

The most frequent adverse reactions (≥20%) in BPd (DREAMM-8) included reduced visual acuity (91%), corneal examination findings (87%), blurred vision (79%), neutropenia (63%), foreign body sensation in eyes (61%), dry eye (61%), thrombocytopenia (55%), eye irritation (50%), photophobia (44%), eye pain (33%), fatigue (27%), upper respiratory tract infection (27%), pneumonia (24%), anaemia (23%), and diarrhoea (23%).

10% (n=23) of patients in BVd arm of DREAMM-7 died due to a fatal SAE and 11% (n=17) in BPd arm in DREAMM-8. Pneumonia and COVID-19 related illness were most frequently reported fatal SAEs.

AEs led to permanent discontinuation of any study treatment in 31% of patients in BVd arm of DREAMM-7 and in 15% in BPd arm of DREAMM-8. AEs leading to dose interruption/delay were very frequent (94% in BVd, 91% in BPd), as also AEs leading to dose reduction (75% in BVd, 61% in BPd). Thus, belantamab mafodotin based treatment requires frequent dose modifications and the SmPC contains extensive warnings to guide physicians according to the severity of the AE.

3.5. Uncertainties and limitations about unfavourable effects

In DREAMM-7 and in DREAMM-8 the AE profile of belantamab mafodotin is affected by previous treatment the patients have been exposed to. Further, as belantamab mafodotin is administered in

triplet combinations, it is not always possible to disentangle belantamab mafodotin specific AEs from AEs caused by bortezomib, pomalidomide or dexamethasone. These combination partners could aggravate some toxicities from belantamab mafodotin and belantamab mafodotin could aggravate toxicities from standard medicinal products. Furthermore, many AEs overlap with manifestations of multiple myeloma (e.g., infections).

The patients in DREAMM-7 and DREAMM-8 are likely to differ from patients treated in everyday clinical practice, typically with a higher burden of comorbidities and of higher ECOG. E.g., patients with current corneal epithelial disease except for mild punctate keratopathy, cardiovascular risk, or active renal condition were excluded.

3.6. Effects Table

Table 53. Effects Table for belantamab mafodotin in RRMM in combination with bortezomib and dexamethasone (data cut-off: DREAMM-7, 2 October 2023) and in combination with bortezomib and dexamethasone (data cut-off: DREAMM-8, 29 January 2024).

Effect	Short Description	Unit	BVd (n=242) BPd (n=150)	DVd (n=246) PVd (n=145)	Uncertainties/ Strength of evidence	Reference
Favourable Effects						
PFS	Median time from randomisation to first disease progression (according to the IMWG response criteria) or death	Months (95%CI)	36.6 (28.4, NR) NR (20.6, NR)	13.4 (11.1,17.5) 12.7 (9.1, 18.5)	HR: 0.41 (0.31,0.53), p<0.00001 (DREAMM-7) Supported by significant OS/DREAMM-7 HR: 0.58 (0.43, 0.79) HR: 0.52 (0.37, 0.73) p<0.001 (DREAMM-8) OS immature, but no sign of detrimental effect: DREAMM-8 HR: 0.77 (0.53, 1.14) Consistent results from secondary endpoints	DREAMM-7 & DREAMM-8
Effect	**Short Description**	**Unit**	**BVd (n=242) + BPd (n=150)**	**DVd (n=246) + PVd (n=145)**	**Uncertainties/ Strength of evidence**	**Reference**
Unfavourable Effects						
Eye disorders	All events	%	84 (80% BVd, 91% BPd)	38 (38% DVd 37% PVd)	Known class effect for MMAF-containing ADCs Grade ≥3 42% vs. 6%	DREAMM-7 & DREAMM-8, pooled data
Thrombo-			75	56	Grade ≥3 59% vs 40%	

cytopenia			(87% BVd, 55% BPd)	(65% DVd, 41% PVd)		
Infections and infestations			75 (70% BVd, 82% BPd)	68 (67% DVd, 68% PVd)	Grade ≥3 38% vs 22%	

Abbreviations: BVd = belantamab mafodotin, bortezomib, dexamethasone; BPd = belantamab mafodotin, pomalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; PFS = Progression free survival; IMWG= International Myeloma Working Group; HR = Hazard ratio; CI = Confidence Interval; MMAF=Monomethyl auristatin-F; ADC=Antibody-drug conjugate

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Statistically significant improvements in terms of PFS were demonstrated in both studies, DREAMM-7 and DREAMM-8, even though in the latter, median PFS in the BPd treatment arm was not reached.

OS is also an important endpoint in demonstration of clinical benefit. For DREAMM-7, a statistically significant OS benefit favours the BVd group vs. the DVd. For DREAMM-8, the available data is limited but do not indicate a detrimental effect for patients exposed to belantamab mafodotin.

These improvements are considered clinically relevant, particularly in a targeted second line patient population. Despite multiple available treatment options, there is a need for new therapies with different MoA in clinical practice to overcome resistance to prior therapies.

The safety profile of belantamab mafodotin is well characterised. Overall, the toxicity from belantamab mafodotin containing triplets is higher than from SoC combinations which is not unexpected due to the additive effects in the triplet regimen. AEs can be at least partly mitigated with monitoring and dose modifications.

The important safety concerns with belantamab mafodotin containing triplets include ocular disorders, thrombocytopenia) and infections.

The most distinct safety concern are eye disorders, a class effect of MMAF-containing ADCs. In DREAMM-7 and DREAMM-8, the majority of patients treated with belantamab mafodotin developed ocular symptoms. Most events were grade 2-3 and AEs resolved with adequate follow-up, with a median resolution time of approximately 3 months. Toxicity to the ocular surface is of concern and can largely impact the quality of life of the patients.

However overall, the safety profile of belantamab mafodotin can be considered manageable considering the additional risk minimisation measures in order to raise awareness of the ocular and other safety aspects to the patient and the treating physician.

3.7.2. Balance of benefits and risks

The improvement in PFS in both studies is considered clinically relevant and supported by several secondary endpoints.

The safety database and the patient exposure is considered sufficient to assess the risk profile in the target population. The safety profile can be considered manageable in the target population which

close monitoring and frequent modifications of the treatment plan and the warnings in the product information and the educational material.

3.8. Conclusions

The overall benefit/risk balance of Blenrep in combination with bortezomib and dexamethasone and pomalidomide and dexamethasone in adults for the treatment of relapsed or refractory multiple myeloma who have received at least one prior therapy including lenalidomide is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Blenrep is not similar to Ninlaro, Kyprolis, Farydak, Darzalex, Abecma, Carvykti and Talvey within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

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(s):

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

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

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 marketing authorisation holder (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**

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

The MAH shall ensure that in each Member State where Blenrep is marketed, all healthcare professionals who are expected to prescribe, or dispense Blenrep, and patients who receive Blenrep have access to/are provided with the following educational materials to be disseminated in line with NCA agreed implementation pathways:

- Educational materials for healthcare professionals
- Patient education materials
- Patient card

The educational materials for healthcare professionals contains the following key messages:

- Detailed information on the ocular effects of belantamab mafodotin, including proper grading
- Description of required ocular exams for patients receiving belantamab mafodotin before each of the first 4 doses of belantamab mafodotin, and as clinically indicated thereafter:
    - Slit lamp examination to provide detailed information on the impact of belantamab mafodotin on the eye, including corneal examination, findings such as superficial punctate keratopathy, microcyst-like epithelial changes and haze, with or without changes in visual acuity.
    - Measurement of best corrected visual acuity to provides a measure of the impact of any corneal exam findings on the visual acuity.
- Key messages to convey during patient counselling:
    - Advise to patients that ocular adverse reactions may occur during treatment.
    - Patients should be advised to administer preservative-free artificial tears at least 4 times a day during treatment.
    - Patients should avoid using contact lenses until the end of treatment.
    - Patients should consult their haematologist/oncologist if ocular adverse reactions occur.

The patient educational materials contains the following key messages:

- Description of eye problems reported with belantamab mafodotin which may occur during treatment.
- Eye exams should be performed before each of the first 4 doses of belantamab mafodotin, and as clinically indicated thereafter.
- Basic details on the anatomy and physiology of the eye and a description of eye exams.

- Patients experiencing eye-related problems may require a dose adjustment to their treatment with belantamab mafodotin, which means either reducing the dose or changing the time between the doses. Your doctor might also ask you to see an eye care professional.
- Tell your haematologist/oncologist about any history of vision or eye problems.
- If you experience changes with your vision whilst on belantamab mafodotin, contact your haematologist/oncologist.
- Your doctor will ask you to use eye drops called preservative-free artificial tears during treatment. Administer them as instructed.
- Trackers for eye drops and appointments.

The patient card contains the following key messages:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.