

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761158Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

## NDA/BLA Multi-disciplinary Review and Evaluation

**Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.**

<b>Application Type</b>	BLA
<b>Application Number(s)</b>	761158
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	December 5, 2019
<b>Received Date(s)</b>	December 5, 2019
<b>PDUFA Goal Date</b>	August 5, 2020
<b>Division/Office</b>	Division of Hematologic Malignancies II/Office of Oncologic Diseases
<b>Review Completion Date</b>	August 5, 2020
<b>Established Name</b>	BLENREP
<b>(Proposed) Trade Name</b>	Belantamab mafodotin-blmf
<b>Pharmacologic Class</b>	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
<b>Code name</b>	GSK2857916
<b>Applicant</b>	GlaxoSmithKline Intellectual Property Development Ltd. England
<b>Formulation(s)</b>	For injection: 100 mg as a lyophilized powder in a single-dose vial for reconstitution and dilution
<b>Dosing Regimen</b>	2.5 mg/kg as an intravenous infusion over approximately 30 minutes once every 3 weeks
<b>Applicant Proposed Indication(s)/Population(s)</b>	(b) (4) for the treatment of adult patients with relapsed and refractory multiple myeloma (b) (4)
<b>Recommendation on Regulatory Action</b>	Accelerated Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	For the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

## Glossary

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ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
AST	Aspartate aminotransferase
BCMA	B-cell maturation antigen
BCVA	Best Corrected Visual Acuity
BLA	Biologics License Application
BLRM	Bayesian Logistic Regression Modeling
BTD	Breakthrough Therapy Designation
CBR	Clinical Benefit Rate
CD38	Cluster of Differentiation 38
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence interval
CIC	Circulating Immune Complexes
CMC	Chemistry, manufacturing, and controls
CPK	Creatinine Phosphokinase
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Event
cys-mcMMAF	Cysteine maleimidocaproyl monomethyl auristatin F
DDI	Drug-drug interaction
Dex	Dexamethasone
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee

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DoR	Duration of Response
DP	Drug product
DRd	Darzalex + Revlimid + dexamethasone
DREAMM	Driving Excellence in Multiple Myeloma
DVd	Darzalex + Velcade + dexamethasone
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMH	Extramedullary hematopoiesis
EO	Extra-orbital
EORTC	European Organization for Research and Treatment of Cancer
EoT	End of Treatment
EPd	Empliciti + Pomalyst + dexamethasone
ERd	Empliciti + Revlimid + dexamethasone
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FTIH	First-Time-in-Human
FVd	Farydak + Velcade + dexamethasone
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GLP	Good Laboratory Practice
GRO	Growth-Regulated Oncogene
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCEC	Human corneal epithelial cells
hERG	Human ether-à-go-go-related gene
HR	Hazard ratio
HRQoL	Health-Related Quality-of-Life
IA	Interim analysis
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IFN- $\gamma$	Interferon gamma
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug
IP	Intraperitoneal

IRC	Independent Review Committee
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
Ixaz	Ixazomib
KC	Keratinocyte chemoattractant
KC/GRO	Keratinocyte chemoattractant/growth-regulated oncogene
Kd	Kyprolis + dexamethasone
KIM-1	Kidney injury molecule-1
KRd	Kyprolis + Revlimid + dexamethasone
Len	Lenalidomide
Lyo	Lyophilized
mAb	Monoclonal antibody
MCP-1	Monocyte chemoattractant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MM	Multiple myeloma
MMAE	Monomethyl auristatin E
MMAF	Monomethyl auristatin F
mPFS	Median Progression-Free Survival
MR	Minimal Response
MRD	Minimal Residual Disease
MRP	Multidrug resistance-associated proteins
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
N-CRM	Neuenschwander continual reassessment method
NDA	New Drug Application
NE	Not Evaluable
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire
NK	Natural Killer
NME	New Molecular Entity
NQ	Non-quantifiable
OATP	Organic anion-transporting polypeptides
ODD	Orphan Drug Designation
OECD	Economic Cooperation and Development
OPQ	Office of Pharmaceutical Quality
ORR	Overall Response Rate
OS	Overall Survival
OSDI	Ocular Surface Disease Index
OSE	Office of Surveillance and Epidemiology

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OSI	Office of Scientific Investigation
P	Pomalyst
PD	Pharmacodynamics
Pd	Pomalyst + dexamethasone
PD	Progressive Disease
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI	Proteasome inhibitor
PK	Pharmacokinetic
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PP	Per protocol
PPI	Patient package insert
PR	Partial Response
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PT	Preferred term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire Multiple Myeloma Module
QoL	Quality of life
RAP	Reporting and Analysis Plan
RCT	Randomized controlled trial
Rd	Revlimid + dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
RP2D	Recommended Phase 2 Dose
RPTEC	Renal proximal tubule epithelial cells
RRMM	Relapsed/refractory multiple myeloma
RTOR	Real-Time Oncology Review
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent Complete Response
SCS	Summary of Clinical Safety
SD	Stable Disease
SOA	Schedule of Activities
SOC	Standard of care
SOC	System Organ Class
SRM	Study Reference Manual
T <sub>1/2</sub>	Serum half life
TEAE	Treatment emergent adverse event
TK	Toxicokinetic
TNF	Tumor Necrosis Factor

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TTP	Time to Progression
TTR	Time to Response
UABV	Urinary albumin excretion
US	United States
USPI	U.S. Prescribing Information
UTPV	Urinary total protein
Vd	Velcade + dexamethasone
VGPR	Very Good Partial Response
Vss	Volume of distribution
WOCBP	Woman of Childbearing Potential
WRO	Written Responses Only

## 1. Executive Summary

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### 1.1. Product Introduction

**Drug:** Belantamab mafodotin (BLENREP)

**Pharmacological Class:** Belantamab mafodotin-blmf is an antibody-drug conjugate (ADC) consisting of an anti-BCMA (B-cell maturation antigen) IgG1 monoclonal antibody conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF, also known as mafodotin).

**Proposed Indication:** (b) (4) for the treatment of adult patients with relapsed and refractory multiple myeloma (b) (4)

**Dosing Regimen:** 2.5 mg/kg as an intravenous (IV) infusion over approximately 30 minutes once every 3 weeks (Q3W).

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of belantamab mafodotin for the following indication:

*Belantamab mafodotin is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.*

This recommendation is based on the observed response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Accelerated approval for belantamab mafodotin is based on the results of the pivotal DREAMM-2 study. DREAMM-2 is a phase 2, open-label, two-arm, multicenter study in patients with relapsed/refractory multiple myeloma (RRMM) who had received at least 3 prior lines of therapy that included a proteasome inhibitor (PI), an immunomodulatory agent and an anti-CD38 monoclonal antibody (mAb). Patients received belantamab mafodotin at a dose of 2.5 mg/kg or 3.4 mg/kg IV every 3 weeks on Day 1 of each 21-day cycle. A total of 95 patients received BLENREP at the recommended dose of 2.5 mg/kg administered intravenously once every 3 weeks. The median age was 65 years (range: 39 to 85 years). Patients in the 2.5 mg/kg dose cohort had received a median of 7 prior lines of therapy; 95% of patients in the 2.5 mg/kg cohort received 4 or more prior lines of therapy.

The primary efficacy endpoint was overall response rate (ORR) assessed by an Independent

Review Committee (IRC), defined as the percentage of patients with a confirmed partial response (PR) or better per International Myeloma Working Group (IMWG) criteria supported by the duration of response (DoR). The ORR in the 2.5 mg/kg treatment group was 31% (97.5% CI: 20.8, 42.6). At the time of data cut-off with a median follow-up of 6.3 months, the median DoR was not reached. Seventy-three percent of responders had a DoR  $\geq$  6 months.

The key safety concern for belantamab mafodotin is ocular toxicity. Other safety concerns include thrombocytopenia, and infusion-related reactions. Recommendations are included in the Warnings and Precautions section of the belantamab mafodotin U.S. Prescribing Information (USPI) to mitigate the risks for these toxicities, and further mitigation strategies for ocular toxicity are discussed below.

Ocular toxicity observed with belantamab mafodotin includes changes in the corneal epithelium (keratopathy) and changes in visual acuity identified on ophthalmic exam, and symptoms such as dry eye and blurred vision. The majority of patients (71%) had at least one event of keratopathy and 44% of patients had an event of severe keratopathy. Other ocular symptoms were only present in 43% of patients with keratopathy, raising the concern that keratopathy could go undetected in the absence of close monitoring. Therefore, close monitoring with ophthalmic exams at baseline and prior to each dose of belantamab mafodotin is necessary to ensure appropriate dose modifications are implemented to mitigate the risks of ocular toxicity. Patients who received the 3.4 mg/kg lyophilized presentation (n=24) also had higher rates of keratopathy (92% vs. 77%) and severe keratopathy (77% vs. 41%) compared to patients who received the 3.4 mg/kg frozen presentation. There is no data with the proposed 2.5 mg/kg to be marketed lyophilized presentation of belantamab mafodotin.

The USPI will include a Boxed Warning to communicate the risks of ocular toxicity and need for ophthalmic monitoring and dose modifications. In addition, a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) will be in place to ensure the risks of ocular toxicity with belantamab mafodotin can be adequately managed in the post-marketing setting. The REMS with ETASU for belantamab mafodotin will require certification of health care facilities and prescribers, enrollment of patients and counseling regarding the risk for ocular toxicity and need for ophthalmic monitoring, and verification that patients are authorized to receive belantamab mafodotin based on documentation of the required ophthalmic exams.

A post-marketing requirement (PMR) will be issued to submit the final study report and datasets from a randomized phase 3 clinical trial to verify and describe the clinical benefit of belantamab mafodotin in patients with RRMM. A PMR to evaluate the ocular toxicity with the lyophilized presentation will also be issued.

This Application was discussed at the Oncologic Drug Advisory Committee (ODAC) meeting on July 14<sup>th</sup>, 2020 (ODAC, 2020).

### 1.3. Benefit-Risk Assessment (BRA)

#### Benefit-Risk Summary and Assessment

Multiple myeloma is the second most common hematologic malignancy, accounting for 1.8% of all cancers and 10% of all hematologic malignancies. The diagnosis is most common in the 6th and 7th decades of life. The introduction of corticosteroids, proteasome inhibitors, immunomodulatory agents, monoclonal antibodies and stem cell transplantation has further extended median survival to 5 to 6 years. However, treatment responses are often transient and patients ultimately relapse; myeloma is not considered curable. Patients who are refractory or relapsed to an immunomodulating agent, proteasome inhibitor and CD38 monoclonal antibodies demonstrate low response rates and have poor prognosis.

Belantamab mafodotin, is a first-in-class, anti-BCMA antibody-drug conjugate with an afucosylated, humanized IgG1 anti-BCMA monoclonal antibody conjugated by a protease-resistant maleimidocaproyl linker to a microtubule-disrupting agent, monomethyl auristatin F (MMAF). The benefit-risk assessment for this BLA is primarily based on Study 205678 (DREAMM-2). DREAMM-2 is an open-label, multicenter trial evaluating two dose cohorts of belantamab mafodotin in patients with RRMM myeloma who had received at least 3 prior lines of therapy that included PI, an immunomodulatory agent and an anti-CD38 mAb. Patients received belantamab mafodotin at a dose of 2.5 mg/kg or 3.4 mg/kg IV every 3 weeks on Day 1 of each 21-day cycle. Patients in the 2.5 mg/kg cohort had received a median of 7 prior lines of therapy and were refractory to an anti-CD38 mAb, an immunomodulatory agent and a PI.

Efficacy was based on the primary endpoint of overall response rate (ORR) determined by an independent review committee (IRC) supported by DoR. The ORR (PR or better, as assessed by the IRC) in the 2.5 mg/kg cohort was 31% (97.5% CI: 20.8, 42.6). At the time of data cut-off for the primary analysis, with a median follow-up of 6.3 months, the median DoR was not reached. Seventy-three percent of responders had a DoR  $\geq$ 6 months. The efficacy in the proposed patient population represents a treatment benefit.

The primary safety concern with belantamab mafodotin is the risk of ocular toxicity.

- Keratopathy was the most frequently reported toxicity with belantamab mafodotin, with an overall incidence of 71%, and 44% of patients experiencing at least one episode of severe keratopathy at the 2.5 mg/kg dose level.

- Treatment with belantamab mafodotin was also associated with a clinically significant decline in visual acuity, including severe vision loss.
- Not all patients with keratopathy had associated ocular symptoms like blurred vision or dry eye. In the absence of close monitoring with frequent ophthalmic exams and appropriate management, keratopathy could go undetected, especially in earlier stages, and patients could develop severe corneal ulcers that may require corneal transplant.
- Higher rates of ocular toxicity were noted in the 24 patients who received the 3.4 mg/kg lyophilized presentation of belantamab mafodotin in the DREAMM-2 trial. There is no efficacy or safety data with the to be marketed 2.5 mg/kg lyophilized presentation. Patients who received the 3.4 mg/kg lyophilized presentation also had higher rates of keratopathy (92% vs. 75%) and keratopathy events leading to dose modifications (71% vs. 51%).
- The mechanism of keratopathy and ocular toxicity with belantamab mafodotin has not been fully characterized.

The USPI will include a Boxed Warning that belantamab mafodotin caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes. The USPI will also include instructions to conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. The ocular toxicity as reported in the DREAMM-2 study with belantamab mafodotin is a unique toxicity among anti-myeloma agents. The review team has determined that the risk of ocular toxicity cannot be mitigated only with accurate labeling and routine oncology care. A risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is necessary to ensure the risks of ocular toxicity with belantamab mafodotin can be adequately managed in the post-marketing setting.

Infusion-related reactions and thrombocytopenia are other important safety concerns. Dose modifications to mitigate the risks of these toxicities are included in the Warnings and Precautions section in the USPI.

Based on the benefit for belantamab mafodotin in conjunction with the REMS with ETASU to mitigate the risk of ocular toxicity and the information in the USPI, the benefit-risk assessment supports approval of belantamab mafodotin for the treatment of adult patients with RRMM who have received at least 4 prior therapies including an anti-CD38 mAb, a PI, and an immunomodulatory agent.

A post-marketing requirement (PMR) will be issued to submit the final study report and datasets from a randomized phase 3 clinical trial to verify and describe the clinical benefit of belantamab mafodotin in patients with relapsed or refractory multiple

myeloma. A PMR to evaluate the ocular toxicity with the lyophilized presentation and an additional PMR to further characterize the ocular toxicity will also be issued.

The benefit-risk of belantamab mafodotin in the proposed patient population in the context of the ocular toxicity was discussed at the Oncologic Drug Advisory Committee (ODAC) meeting on July 14<sup>th</sup> (ODAC, 2020).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Multiple myeloma (MM) is the second most common hematologic malignancy and accounts for 1.8% of all cancers and 10% of all hematologic malignancies.</li> <li>Therapy for patients with relapsed or refractory myeloma has improved considerably over the past three years with approval of multiple new therapies with improvement in response rate and progression free survival.</li> <li>However, MM remains incurable with a 5-year survival rate of 52%.</li> </ul>	Relapsed/refractory multiple myeloma (RRMM) is a serious and life-threatening condition.
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>There are multiple drugs approved for use in relapsed/refractory multiple myeloma, and combination regimens are considered standard of care.</li> <li>Potential treatments include alkylating agents, corticosteroids, immunomodulatory drugs, proteasome inhibitors (PI) and monoclonal antibodies (mAb).</li> <li>Despite availability of multiple therapies, patients eventually relapse, and MM remains incurable.</li> </ul>	There is an unmet medical need to improve the outcomes of patients with RRMM who have received multiple lines of therapy and are refractory to the commonly used classes of drugs such as a PI, an IMiD and an anti-CD38 mAb.
<a href="#">Benefit</a>	<ul style="list-style-type: none"> <li>Assessment of the clinical benefit of belantamab mafodotin was based on the efficacy results of the DREAMM-2 study.</li> <li>DREAMM-2 is phase 2, open-label, two-arm, multicenter study conducted in patients with RRMM. Patients in the 2.5</li> </ul>	<ul style="list-style-type: none"> <li>The efficacy in the proposed patient population represents a treatment benefit.</li> <li>A post-marketing requirement (PMR) to</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>mg/kg dose cohort had received a median of 7 lines of therapy and were refractory to an anti-CD38 mAb, an immunomodulatory agent and a PI.</p> <ul style="list-style-type: none"> <li>The ORR assessed by IRC for the 2.5 mg/kg dose was 31% (97.5% CI: 20.8, 42.6). At the time of data cut-off, with a median follow-up time of 6.3 months, the median duration of response (DoR) was not reached.</li> </ul>	<p>confirm the benefit of belantamab mafodotin in a randomized clinical trial in patients with relapsed or refractory MM will be issued.</p>
<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>In the 2.5 mg/kg cohort of DREAMM-2, 98% of patients had at least one treatment-emergent adverse event (TEAE), 82% of patients had a severe (Grade 3-4) TEAE, 40% of patients had a serious TEAE, and 3% of patients had a fatal TEAE. The key safety concerns for belantamab mafodotin include ocular toxicity, thrombocytopenia, and infusion-related reactions.</li> <li>The primary safety concern with belantamab mafodotin is the risk of ocular toxicity. The ocular toxicity as reported in the DREAMM-2 study with belantamab mafodotin is a unique toxicity among anti-myeloma agents.</li> <li>Ocular toxicity of keratopathy was the most frequently reported toxicity with belantamab mafodotin, with an overall incidence of 71% and was also associated with a clinically significant decline in visual acuity, including severe vision loss and corneal ulcers.</li> <li>Not all patients with keratopathy had associated ocular symptoms like blurred vision or dry eye. In the absence of close monitoring with frequent ophthalmic exams and appropriate management, keratopathy could go undetected, especially in earlier stages, and patients could develop severe corneal ulcers that may require corneal transplant.</li> </ul>	<ul style="list-style-type: none"> <li>The Warnings and Precautions in the USPI details the serious risks of the drug, including risks of ocular toxicity, infusion-related reactions and thrombocytopenia, and mitigation strategies.</li> <li>Close monitoring with ophthalmic exams at baseline and prior to each dose of belantamab mafodotin is necessary to ensure appropriate dose modifications are implemented to mitigate the risk of ocular toxicity.</li> <li>The USPI will include a Boxed Warning to communicate the risks of ocular toxicity and need for ophthalmic monitoring and dose modifications.</li> <li>A risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) will be in place to ensure the risks of belantamab</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• Patients who received the 3.4 mg/kg lyophilized presentation also had higher rates of keratopathy (92% vs. 75%), severe keratopathy (77% vs. 41%) and keratopathy events leading to dose modifications (71% vs. 51%).</li> <li>• The mechanism of keratopathy and ocular toxicity with belantamab mafodotin has not been fully characterized.</li> </ul>	<p>mafodotin can be adequately managed in the post-marketing setting.</p> <ul style="list-style-type: none"> <li>• A PMR to evaluate the ocular toxicity with the lyophilized presentation and an additional PMR to characterize the keratopathy with belantamab mafodotin will also be issued.</li> <li>• The benefit-risk of belantamab mafodotin in the proposed patient population in the context of the observed ocular toxicity was discussed at the Oncologic Drug Advisory Committee (ODAC) meeting on July 14<sup>th</sup> (ODAC, 2020).</li> </ul>

### 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
	<input checked="" type="checkbox"/> Patient reported outcome (PRO)	Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	



Bindu Kanapuru  
 Cross-Disciplinary Team Leader

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

#### The Applicant's Position:

Multiple myeloma (MM) is an incurable malignant plasma cell disorder, which is characterised by the uncontrolled proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin protein (M-protein) [Furukawa, 2015; Kumar, 2004]. Clinical features of MM include bone pain and pathologic fractures, hypercalcaemia, renal failure, anemia, thrombocytopenia, and infections [Kumar, 2004; Rajkumar, 2011].

MM accounts for 1.8% of all new cancer cases and 2.1% of all cancer deaths. About 32,110 new cases (18,130 in men and 13,980 in women) and about 12,960 deaths are estimated to occur (6,990 in men and 5,970 in women) in the United States (US) in 2019 [SEER, 2019]. A higher incidence of MM is observed among males than females (2.3 vs. 1.9 per 100,000) (Ferlay, 2018). The incidence of MM increases with age, and peaks after 65 years of age; it is rarely observed in population <45 years old [Ferlay, 2018]. Based on MM cases diagnosed from 1992 to 2015 in SEER, MM prevalence in 2015 was higher in African-Americans than in any other US race/ethnicity (African American: 0.0543%; White: 0.0334%) [SEER, 2019].

There is no single standard treatment for patients with relapsed/refractory multiple myeloma (RRMM) [Quach, 2012]. Patients with heavily pretreated MM that are daratumumab refractory have an expected median OS ranging from 6.6 to 9.3 months. The median progression-free survival (mPFS) for this population is 2.3 – 3.4 months [Pick, 2018; Gandhi, 2019]. These data indicate that while objective response can be achieved in about 30% of patients, they are usually not durable [Gandhi, 2019].

To date, 11 drugs have been approved for the treatment of MM patients in the US, 5 of which have one of their approved indications in patients with RRMM who have received at least 3 prior therapies: daratumumab, elotuzumab, bortezomib, carfilzomib, and selinexor. Of these products, carfilzomib, elotuzumab, and selinexor are approved as part of combination regimens, while bortezomib and daratumumab are approved as monotherapy. Those treatments, if applied as monotherapy, achieve an ORR of 22.9 and 29.2%, respectively, but some other products have no activity on their own and rely on combination partners for synergy (e.g., elotuzumab, selinexor) [DARZALEX USPI; EMLICITI USPI; XPOVIO USPI; VELCADE USPI; KYPROLIS USPI].

As per the FDA Guidance for Industry, *Expedited Programs for Serious Conditions – Drugs and Biologics*, a drug is not considered available therapy if granted accelerated approval based on a

surrogate endpoint and clinical benefit has not been verified by postapproval studies [FDA, 2014]. Therefore, there are currently no FDA approved available therapies for patients failing anti-CD38 therapies (e.g., daratumumab). In a single-arm trial, selinexor in combination with dexamethasone has demonstrated an Overall Response Rate (ORR) of 25% in 5<sup>th</sup> line treatment; based on these surrogate endpoint data it was granted accelerated approval [XPOVIO USPI]. Refractory MM, especially after failing all treatments, including CD38 monoclonal antibody (mAb), continues to be an area of high unmet medical need, where new therapies with novel mechanisms are necessary.

**The FDA’s Assessment:**

The Applicant states that there are no FDA-approved available therapies for patients failing anti-CD38 mAb therapies (e.g., daratumumab). Although selinexor was granted accelerated approval, and therefore is not considered an “available therapy” in terms of the qualifying criteria for determining whether a drug meets criteria for accelerated approval, selinexor is an available, FDA-approved therapy for the treatment of patients who have failed daratumumab therapy.

**2.2. Analysis of Current Treatment Options**

**The Applicant’s Position:**

Nineteen regimens (inclusive of monotherapy and combination therapies) are FDA-approved for the treatment of RRMM and are outlined in Table 1. Current National Comprehensive Cancer Network (NCCN) guidelines recommend that triplet regimens should be used as the standard therapy for patients with MM; however, elderly or frail patients may be treated with doublet regimens [Kumar, 2018]. Since the approval of daratumumab in 2015, only one medicine, selinexor, has been approved for the treatment of patients with RRMM whose disease is refractory to a proteasome inhibitor (PI), an immunomodulatory drug (IMiD) and an anti-CD38 monoclonal antibody [XPOVIO USPI].

**Table 1. Currently Available Therapies for the Treatment of RRMM**

Drug	Approval	Indication	Endpoint	Trial Design/Results
Velcade (bortezomib)	Accelerated (2003)	MM, at least 2 prior lines	ORR	Single-arm trial: ORR 28%
Velcade (bortezomib)	Regular (2005)	MM, 1-3 prior lines	TTP/OS	RCT: V vs. dex TTP: 6.2 months vs. 3.5 months (HR=0.55) OS: HR=0.57
Doxil Liposomal (doxorubicin HCl)	Regular (2007)	MM, at least 1 prior line	TTP	RCT: Doxil + V vs. V TTP: 9.3 vs. 6.5 months (HR=0.55)
Revlimid (lenalidomide) with dex	Regular (2005)	MM, at least 1 prior line	TTP	RCT: Rd vs. dex Study 1: TTP: 13.9 vs. 4.7 months (HR=0.285) Study 2: TTP: 12.1 vs. 4.7 months (HR=0.324)

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<b>Drug</b>	<b>Approval</b>	<b>Indication</b>	<b>Endpoint</b>	<b>Trial Design/Results</b>
Kyprolis (carfilzomib)	Accelerated (2012)	MM, at least 1 prior line	ORR	Single-arm trial: ORR 23%
Kyprolis with Rd	Regular (2015)	MM, 1-3 prior lines	PFS	RCT: KRd vs. Rd PFS: 26.3 vs. 17.6 months (HR=0.69)
Kyprolis with dex	Regular (2016)	MM, 1-3 prior lines	PFS	RCT: Kd vs. Vd PFS: 18.7 vs. 9.4 months
Pomalyst (pomalidomide)	Accelerated (2013)	MM, at least 2 prior lines, including len and bortez	ORR	RCT: P vs Pd ORR: 7.4% vs. 29.2%
Pomalyst (pomalidomide) with dex	Regular (2015)	MM, at least 2 prior lines, including len and PI	PFS/OS	RCT: Pd vs. dex PFS: 3.6 vs. 1.8 months (HR=0.45) OS: 12.4 vs. 8.0 months (HR=0.70)
Farydak (panobinostat) with Vd	Accelerated (2015)	MM, at least 2 prior lines, including bortez and IMiD	PFS	RCT: FVd vs. Vd PFS: 10.6 vs. 5.8 months (HR=0.52)
Ninlaro (ixazomib) with Rd	Regular (2015)	MM, at least 1 prior line	PFS	RCT: Ixaz + Rd vs. placebo + Rd PFS: 20.6 vs. 14.7 months
Darzalex (daratumumab)	Accelerated (2015)	MM, at least 3 prior lines, including PI and IMiD	ORR	Single-arm trial ORR: 29% (median 5 prior lines of therapy)
Darzalex with Rd	Regular (2016)	MM, at least 1 prior line	PFS	RCT: DRd vs. Rd PFS: NE vs. 18.4 months (HR=0.37) ORR: 91.3%
Darzalex with Vd	Regular (2016)	MM, at least 1 prior line	PFS	RCT: DVd vs. Vd PFS: NE vs. 7.2 months (HR=0.39) ORR: 79.3% (median 2 prior lines of therapy)
Darzalex with Pd	Regular (2017)	MM, at least 2 prior lines, including len and PI	ORR	Single-arm trial ORR: 59.2% (median 4 prior lines of therapy)
Empliciti (elotuzumab) with Rd	Regular (2015)	MM, 1-3 prior lines	PFS	RCT: ERd vs. Rd PFS: 19.4 vs. 14.9 months (HR=0.70)
Empliciti (elotuzumab) with Pd	Regular (2018)	MM, at least 2 prior lines, including len and PI	PFS	RCT: EPd vs. Pd PFS: 10.3 vs. 4.7 months (HR=0.54)
Ninlaro (ixazomib) with Rd	Regular (2015)	MM, at least 1 prior line	PFS	RCT: Ixaz + Rd vs. placebo + Rd PFS: 20.6 vs. 14.7 months
Xpovio (selinexor)	Accelerated (2019)	MM, at least 4 prior lines, including 2 PIs, 2 IMiDs, and anti-CD38 mAb	ORR	Single-arm trial ORR: 25.4% (median 7 prior lines of therapy)

Abbreviations: MM = multiple myeloma; ORR = overall response rate; TTP = time to progression; OS = overall survival; RCT = randomized controlled trial; V = Velcade; dex = dexamethasone; HR = hazard ratio; Rd = Revlimid + dex; PFS = progression-free

Version date: June 11, 2019 (ALL NDA/ BLA reviews)

**Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.**

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survival; KRd = Kyprolis + Rd; Kd = Kyprolis + dex; Vd = Velcade + dex; len = lenalidomide; PI = proteasome inhibitor; P = Pomalyst; Pd = Pomalyst + dex; FVd = Farydak + Velcade + dex; lxaz = ixazomib; IMiD = immunomodulatory drug; DRd = Darzalex + Revlimid + dexamethasone; NE = not estimable; DVD = Darzalex + Velcade + dexamethasone; ERd = Emlipiti + Revlimid + dexamethasone; EPd = Emlipiti + Pomalyst + dexamethasone  
(Source: FDA Multi-Discipline Review for NDA 212306, [https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2019/212306Orig1s000MultidisciplineR.pdf]; modified to include data from XPOVIO USPI.)

Although several new agents have been recently approved in the more heavily pretreated RRMM setting, there remains an unmet medical need for these patients, with room for tolerable and innovative therapies with novel mechanisms of action to be considered in the treatment armamentarium for RRMM.

**The FDA's Assessment:**

The FDA agrees with the Applicant's assessment of the current treatment options for the relevant MM population studied in the clinical studies contained in this application. In addition to the regimens listed above, the FDA notes that isatuximab in combination with pomalidomide and dexamethasone was approved in 2020 for the treatment of adult patients with MM who have received at least two prior therapies including lenalidomide and a PI. Additionally, daratumumab hyaluronidase (Darzalex Faspro) was approved in 2020 as monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.

### **3. Regulatory Background**

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#### **3.1. U.S. Regulatory Actions and Marketing History**

**The Applicant's Position:**

Belantamab mafodotin (GSK2857916) is not currently registered (or approved) in the US or in any other part of the world.

**The FDA's Assessment:**

The FDA agrees that belantamab mafodotin is not currently approved in the United States or in any other part of the world.

#### **3.2. Summary of Presubmission/Submission Regulatory Activity**

The clinical trials included in this application were conducted under IND 119333, which was opened in the US on January 31, 2014 for the treatment of patients with multiple myeloma.

Key regulatory activities relevant to the monotherapy indication in this original Biologics License Application (BLA) are summarized in Table 2.

**Table 2. Key FDA Interactions**

Date	Regulatory Activity	Details
December 2013	Pre-IND Meeting	Discuss study design, quality, and non-clinical safety to support FTIH study BMA117159 (DREAMM-1).
March 2017	Type C WRO	CMC development
June 2017	Orphan Designation	ODD number: 17-5905
October 2017	Breakthrough Therapy Designation (BTD)	BTD granted for development in multiple myeloma patients who have failed at least 3 prior lines of therapy including an anti-CD38 antibody and are refractory to a proteasome inhibitor and an immunomodulatory agent
February 2018	BTD Orientation Meeting	Discussed design of pivotal Phase 2 Study 205678 (DREAMM-2), CMC and nonclinical development
March 2018	Written Review of Protocol	Comments provided for Phase 2 study DREAMM-2 protocol synopsis
April 2018	Type B CMC- Meeting	CMC update
August 2018	Type C WRO	Clinical Pharmacology
May 2019	Type B Pre-BLA Meeting	Discuss clinical contents and organization of proposed BLA
July 2019	Type B CMC Pre-BLA Meeting	Discuss CMC contents and organization of proposed BLA

Abbreviations: IND = Investigational New Drug; FTIH = First-Time-in-Human; DREAMM = Driving Excellence in Multiple Myeloma; WRO = Written Responses Only ; CMC = Chemistry, Manufacturing, and Controls; ODD = Orphan Drug Designation; BTD = Breakthrough Therapy Designation; CD38 = Cluster of Differentiation 38; BLA = Biologics License Application.

#### **Real-Time Oncology Review (RTOR) pilot**

BLA 761158 is reviewed under the FDA's RTOR pilot program.

#### **The FDA's Assessment:**

The Applicant has adequately described the pre-submission regulatory activities related to this application.

## **4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

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#### **4.1. Office of Scientific Investigations (OSI)**

OSI conducted inspections at 3 domestic clinical sites and 2 foreign contract research organizations (CROs) in support of BLA 761158. Regulatory deficiencies were noted at one clinical site (#235365), but were not determined to be significant. OSI concluded that the study data derived from the clinical sites are considered reliable and the CROs maintained adequate oversight of the clinical trial.

#### **4.2. Product Quality**

Refer to the Office of Product Quality review for specific recommendations regarding the product quality. The FDA Product Quality review team recommended approval.

#### **4.3. Clinical Microbiology**

Refer to the Office of Microbiology review for specific recommendations regarding the drug substance and drug product microbiology. The FDA Microbiology review team recommended approval.

#### **4.4. Devices and Companion Diagnostic Issues**

Not applicable.

### **5. Nonclinical Pharmacology/Toxicology**

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#### **5.1. Executive Summary**

Belantamab mafodotin (designated as GSK2857916) is an antibody-drug conjugate (ADC) with the pharmacologic class of BCMA-directed antibody and microtubule inhibitor conjugate. The humanized antibody component (GSK2857914) of belantamab mafodotin is an IgG1 isotype, afucosylated to enhance binding to FcγR IIIa V and antibody-dependent cellular cytotoxicity (ADCC) activity. The antibody is conjugated (at the inter-chain cysteine residues) to the microtubule inhibitor, MMAF, via a protease resistant maleimidocaproyl (mc) linker. Belantamab mafodotin has an average drug-antibody ratio (DAR) of approximately 4. The target of the antibody, BCMA, is a non-glycosylated integral membrane type I protein that is preferentially expressed in mature B lymphocytes. A member of the TNFR (Tumor Necrosis Factor receptor) superfamily, BCMA binds to APRIL (A Proliferation-Inducing Ligand) and BAFF (B-cell Activating Factor), activating both the NF-Kappa B and JNK pathways. BCMA mRNA is expressed at higher levels in CD138+ plasma cells from MM patients compared to normal donors. Plasmacytoid dendritic cells (pDC) also express BCMA mRNA, but at lower levels than CD138+ plasma cells.

Belantamab mafodotin binds to cell surface BCMA and is internalized. Once inside the cell, free cytotoxic drug with the linker attached (cys-mcMMAF) is released, disrupting the microtubule network, leading to cell cycle arrest and apoptosis. Belantamab mafodotin was shown to mediate apoptosis and of BCMA-expressing tumor cells through ADCC, which enhance recruitment and activation of immune effector cells. Anti-tumor activity was observed in mouse tumor models and lasted during treatment and in some animals, up to the last measurement taken approximately 5 weeks after the last dose of the ADC.

No stand-alone safety pharmacology studies were conducted, and safety pharmacology assessments were incorporated into the GLP-compliant general toxicology studies in Wistar Han rats and cynomolgus monkeys. Increases in heart rate (16%) were observed in male monkeys after 5 weekly doses of 10 mg/kg and were considered related to their deteriorating clinical condition. Cys-mcMMAF had no detectable effect on ionic currents in human embryonic kidney (HEK)293 cells stably expressing hERG channels at concentrations up to 100  $\mu$ M.

Belantamab mafodotin was cleared slowly in animals with the half-life ranging from 4 days in monkeys to 11 days in rats. Exposures to belantamab mafodotin generally increased dose proportionally with an increase in dose level; there were no major differences in plasma exposure between males and females and no evidence of accumulation with repeated dosing. Plasma concentrations were overall comparable between belantamab mafodotin and the antibody, GSK2857914, and there was less than 3% of deconjugated cys-mcMMAF when compared to the total conjugated MMAF. The PK profile of the ADC (stability and metabolism) in humans was similar to that of the rat and monkey. The PK profile, together with the knowledge that toxicities of ADC are generally related to the small molecule (i.e. active in both rodents and non-rodents), support the use of these nonclinical species in the toxicity evaluation of belantamab mafodotin. Belantamab mafodotin could be detected in the liver, kidney, connective tissue of the eyes and eyelids, lacrimal and Harderian glands, and muscle of the eyelids in rats. Cys-mcMMAF liberated from belantamab mafodotin was detected at low levels in the liver, bone marrow, kidney, Harderian gland and extra-orbital (EO) lacrimal gland, but was not detected in the cornea, eyelid or whole eye. The T<sub>max</sub> in rats and monkeys was 0.25 to 3 hours for belantamab mafodotin; for cys-mcMMAF, it was 0.25 to 48 hours and in an elimination study in rats, cys-mcMMAF was predominantly excreted in the urine.

The only pharmacologically relevant species able to capture on-target BCMA-related toxicities for belantamab mafodotin is the cynomolgus monkey. To capture any non-specific toxicities related to the payload (MMAF), general toxicology and ocular toxicology studies were conducted in the Wistar Han rat and New Zealand White Rabbit. In the GLP compliant repeat-dose general toxicology studies, rats were dosed for 3 or 13 weeks with intravenous (IV) doses (10-minute infusion) of 0, 3, 10, or 30 mg/kg belantamab mafodotin, with 12-week recovery

periods. The 3-week and 13-week rat studies utilized weekly and every 3 weeks (q3w) dosing regimens, respectively. Monkeys were dosed in GLP-compliant repeat-dose general toxicology studies for 3 or 13 weeks with IV bolus doses of 0, 1, 3, or 10 mg/kg belantamab mafodotin, with 12-week recovery periods. Toxicities were generally observed in both species, although early mortality was only observed in monkeys administered 10 mg/kg/week of the ADC in the 13-week study. After receiving 5 doses, one male monkey was sacrificed moribund due to deteriorating clinical condition. The cause of moribundity is unclear but ADC-mediated pro-inflammatory responses may have contributed to this event. This animal presented with deposits containing monkey-specific IgG and/or M IgM in the kidney, within the blood vessels in the gastrointestinal tract, and in the Kupffer cells and/or sinusoidal lining cells in the liver.

Treatment of animals with belantamab mafodotin resulted in pro-inflammatory responses as indicated by hematology parameters (e.g. increased WBCs and/or differentials) and histopathology observations (multi-organ inflammation). Belantamab mafodotin-related toxicities were seen in the kidneys, liver, male and female reproductive organs, organs of the hematopoietic system, lung, eye, teeth, gastrointestinal tract, heart, bone (femur/femorotibial joint), mammary gland, injection site, and increased macrophages in several organs (associated with inflammatory clinical pathology changes). The kidney toxicity with proteinuria and enzymuria was the dose limiting toxicity in rats and monkeys. Vascular effects were observed in monkeys only. Prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (APTT), and hemorrhage were observed mainly in monkeys after single (i.e., before ADA and immune complex development) and repeated doses. Dose-dependent bone marrow suppression was observed in rats, with increased incidence and severity when rats were dosed weekly x 3 than q3w x 13. Toxicity findings were generally reversible at tolerated doses, except for progressive lung toxicity and effects on testes/epididymides and male pituitary gland in rats. Several findings were observed with studies conducted with the free payload in pilot or GLP toxicology studies; inflammatory effects were seen in daily x 5 studies conducted with the payload in rats and monkeys (Studies 1019-010 and 1019-009; data not presented in this review).

Reproductive and developmental studies were not conducted since cytotoxic (i.e. genotoxic) drugs such as belantamab mafodotin which target rapidly dividing cells, are expected to be embryo/feto toxic and teratogenic. This position is consistent with the ICH S9 guidance.

The linker-payload, cys-mcMMAF, was not genotoxic in GLP in vitro studies (Ames test and in vitro mammalian cell) or in an in vivo rat bone marrow micronucleus study measuring micronuclei in polychromatic erythrocytes. The Applicant notes that the negative results may be due to the low cell permeability of MMAF (due to its charged C-terminal phenylalanine). In a non-GLP study, belantamab mafodotin was genotoxic in an in vitro micronucleus screening assay in human lymphocytes, with a statistically significant increase in the number of micronucleated binucleate cells that exceeded the laboratory control range. MMAE, also a

monomethyl auristatin, was positive in a rat bone marrow micronucleus genetic toxicology study (letter of authorization to this data has been included, see Section 5.2). The genotoxic risk for belantamab mafodotin will be included in labeling. Because the genotoxicity of belantamab mafodotin is through an aneugenic mechanism, it will support a contraception duration of  $5 \times T_{1/2} + \text{one month}$  (4 months) in females, after the last dose. The recommendation for duration of contraception in males for genotoxic drugs is 6 months. These recommendations are based on the FDA guidance, *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry*.

The effects on male reproductive organs occurred at doses  $\geq 10 \text{ mg/kg}$  every 3 weeks in rats and  $10 \text{ mg/kg/week}$  in monkeys. The Week 3/4 AUCs at these doses from the 3- and 13-week general toxicology studies in rats and monkeys were  $26,000 \text{ hr} \cdot \mu\text{g/mL}$  and  $21,600 \text{ hr} \cdot \mu\text{g/mL}$ , respectively. Female reproductive organ toxicity was observed at doses  $\geq 10 \text{ mg/kg/week}$  in the 3-week repeat dose toxicology study in rats (Week 3/4 AUC =  $17,500 \text{ hr} \cdot \mu\text{g/mL}$ ). The animal:human safety margins for these toxicities at  $\sim 20,000$  to  $25,000 \text{ hr} \cdot \mu\text{g/mL}$  in animals, based on human exposure of  $4,666 \text{ hr} \cdot \mu\text{g/mL}$  at the recommended dose of  $2.5 \text{ mg/kg}$ , provide  $\sim 4$ -fold margins, which will be communicated in labeling.

Also included in labeling were recommendations for nursing mothers for how long to wait to breastfeed after the last dose. A recommendation of  $5 \times T_{1/2}$  rounded up to 3 months was included in Section 8.2 of the package insert.

Other toxicity studies showed GSK2857914 to cause cytokine release, with  $\text{IFN-}\gamma$  and  $\text{TNF-}\alpha$  produced predominantly by the NK cells, and IL-8 by monocytes. Belantamab mafodotin increased mitoses of corneal epithelial cells with bilateral single cell necrosis in rats. Studies conducted with the ADC in rats showed corneal single cell necrosis in single-dose (Study R29778), weekly  $\times 3$  (Study R30467G), and every-3-week  $\times 4$  (13-week) toxicology studies. Corneal opacity was observed in a study conducted in rats with cys-mc-MMAF with a daily  $\times 5$  schedule (Study 1019-010). Only results from the 13-week ADC toxicology study are presented in this review. To further investigate ADC-related ocular toxicities, the Applicant conducted a study in rabbits, which showed similar effects. Belantamab mafodotin does not bind to rat BCMA and is not expected to bind rabbit BCMA. Bioimaging in rats showed that fluorescently labeled belantamab mafodotin was taken up throughout the body by a mechanism unrelated to BCMA receptor expression on the cell membrane. In vitro studies suggest that a non-specific mechanism of cellular uptake of belantamab mafodotin may be through macropinocytosis. Primary cells (human corneal epithelial cells and renal proximal tubule cells) pretreated with the macropinocytosis inhibitor, EIPA (5-(N-ethyl-N-isopropyl)amiloride), showed lower levels of belantamab mafodotin-induced apoptotic markers Caspase 7/8 compared to no EIPA treatment. Of note, this was observed with only one human corneal epithelial cell donor. Therefore, while macropinocytosis may be a mechanism of non-specific uptake of belantamab mafodotin, more data is needed to make a definitive conclusion.

Additionally, tissue cross-reactivity studies showed antigen-specific staining of belantamab mafodotin in human spleen. Membranous staining was observed in the perivascular areas and scattered mononuclear cells in the lung. Potential cross-reactivity was also observed in blood vessel walls/perivascular tissue and connective tissue. Cytoplasmic granular staining was observed in human heart, kidney, and liver tissue, and in the monkey spleen and lymph node.

In summary, belantamab mafodotin acts through multiple mechanisms to cause cell death driven by the payload and the antibody component. The toxicities observed in animals have generally been observed in patients. Potential reproductive toxicities based on the mechanism of action and genotoxicity will be communicated in the product labeling. There are no nonclinical issues to preclude approval of belantamab mafodotin for the proposed indication.

## 5.2. Referenced NDAs, BLAs, DMFs

### The Applicant's Position:

A Letter of Authorization/Right of Reference was issued by Seattle Genetics for Adcetris® (brentuximab vedotin). This authorization includes the right of use for nonclinical safety data related to monomethyl auristatin-F (MMAF), including cys-mcMMAF and mcMMAF variants.

### The FDA's Assessment:

The Letter of Authorization (LOA) from Seattle Genetics submitted under Module 1.4.1. permits GlaxoSmithKline (GSK) to reference the information in Adcetris product label in support of BLA 761158. The LOA from Seattle Genetics also permits GSK the right of use for nonclinical safety data related to MMAF, including cys-mcMMAF and mcMMAF variants; these study reports were included in the BLA 761158 submission and are independent of the Adcetris BLA submission.

## 5.3. Pharmacology

### Primary Pharmacology

#### **Mechanism of Action**

##### *BCMA and Fc-Receptor Binding*

Binding of belantamab mafodotin to human and monkey BCMA has been demonstrated using Biacore and the affinity shown to be within 2-fold, with monkey KD of 0.7 nM (0.1 µg/mL) and human KD of 1 nM (0.2 µg/mL) at 25°C; the KD = 4 and 8 nM at 37°C for monkeys and humans, respectively. According to the Nonclinical Overview provided by the Applicant, belantamab mafodotin does not bind to rat BCMA (data was not submitted to the BLA) and it is unlikely to bind to rabbit BCMA, based on BCMA protein sequence homology analysis. Belantamab mafodotin also bound human FcγR I, FcγR IIIa V, and FcRn with KDs of 7, 28, and 52 nM,

respectively. The KD for the fucosylated antibody (GSK2800525) to FcγR IIIa V was 329 nM, demonstrating that afucosylation of the antibody component of belantamab mafodotin enhanced binding to FcγR IIIa V. Belantamab mafodotin bound to monkey FcγR III with a KD of 61 nM (Study No. 2013N175824). Therefore, based on the binding studies, the cynomolgus monkey is the only relevant animal species for measuring on-target and payload-driven toxicities.

#### *Cell Internalization Mediated by BCMA Binding*

GSK2857914 (i.e. the antibody component of belantamab mafodotin) was used in the confocal microscopy method to measure receptor internalization and recycling. In GSK2857914-treated NCI-H929 cells (MM tumor cell line that expresses high levels of BCMA) detected using a fluorophore-labeled secondary antibody for GSK2857914, the levels of surface bound GSK2857914 antibody were reduced within 1 hour, internalized antibody could be detected, and total cellular levels of GSK2857914 continued to decrease for 7 hours after the original pulse treatment. The re-appearance of unbound BCMA surface receptor, detected with a different second antibody, occurred as quickly as 1 hour following GSK2857914 binding and continued to increase (Study No. 2013N177426). It is unclear what amount of surface BCMA receptor was recycled following GSK2857914-induced internalization, versus the levels already on the surface of the cells and newly synthesized protein. In experiments using flow cytometry to measure the binding of belantamab mafodotin to NCI-H929 cells, surface binding occurred within the 15 minute treatment period and decreased (presumably via internalization) and approached control levels by 16 to 24 hours after treatment. BCMA increased on the cell surface after repeated treatment with belantamab mafodotin (Study No. 2013N176113). The results with belantamab mafodotin were overall consistent with the more extensive internalization and recycling study conducted with GSK2857914.

#### *Cell Cycle Arrest and Apoptosis*

The mechanisms of anti-tumor activity for belantamab mafodotin include cell cycle arrest and apoptosis mediated by both MMAF and ADCC. Chronic treatment of NCI-H929 cells with belantamab mafodotin showed concentration-dependent increases in payload-driven active (cleaved) Caspase 3 (CC3), a marker of apoptosis, with nearly all cells showing this marker after 72 hours of treatment with belantamab mafodotin at concentrations of 1 and 10 µg/mL. CC3 levels peaked in cells that expressed high and low levels of BCMA on the cell surface following 4 and 33 hours of treatment, respectively (Study No. 2013N176113). Cell cycle analysis by flow cytometry showed that belantamab mafodotin induced dose- and time-dependent G2/M arrest in MM cell lines. Belantamab mafodotin also induced apoptosis of patient derived CD138+ MM cells in a concentration-dependent manner based on annexin V/PI positivity and increased caspase 3/7 activity, measured by flow cytometry [Study No. 2013N176111 and 2014N219883].

#### *ADCC and Belantamab Mafodotin*

Numerous ADCC assays were conducted with human peripheral blood mononuclear cells (PBMCs) as effector cells and BCMA-expressing target cells (Effector:Target ratio = 50:1) to identify a lead humanized CA8 antibody candidate that could bind to BCMA, elicit an acceptable level of ADCC, and have low potential for immunogenicity. These assays were conducted with the chimeric parent antibody (CA8), the humanized antibody component (fucosylated, GSK2800525; and afucosylated, GSK2857914), and belantamab mafodotin. All showed ADCC activity. The ADCC activity of the chimeric parent and humanized antibody component were increased with defucosylation. Conjugation to MMAF did not significantly alter ADCC activity. The GSK2857914 EC50 values for ADCC obtained in MM cell lines ranged from 0.57 ng/mL (NCI-H929 cells) to 111 ng/mL (JLN3 cells). Soluble BCMA (which can be shed from cells in vitro and in vivo) and/or APRIL (a BCMA ligand) reduced the ADCC activity. The GSK2800525, GSK2857914, and belantamab mafodotin EC50s for ADCC activity in ARH77-10B5 cells (plasma cell leukemia cell line stably transfected with human BCMA to express high levels) were 30, 1, and 2 ng/mL, respectively (Study No. 2011N125945). Additionally, GSK2857914 directly added to blood samples from 4 healthy donors resulted in decreased numbers of plasmablasts by flow cytometry following overnight incubation compared with a control antibody. The mean EC50 value was 129 ng/mL (range: 34 to 222 ng/mL; Study No. 2013N183018).

#### *Payload-Driven Cell Growth Inhibition and cell death*

The IC50 (concentration that demonstrates 50% maximal inhibition) for cell growth when MMAF was conjugated to the fucosylated antibody (GSK2800525) ranged from 3 to 244 ng/mL in BCMA-expressing (including MM) cell lines, with the level of inhibition corresponding to the level of BCMA expression. There was no growth inhibitory activity in cell lines with no or only trace BCMA expression. The IC50 for growth inhibitory activity of belantamab mafodotin was determined in two BCMA-expressing MM cell lines and was comparable to the fucosylated ADC (Study No. 2011N125948), which is expected since the conditions of the assay only measured payload-driven cytotoxicity. Following 21 days of treatment, belantamab mafodotin also demonstrated cytotoxicity in MM colonies (consisting of >50 cells grown in a methylcellulose matrix for 21 days), with colony inhibition IC50 values ranging from 6 to 70 ng/mL (Study No. 2013N176111).

Belantamab mafodotin and GSK2857914 (the antibody component of belantamab mafodotin) were evaluated for their effects on the release of immunogenic cell death (ICD) biomarkers via enzyme linked immunosorbent assay (ELISA) or changes in protein expression and/or phosphorylation using Western Blot. The Applicant defined the following markers as ICD biomarkers: high mobility group box 1 (HMGB1), phosphorylated eukaryotic initiation factor-2 (p-eIF2 $\alpha$ ), phosphorylated PKR-like ER kinase (p-PERK), cleavage of BAP31, and Heat Shock Proteins 70 and 90 $\alpha$  (HSP70 and HSP90 $\alpha$ ). Release of HSP70 and HSP90 $\alpha$  were observed following 72 and 48 hours of 0.1 and 1  $\mu$ g/mL belantamab mafodotin treatment, respectively. Phosphorylation of eIF2 $\alpha$ , cleavage of BAP31 and a slight increase in HMGB1 release were observed after 72 hours of 1  $\mu$ g/mL belantamab mafodotin treatment. Phosphorylation of

PERK and release of IL-8 were observed following 48 and 72 hours of 10 µg/mL belantamab mafodotin treatment, respectively. These effects were not observed with GSK2857914 (Study No. 2019N397960).

In an in vitro experiment, when belantamab mafodotin-treated NCI-H929 cells were co-cultured with immature dendritic cells (iDCs), the result was increased expression of surface markers CD40, CD83, and CD86, consistent with dendritic cell activation/maturation (Study No. 2016N304715).

The Applicant conducted in vivo studies, using, the EL4-hBCMA syngeneic tumor model, to investigate the role of CD4 and CD8 positive cells on the activity of the belantamab mafodotin and the potential for ICD. This model has several limitations in that it is a mouse lymphoma cell line expressing human BCMA and its predictive value for human disease is uncertain. In one study with this model, depletion of CD8+ cells reduced the overall survival benefit of mice treated with 15 mg/kg belantamab mafodotin administered intraperitoneally (IP) twice a week for 3 weeks (Study No 2018N359715). In a separate EL4-hBCMA syngeneic tumor model study, mice were IP dosed with 15 mg/kg belantamab mafodotin every two days for three total doses. In tumor samples from belantamab mafodotin-treated mice compared to controls, there were increased levels of tumor infiltrating lymphocytes (TILs), peripheral CD8+ cells and calreticulin measured by immunohistochemical staining (Study No. 2019N395916).

When doses of 1, 3, 10, 15, 20, and 30 mg/kg belantamab mafodotin were administered IP twice a week for 3 weeks to EL4-hBCMA mice, there was tumor free survival after 60 days in a dose-dependent manner. The antibody component of belantamab mafodotin (GSK2857914, 30 mg/kg) had improved survival compared to the same dose of GSK2800525 (i.e. fucosylated antibody) with Fc disabling mutations; however, this 30 mg/kg dose of GSK2857914 did not have the same durable response as 30 mg/kg belantamab mafodotin. This finding provides support that MMAF contributes to durable tumor regression. The tumor free surviving mice from the dose escalation portion of this study were re-challenged with either parental EL4 cells or EL4-hBCMA cells and the responses to belantamab mafodotin were compared to naïve mice. No additional tumor growth was observed in re-challenged mice, but was in naïve mice (Study No. 2019N396819).

Additionally, in a study using flow cytometry to detect a fluorescence cell membrane dye (PKH67) on MM cell lines as a measure of phagocytosis by macrophages, 2 and 10 µg/mL belantamab mafodotin promoted phagocytosis compared to an isotype control MMAF ADC (Study No. 2013N176111). The results indicate that the ADC has antibody-dependent cellular phagocytosis (ADCP) activity.

#### *Specificity for BCMA-Expressing Tissues*

The Applicant provided data on BCMA surface expression in cells derived from MM patients and in normal human tissues. Higher BCMA expression was reported in MM cells. While this

data suggests that there is low risk for toxicity to normal tissues with treatment of belantamab mafodotin, FDA notes that this is not consistent with the observation of toxicities to normal tissues in animal toxicology studies (or in patients; see the clinical sections of the review). In addition, previous publications on ADCs indicate that toxicities are mainly related to the payload and not confined to the site of target expression (Saber and Leighton, Regulatory Toxicology and Pharmacology 2015; Saber et al, Regulatory Toxicology and Pharmacology 2019).

### Secondary Pharmacology

#### Data:

GSK2857914 [unconjugated afucosylated mAb (parent anti-BCMA antibody)] blocks the binding of BAFF and APRIL ligands to B-cell maturation antigen (BCMA) and stimulation of NFκB signalling in MM cell lines. GSK2857914 has no agonist activity on NFκB signalling in the absence of cross-linking agents or immobilization to a solid substrate.

Belantamab mafodotin is selectively cytotoxic to BCMA-expressing MM cells in coculture experiments with non-BCMA expressing cells, i.e., no bystander cytotoxicity

A single-dose male monkey study showed a pharmacodynamic effect selectively on BCMA-expressing cells in the blood. A significant reduction in the numbers of free BCMA+ plasma cells and IgE levels and modest reduction in immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM) levels were observed.

#### The Applicant's Assessment:

In summary, belantamab mafodotin showed selective cytotoxicity against BCMA-expressing cells with limited bystander killing of other immune cell types. Belantamab mafodotin does not activate NF-κB-mediated proinflammatory pathways in vitro.

#### The FDA's Assessment:

FDA overall concurs with the Applicant's assessment based on results from Study No. 2011N12948, 2013N175851, 2011N125952, and 2013N176111. FDA also notes that the IC50s were 1.6-1.8 µg/mL for GSK2800525- and GSK2857914-inhibition of BAFF- and APRIL-induced NF-κB signaling. BAFF and APRIL are ligands of BCMA and involved in survival. Additionally, while the Applicant discusses selective cytotoxicity against BCMA-expressing cells in vitro, as discussed under "Primary Pharmacology" (FDA assessment), one cannot not ignore MMAF-related toxicities. The dose of belantamab mafodotin or GSK2857914 in the single-dose pharmacodynamic male monkey study noted above (Study No. 2013N163514), was 1 mg/kg (n=3/group). The magnitude of the reduction in IgE levels was 50 to 75% compared to baseline; and, for IgG and IgM levels was <25%. The increase in IL-2, GM-CSF, IFNγ, IL-6, IL-8, and TNFα cytokines was 3-, 10-, 5-, 40-, 300-, and 5-fold, respectively, above baseline in some animals at

timepoints  $\geq 49$  days post dose, suggesting some delayed risk of cytokine release.

### Safety Pharmacology

#### Data:

In vitro: A single Good Laboratory Practice (GLP) in vitro safety pharmacology study assessing the potential for delayed ventricular repolarization (e.g., hERG assay) was conducted with cys-mcMMAF (the active cytotoxic moiety released from belantamab mafodotin). Cys-mcMMAF had no detectable effect on ionic currents in human embryonic kidney (HEK)293 cells stably expressing human ether-à-go-go-related gene (hERG) channels at concentrations up to 100  $\mu\text{M}$ .

In vivo: Standalone in vivo safety pharmacology studies were not conducted with belantamab mafodotin as it will be used in patients with advanced cancer, this is in accordance with ICH S9 guidance, as well as with all other relevant ICH guidances on safety.

Safety pharmacology evaluations of potential cardiovascular effects were incorporated into the definitive (GLP) IV toxicity studies in monkeys (given once weekly for 3 or 13 weeks by IV bolus injection, up to 10 mg/kg/week, to a total of 48 monkeys); parameters included heart rate, electrocardiogram (ECG) waveform evaluation and QTc evaluation. There were no belantamab mafodotin-related ECG waveform abnormalities, arrhythmias or QTc changes; nor were there ECG-related findings with cys-mcMMAF or GSK2857914 in the 5-day or 4-week study, respectively. Increases in heart rate (16%) observed in male monkeys after 5 weekly doses of 10 mg/kg were considered related to their deteriorating clinical condition. No changes in heart rate were noted in female animals. Evaluations of blood pressure, respiratory rate and heart rate in the 5-day monkey study with cys-mcMMAF did not identify any treatment-related changes.

Although no formal assessment of effects on the central nervous system was undertaken, no clinical observations indicative of neurobehavioral effects were observed in the rat or monkey toxicology studies with belantamab mafodotin or cys-mcMMAF.

#### The Applicant's Position:

Overall, there were no clinically relevant findings in safety pharmacology endpoints that examined the potential effects of belantamab mafodotin on the cardiovascular system, nor were there indications of neurobehavioural effects, and cys-mcMMAF did not inhibit hERG tail current in the hERG assay.

#### The FDA's Assessment:

FDA concurs with the Applicant, but notes that there was large animal variability in the GLP 13-week general toxicology study in monkeys (e.g., +20 msec differences in QTc interval in controls postdose compared to pretreatment).

## 5.4. ADME/PK

Data:

<p><b>Absorption</b></p> <ul style="list-style-type: none"><li>• <i>Single dose IV PK studies in mice, rats and monkeys [Report numbers 2013N175927, 2012N140200, 2013N157994 and 2012N143303].</i></li><li>• <i>PK following IP Administration [Report 2013N176011].</i></li></ul>
<p>Preliminary PK of belantamab mafodotin were investigated in mice, rats and monkeys during single dose IV (1 mg/kg) or IP (4 mg/kg, mouse only) studies. The plasma concentrations of antibody-drug conjugate (ADC) and (total monoclonal antibody [mAb]) within the nonclinical species were similar, suggesting stability of the drug conjugate in circulation. Belantamab mafodotin was cleared slowly in animals; ranging from 8 to 26 mL/kg/day, which is considerably lower than the glomerular filtration rate [3000 to 20,000 mL/kg/day; Davies, 1993] and indicates little clearance of belantamab mafodotin by renal routes. <math>V_{ss}</math> was low, ranging from 103 to 129 mL/kg, which is less than extracellular fluid volume [200 to 300 mL/kg; Davies, 1993] and suggests that the compound was mainly confined to the systemic circulation. <math>T_{1/2}</math> of belantamab mafodotin in mice, rats and monkeys was approximately 9, 11 and 4 days, respectively. Similar conclusions were drawn following IP administration to male mice, where the relative bioavailability of belantamab mafodotin for the IP route was approximately 80%.</p>
<p><b>Distribution</b></p> <ul style="list-style-type: none"><li>• <i>in vitro Plasma Protein Binding of cys-mcMMAF in Human Plasma [Report 2019N400355]</i></li><li>• <i>Uptake of Vivotag-680 Labelled GSK2857916 into HCEC and RPTEC [Report 2019N409936]</i></li><li>• <i>Biodistribution of fluorescently labelled GSK2857916 (30 mg/kg) in rats using optical imaging [Report 2018N358667]</i></li><li>• <i>Distribution of GSK2857916 and cleaved cys-mcMMAF in rat eye and other tissues following single IV administration (30 mg/kg) [Report 2018N394006]</i></li></ul>
<p>Cys-mcMMAF exhibited low protein binding in human plasma in a concentration-dependent manner. The unbound percentages in the 3 donors ranged from 49.1 to 61.8% at 0.5 ng/mL, from 68.8 to 70.7% at 5 ng/mL, and from 80.9 to 88.7% at 50 ng/mL.</p> <p>Following incubation of belantamab mafodotin with HCEC and RPTEC, there was evidence for co-location of drug with lysosomes and catabolism to release cys-mcMMAF.</p> <p>Following a single IV administration of fluorescently-labelled belantamab mafodotin or GSK2857914 to rats, the fluorescent signal of both antibodies in liver, kidney and eyes was similar, suggesting that the biodistribution of belantamab mafodotin was not affected by the presence of the conjugated payload. Both antibodies were associated with connective tissue</p>

<p>in the eye and eyelids, lacrimal and harderian glands and liver, as well as muscle in the eyelids but were not observed in the cornea or glands in the eyelids. The fluorescent signal was higher in liver and kidneys compared to the eye. Cys-mcMMAF liberated from belantamab mafodotin was detected at very low levels in liver, bone marrow, kidney, harderian gland and EO lacrimal gland, but was not detected in the cornea, eyelid or whole eye.</p>
<p><b>Metabolism</b></p> <ul style="list-style-type: none"><li>• <i>Stability of GSK2857916 in vitro in Rat, Monkey and Human Plasma at 37°C [Report 2014N206529]</i></li><li>• <i>Metabolism of <sup>3</sup>H-cys-mcMMAF in Rat, Monkey, and Human Hepatic S9 [Report 2018N393077]</i></li><li>• <i>Metabolism and Excretion of <sup>3</sup>H-cys-mcMMAF Following IV Administration to Rats [Report 2018N393078]</i></li></ul>
<p><b>In vitro</b></p> <p>Belantamab mafodotin was largely stable when incubated in rat, monkey or human plasma at 37°C, as less than approximately 3% of the total MMAF conjugated to the antibody was released as free cys-mcMMAF over a 96-hour period.</p> <p>Following incubation of <sup>3</sup>H-cys-mcMMAF with rat, monkey and human hepatic S9 fractions, the metabolism was characterized primarily by non-enzymatic transformations and to a minor degree by oxidative and conjugative metabolism. Cys-mcMMAF (the linear isomer, SGD-1362) underwent mainly hydrolysis on its saturated maleimide ring, which then dehydrated to form a 3-oxo thiomorpholine moiety [the cyclic isomer of cys-mcMMAF (also known as SGD-1462)].</p> <p><b>In vivo</b></p> <p>Following a single IV administration of 10 mg/kg <sup>3</sup>H-cys-mcMMAF to rats, the major component in urine was cys-mcMMAF (linear isomer; SGD-1362), with all other identified metabolites each accounting for less than 1% of the radioactive dose. The major component in feces was the cyclized isomer of cys-mcMMAF, SGD-1462, with all other identified fecal metabolites each accounting for less than 5% of the radioactive dose.</p>
<p><b>Excretion</b></p> <p><i>Metabolism and Excretion of <sup>3</sup>H- cys-mcMMAF Following IV Administration to Rats [Report 2018N393078]</i></p>
<p>Following a single IV administration of 10 mg/kg <sup>3</sup>H-cys-mcMMAF to rats, the majority of the radioactive dose was excreted in the feces (approximately 83%). Urinary excretion (approximately 13%) was a minor route. Radioactivity was excreted rapidly, with 94% of the administered dose recovered in the first 48 hours after dosing. The total recovery of radioactivity over the 7-day collection period was 96%.</p>
<p><b>TK data from general toxicology studies</b></p>

*3 and 13 week repeat dose toxicology studies in rats and monkeys; Reports 2013N174857, 2018N374327, 2013N158643 and 2018N375127.*

**Rat:** There was no marked difference in systemic exposure to belantamab mafodotin (ADC or total mAb) between males and females. Gender-averaged systemic exposure increased approximately proportionally with increasing dose and whilst there was a slight increase in systemic exposure on Day 15 compared to Day 1 in the 3-week study, there was no marked difference in systemic exposure between Week 10 and Week 4 in the 13-week study. The mean half-life of belantamab mafodotin (ADC and total mAb), calculated in the 3-week study, was approximately 11 days.

**Monkey:** There was no marked difference in systemic exposure to belantamab mafodotin (ADC or total mAb) between males and females. Gender-averaged systemic exposure increased approximately proportionally with increasing dose and there were no marked differences in systemic exposure between Day 1 and Day 15 of the 3-week study, or between Week 4 and Week 13 of the 13-week study. The mean half-life of belantamab mafodotin (ADC and total mAb), calculated in the 3-week study, was approximately 4 days.

Abbreviations: ADC = Antibody drug conjugate; EO = Extra-orbital; HCEC = Human corneal epithelial cells; IV = Intravenous; IP = Intraperitoneal; mAb = Monoclonal antibody; PK = Pharmacokinetic(s); RPTEC = Renal proximal tubule epithelial cells;  $T_{1/2}$  = Serum half-life; TK = Toxicokinetic;  $V_{ss}$  = Volume of distribution.

#### The Applicant's Position:

The PK of belantamab mafodotin have been adequately characterized, and the PK profile in humans is similar to that of the rat and monkey and supports the use of these nonclinical species in the toxicity evaluation of belantamab mafodotin. Taken together, these data support the safe use of belantamab mafodotin in the proposed patient population under the prescribed therapeutic dosage regimen.

#### The FDA's Assessment:

FDA concurs with the Applicant's assessment on the absorption of belantamab mafodotin; but notes that while the ADC was mainly confined to the systemic circulation, MMAF will eventually come off and distribute into organs and tissues. Also, when the Applicant notes there is "similar" exposure between the ADC and mAb, this wording is referring to differences less than 2-fold. Clearance was faster in monkeys compared to rats and mice.

Overall, the FDA concurs with the Applicant's assessment on the distribution of belantamab mafodotin and has the following additional observations regarding the data. In the uptake study in human corneal epithelial cells (HCEC) and renal proximal tubule epithelial cells (RPTEC) cells, uptake of belantamab mafodotin and co-localization of belantamab mafodotin with the lysosomes was measured using spinning disk confocal microscopy and lysotracker green; cell-associated cys-mcMMAF was quantified using LC-MS/MS from bulk HCEC and RPTEC cultures. The results of the study suggest that cells catabolize belantamab mafodotin, releasing cys-

mcMMAF. In the in vivo optical imaging study in rats, the Applicant assessed the levels of belantamab mafodotin in the eye and how fast it was cleared (Study No. 2018N358667). The data showed no difference in the increase in the amount of signal observed between the fluorescently labelled GSK2857916 and control antibody and that the signal returned to baseline between Days 14 and 35 (last timepoint taken) postdose. Due to the lack of appropriate controls (e.g., treatment with control antibody increased the fluorescent signal), there is currently no reliable data available on the pharmacokinetics of belantamab mafodotin in the eye, its accumulation, and any information on whether a change in dosing regimen could potentially reduce exposure/toxicity. Additionally, in this study, despite lower belantamab mafodotin levels in the eye compared to the liver when measured optically, when immunoassay was used for detection, the concentrations were higher in the eyes compared to the liver, indicating that the detection method can affect the results. Of note, even when measured levels were higher in the eye than the liver, the GSK287916 levels in these tissues were less than 1% of the levels in serum.

FDA concurs with the Applicant's assessment on the metabolism and excretion of belantamab mafodotin. In the study describing results from the rat, monkey and human hepatic S9 fractions, SGD-1362 was mainly detected (~60 to 70%), followed by SGD-1462 (~20 to 30%), and the stereoisomer of SGD-1362 (M16; ~5 to 7%). There were no major differences among the species tested and other metabolites were present at less than 2%. Plasma stability was also assessed by measuring free payload using UHPLC-MS/MS

FDA concurs with the Applicant's assessment of the toxicokinetic data from the repeat-dose GLP toxicology studies; the data are shown below for animal:human comparisons for labeling purposes. The AUC at the lowest dose with effects on reproductive organs (10 mg/kg) was approximately 20000 hr\*µg/mL in both monkeys and rats. An increase in the plasma levels of cys-mcMMAF was observed with repeated dosing of belantamab mafodotin, although the levels of cys-mcMMAF were <1% the exposure of the ADC.

### Rat

#### ADC (Belantamab mafodotin)

Dose (mg/kg/week)	Cmax (µg/mL)				AUC <sub>0-t</sub> (hr*µg/mL)			
	Week 1	Week 4	Week 4	Week 10	Week 1	Week 4	Week 4	Week 10
3	77.3	103	119	131	3615	6100	10000	10500
10	266	303	426	451	11950	21750	33900	37300
30	836	764	1090	1250	33200	48600	85500	90200

#### mAb (GSK2857914)

Dose (mg/kg/week)	Cmax (µg/mL)				AUC <sub>0-t</sub> (hr*µg/mL)			
	Week 1	Week 4	Week 4	Week 10	Week 1	Week 4	Week 4	Week 10
3	73.2	105	115	133	3730	7160	12100	12700
10	226	300	414	406	11800	25750	39600	42400

30	718	771	1080	1160	31950	57000	97600	107000
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Cys-mcMMAF

Dose (mg/kg/week)	C <sub>max</sub> (ng/mL)				AUC <sub>0-t</sub> (hr*ng/mL)			
	Week 1	Week 4	Week 4	Week 10	Week 1	Week 4	Week 4	Week 10
3	1.2	3.9	NQ	NQ	NC	258	NC	NC
10	4.1	17	1.30	1.71	273	1245	42.5	66.0
30	17	53	3.01	6.81	979	2785	242	391

NC = Not calculated. NQ = Not quantifiable (<0.5 ng/mL). t = 168 in 3-week rat study and 504 in the 13-week rat study.

- Mean T<sub>max</sub> range for the ADC was 0.25 hours in rats.

**Monkey**ADC (Belantamab mafodotin)

Dose (mg/kg/week)	C <sub>max</sub> (µg/mL)				AUC <sub>0-t</sub> (hr*µg/mL)			
	Week 1	Week 4	Week 4	Week 13	Week 1	Week 4	Week 4	Week 13
1	22.3	27.5	26.9*	27.3*	865	1235	1170*	1139*
3	58.7	63.3	83.7	93.9	2335	3756	5230	6270
10	249	292	311	NA	11200	21500	21500	NA

mAb (GSK2857914)

Dose (mg/kg/week)	C <sub>max</sub> (µg/mL)				AUC <sub>0-t</sub> (hr*µg/mL)			
	Week 1	Week 4	Week 4	Week 13	Week 1	Week 4	Week 4	Week 13
1	21.1	27.3	26.5*	29.0*	947	1520	1370*	1500*
3	57.7	68.2	91.3	103	2670	4623	5980	8030
10	236	307	368	NA	12600	25800	29400	NA

Cys-mcMMAF

Dose (mg/kg/week)	C <sub>max</sub> (ng/mL)				AUC <sub>0-t</sub> (hr*ng/mL)			
	Week 1	Week 4	Week 4	Week 13	Week 1	Week 4	Week 4	Week 13
1	0.72	0.5	0.181	6.00	15.9	12.2	2.56	NC
3	2.0	2.0	0.412	24.0	66.0	73.6	27.1	25.3
10	4.7	5.4	NR	NA	208	351	NR	NA

NA = No high dose animals were dosed during Week 13. \* = Plasma concentrations from one animal at 1 mg/kg/week were lower than that observed from the other animals administered 1 mg/kg/week. The AUC values during Weeks 4 and 13 from this animal are not included in the mean calculations. NR = Not reportable. The concentrations are not reportable because of the potential of GSK2857916 to inflate cys-mcMMAF concentration when processed at ambient temperature. NC = Not calculated. Some animals had insufficient or no plasma concentration values to calculate AUC. The animals with no AUC value (NC) were assigned a value of zero to calculate the mean AUC. t = 167 in 3-week monkey study and 168 in the 13-week monkey study.

- Mean T<sub>max</sub> range was 0.25 to 3 hours for the 13-week monkey study for both the ADC and mAb; mean T<sub>max</sub> range was 0.25 to 48 hours for MMAF (for rats and monkeys).

**5.5. Toxicology****5.5.1. General Toxicology**Data:

Belantamab mafodotin is intended for the treatment of advanced cancers. Therefore, the toxicology program was designed in accordance with ICH S9 guidance, as well as with all other relevant ICH guidances on safety. All definitive studies were carried out in an Economic Co-Operation and Development (OECD) member country in accordance with the OECD Test Guidelines in full compliance with GLP regulations.

The toxicities observed following 13 weeks of dosing in rat and cynomolgus monkey were generally similar to those noted in the 3-week GLP toxicity studies, with progression of some findings to lower doses and/or extension of the toxicity to new target organs. Focal or multifocal luteinized nonovulatory follicles were observed in the ovaries of rats in the 3-week repeat-dose toxicology study, at doses of 10 mg/kg and above, which were not reproduced in the 13-week rat study (possibly because dosing was every 3 weeks providing sufficient time for recovery between doses), nor seen in either monkey study. The 13-week rat and monkey studies are presented below. Findings considered related to test item treatment are presented below.

### **3-Month (Once Every 3-Weeks) IV Infusion Toxicity Study in Rats Followed by a 12-Week Off Dose Period [Report 2018N374327 (R32025G)]**

#### **Key Study Findings**

- Belantamab mafodotin was tolerated at doses up to 30 mg/kg/dose following once every 3 weeks dosing for 3 months by IV infusion.
- Adverse microscopic findings were seen in the lung (all doses); teeth/incisors (degeneration) and testes (tubular degeneration/atrophy) at  $\geq 10$  mg/kg/dose; kidney (tubular degeneration/regeneration) at 30 mg/kg/dose. Non adverse microscopic findings were seen in the eye/cornea (increased mitoses at all doses and single cell necrosis at  $\geq 10$  mg/kg/dose) at  $\geq 3$  mg/kg/dose; male mammary gland (lobular atrophy) and spleen (congestion) at  $\geq 10$  mg/kg/dose; and liver (extramedullary hematopoiesis, males only) at 30 mg/kg/dose.
- Following the 12-week off-dose period, there was evidence of progression of the microscopic changes in the lungs at  $\geq 10$  mg/kg/dose and testes at 30 mg/kg/dose, changes were still present in the testes/epididymides and male pituitary gland at  $\geq 10$  mg/kg/dose, other changes were fully reversible.

Conducting laboratory and location:

(b) (4)

GLP compliance: **Yes**

On (b) (4) the legal entity (b) (4) was renamed (b) (4)

Methods

Dose and Frequency of Dosing:	0 (vehicle), 3, 10 or 30 mg/kg/dose, once every 3 weeks for 3 months (Weeks 1, 4, 7 and 10)
Route of Administration:	10-minute IV infusion
Formulation/Vehicle:	25 mM aqueous citrate buffer containing 0.05 mM EDTA, 200 mM Trehalose and 0.02% polysorbate 80 (pH 6.2 ± 0.3)/Solution
Species/Strain:	Wistar Han IGS rats
Number/Sex/Group:	Main study – 12/sex/group
Age:	Approximately 14 weeks.
Satellite Groups/Unique Design:	6/sex/group added at each dose level for TK evaluation. Blood samples were obtained for the detection of anti-drug antibodies (ADA – Immunogenicity) from all main, TK and recovery animals 6/sex/group added at 0, 10 and 30 mg/kg/dose levels for 12-week off-dose period Urinary biomarkers and cytokines were also measured on this study.
Deviation from Study Protocol	None
Affecting Interpretation of Results:	

**Observations and Results: changes from control**

Parameters	Major findings
<b>Mortality</b>	One unscheduled death (vehicle-treated animal) during the dosing period which was not test item-related.
<b>Clinical Signs</b>	There were no test item-related clinical signs.
<b>Body Weights</b>	No body weight gain or slight body weight loss was seen males given ≥10 mg/kg/dose. ↓ food consumption noted after each dose at 30 mg/kg/dose (both sexes).
<b>Ophthalmoscopy</b>	No relevant test item-related changes.
<b>Hematology</b>	Hematology and coagulation parameter changes noted at ≥10 mg/kg/dose during the dosing phase. Sinusoidal extramedullary hematopoiesis (minimal) was present in the liver and correlated with higher liver weights (males only). Changes were considered to be a compensatory hematopoietic response to the changes in red cell parameters which comprised ↓ hemoglobin concentration, hematocrit and mean corpuscular volume (both sexes); ↓ mean corpuscular hemoglobin (males); ↑ reticulocytes and red cell distribution width (both sexes). Bone marrow cytology showed ↓ in M:E ratios at ≥10 mg/kg/dose, with minimal to mild increases in immature cells from erythroid lineage indicative of erythropoiesis, correlating with ↑ in reticulocyte counts in the peripheral blood. Increases in neutrophils, white blood cells, and lymphocytes were also seen at ≥10 mg/kg/dose from Week 4. At Week 12/13, there were also increases in monocytes in males given ≥10 mg/kg/dose and females given 30 mg/kg/dose; and increases in large unstained cells at given 30 mg/kg/dose.

	Higher fibrinogen concentration was also noted in males given $\geq 10$ mg/kg/dose and females given 30 mg/kg/dose. No changes were noted at the end of the off-dose period.
<b>Clinical Chemistry</b>	Clinical chemistry changes were observed at 30 mg/kg/dose during the dosing phase, these included: $\uparrow$ in ALT and AST activity and $\uparrow$ cholesterol, total protein and albumin concentrations in males and females; $\uparrow$ calcium concentration in males only. $\downarrow$ in triglyceride concentration were noted in females given 30 mg/kg/dose during the dosing phase. There were no clinical chemistry changes following the 12-week off-dose period.
<b>Urinalysis</b>	There were no test item-related urinalysis changes at any dose.
<b>Renal Biomarker Analysis</b>	Urinary renal biomarkers changes were observed at 30 mg/kg/dose during the dosing phase, these included: $\uparrow$ UABV values (normalized to urine volume) for males and females; mean UTPV values for these rats were also increased. $\uparrow$ KIM-1 values males only. Following 12/13 week off-dose period, $\uparrow$ UABV values were still apparent; but, showed partial recovery. Mean UTPV and KIM-1 for these rats were comparable to the concurrent control mean, indicative of complete recovery.
<b>Gross Pathology</b>	Findings were present in the lungs, testes/epididymides, and/or spleen of male and/or female rats. <b>Lung:</b> Numerous pale white/tan areas in males given $>3$ mg/kg/dose and females given $>10$ mg/kg/dose. <b>Testes/Epididymides:</b> Testes were small, soft with abnormal discoloration (pale tan/opaque, dark areas) and epididymides were small, soft with occasional dark areas at $>3$ mg/kg/dose. <b>Spleen:</b> Enlarged in one male rat at 30 mg/kg/dose. Findings were still present in the lungs and testes/epididymides of male and/or female rats $\geq 10$ mg/kg/dose following the 12-week off-dose period.
<b>Organ Weights</b>	$\uparrow$ splenic weights relative to body weight were present in male and female rats and $\uparrow$ liver weights (males only) at 30 mg/kg/dose. Non-dose related $\downarrow$ in absolute testicular weights in male rats at $\geq 10$ mg/kg/dose. Liver weights relative to body weight were increased in males at 30 mg/kg/dose. Organ weight changes still present in the testes of males $\geq 10$ mg/kg/dose following the 12-week off-dose period.
<b>Histopathology</b>	Test item-related findings were observed in the lung and eye/cornea at $\geq 3$ mg/kg/dose; spleen, teeth/incisors, testes/epididymides and male mammary gland and pituitary gland at $\geq 10$ mg/kg/dose; and kidney and male liver at 30 mg/kg/dose. Adverse microscopic findings were noted in the lung at all doses (minimal to moderate increase in alveolar macrophages with eosinophilic material and perivascular inflammatory cell infiltrates in animals given $\geq 3$ mg/kg/week, and neutrophilic alveolar inflammation around terminal airways with type 2 pneumocyte hypertrophy/hyperplasia in one female given 10 mg/kg/dose); teeth/incisors (minimal to moderate degeneration affecting ameloblasts and odontoblasts with altered tooth matrices) and testes (marked tubular degeneration/atrophy) at $\geq 10$ mg/kg/dose; and kidney (minimal to slight tubular degeneration/regeneration) at 30 mg/kg/dose. Non adverse microscopic findings were seen in the eye/cornea (increased mitoses consisting of several basal cells that appeared arrested in anaphase at all doses and single cell necrosis at $\geq 10$ mg/kg/dose) at $\geq 3$ mg/kg/dose; male mammary gland (lobular atrophy) and spleen (minimal to slight congestion) at $\geq 10$ mg/kg/dose; and liver (minimal extramedullary hematopoiesis, males only) at 30 mg/kg/dose.

	<p>Changes considered to be secondary to the seminiferous tubular degeneration/atrophy were seen in the epididymides (aspermia) and male pituitary (minimal increased cytoplasmic vacuolation of secretory cells).</p> <p>Following the 12-week off-dose period, there was evidence of progression of the microscopic changes in the lungs at <math>\geq 10</math> mg/kg/dose and testes at 30 mg/kg/dose, and changes were still present in the testes/epididymides and male pituitary gland at <math>\geq 10</math> mg/kg/dose. All other microscopic changes were fully reversible.</p>
<p><b>Other evaluations (skeletal troponin I, aldolase, cytokines, immunogenicity)</b></p>	<p>No test item-related serum sTnI or aldolase findings.</p> <p>Changes in cytokines comprised <math>\uparrow</math> in TNF-<math>\alpha</math> levels (both sexes 30 mg/kg/dose); <math>\uparrow</math> KC/GRO levels <math>\geq 10</math> mg/kg/dose (both sexes). All increases were reversible following the off-dose period.</p> <p>Two TK males given 30 mg/kg/dose were confirmed positive for ADA, with an increase in titer with repeated dosing. During the off-dose phase, one male previously given 30 mg/kg/dose was confirmed positive for ADA.</p>

Abbreviations: ADA = Anti-drug antibodies; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; KC/GRO = Keratinocyte chemoattractant/growth-regulated oncogene; KIM-1 = Kidney injury molecule-1; TNF = Tumor necrosis factor; TK = Toxicokinetic; UABV = Urinary albumin excretion; UTPV = Urinary total protein excretion.

**A 13-Week (Once Weekly) IV Dose Toxicity Study in Cynomolgus Monkeys Followed by a 12-Week Off-Dose Period [Report No. 2018N375127 (P71346G)]**

Key Study Findings

- The dose of 10 mg/kg/week was not tolerated due to immune complex disease, (severe kidney and vascular changes in multiple organs, red blood smear morphological change suggestive of red blood cell membrane damage) that necessitated cessation of dosing after 5 doses, with the early euthanasia of one male on Day 33, and necropsy of the remaining main study monkeys given 10 mg/kg/week during Week 7, likely associated with ADA.
- Adverse pathological changes at 10 mg/kg/week were noted in the kidneys esophagus and intestinal tract, mesenteric lymph node, and thymus and in the spleen, various lymph nodes, and thymus. Seminiferous tubule degeneration noted in the testis was fully reversible after 12-weeks off-dose. Minimal hepatocellular necrosis, considered adverse based on its correlation with increases in liver enzymes was seen at both 3 and 10 mg/kg/week.
- Non-adverse inflammatory microscopic findings included reversible increases in macrophages in multiple organs at  $\geq 3$  mg/kg/week, characterized by increased MCP-1 concentrations as well as neutrophil, monocyte and large unstained cell counts, C-reactive protein and fibrinogen concentrations, with decreased red cell mass parameters, including platelet and reticulocyte counts and mild increases in complement components.

Conducting laboratory and location:



Canada

GLP compliance: **Yes**

Methods

Dose and Frequency of Dosing: 0 (vehicle), 1, 3 or 10 mg/kg, once weekly for up to 13 weeks

Route of Administration: IV (bolus)

Formulation/Vehicle: 25 mM aqueous citrate buffer containing 0.05 mM EDTA, 200 mM Trehalose and 0.02% ps80 (pH 6.2)/Solution

Species/Strain: Cynomolgus monkey

Number/Sex/Group: Main study 3/sex/group

Age: Approximately 2 years

Satellite Groups/Unique Design: Blood samples were obtained for the detection of anti-drug antibodies and circulating immune complexes (ADA, CIC – Immunogenicity) 12-week off-dose period (2/sex/group 0, 3 and 10 mg/kg/dose groups only). ECG recordings were performed in this study. Immunophenotyping, urinary biomarkers, immunoglobulin and cytokine analysis.

Deviation from Study Protocol Affecting Interpretation of Results: None

**Observations and Results: changes from control**

Parameters	Major findings
<b>Mortality</b>	10 mg/kg/week resulted in a deteriorating clinical condition that necessitated cessation of dosing after 5 doses; with the early euthanasia of one male, and necropsy of the remaining main study monkeys during Week 7.
<b>Clinical Signs</b>	↓ activity/muscle tone, thinness/prominent backbone with reduced appetite, signs of dehydration, cold to touch, slight tremors, hunched posture and/or skin pallor were noted predominantly in animals administered 10 mg/kg/week, with an increased severity in the early-euthanized male.
<b>Body Weights</b>	No effects on body weights. Consistent with the clinical observations of thinness/prominent backbone noted at 10 mg/kg/week, ↑ incidence in the frequency and/or number of animals with reduced appetite during Week 5 of dose administration which was not noted during the off-dose period.
<b>Ophthalmoscopy</b>	No relevant test item-related changes.
<b>Hematology</b>	At 10 mg/kg/week, red blood smear morphological changes, suggestive of red blood cell membrane damage (minimal to mild degree of schistocytes and/or spherocytes and/or central pallor), were related, 2 weeks after the last dose, to decreases in red blood cell mass, with evidence of regeneration including increases in red blood cell distribution width and mild increases in reticulocyte counts.

	<p>Changes in hematology parameters at 3 mg/kg/week, included ↑ monocyte counts, ↓ reticulocyte, and platelet counts (both sexes) and ↑ neutrophil counts (both sexes). After the off-dose period, changes were no longer observed and/or had reached pre-study values.</p> <p>↓ in NK cell absolute counts and relative percentage was observed at ≥ 3 mg/kg/week which were fully or partially reversible at 10 mg/kg/week but not at 3 mg/kg/week following a 12-week off-dose period.</p> <p>Minimal ↑ in M:E ratio, with a slight ↑ in the number of active macrophages, a slight left shift in the maturation sequence of the erythroid cell line and a slight increase in the number of metarubricytes with irregular nuclear shapes at ≥ 3 mg/kg/week.</p> <p>Following the 12-week dose off period, a slight ↑ in the number of metarubricytes with binucleation and mitotic figures was observed at 10 mg/kg/week, with a minimal ↑ in the proportion of early precursors (mainly rubricytes) in one of the affected females. At 3 mg/kg/week, a minimal decrease in the M: E ratio was still present.</p>
<b>Coagulation</b>	<p>↑ fibrinogen concentrations were observed at 10 mg/kg/week (both sexes); moderate prolongation in mean APTT (females 10 mg/kg/week).</p> <p>After the off-dose period, changes identified were no longer observed and/or had reached pre-study values.</p>
<b>ECG</b>	<p>No test item-related effects in ECG parameters (PR, QRS, QT and QTc) were observed in males and females. Increases in heart rate (16%) observed in male monkeys after 5 weekly doses of 10 mg/kg were considered related to their deteriorating clinical condition. No changes in heart rate were noted in female animals.</p>
<b>Clinical Chemistry</b>	<p>Changes in clinical chemistry parameters, including dose related ↑ in AST , ALT , GGT, GLDH, ALP, cholesterol, phosphorus, albumin and direct and indirect bilirubin, at doses of ≥3 mg/kg/week and increased MCP-1 concentrations at ≥1 mg/kg/week. Following the off-dose period, changes identified were no longer observed and/or had reached pre-study values.</p>
<b>Urinalysis</b>	<p>There were no test item-related urinalysis changes.</p>
<b>Urinary Renal Biomarkers</b>	<p>Renal damage biomarkers showed elevated urinary albumin and total protein excretion values in individual animals at Week 4 and in group means at Weeks 6/5 and 7 at 10 mg/kg/week (up to 70X and 13X, when compared to pre-study values, respectively), most evidently in Animal No. 4004 in Week 4 (433X and 60X, respectively), with changes also noted in one female given 3 mg/kg/week at Week 13 (17X and 44X, respectively) with the urine sample noted as slightly red. The urinary albumin concentration for one female given 3 mg/kg/week was also increased at Week 13 (8.3X).</p> <p>At the end of the 12-week off-dose period, urinary albumin and total protein excretion values were comparable to pretreatment values.</p>
<b>Gross Pathology</b>	<p>At dosing termination, findings were seen ≥3 mg/kg/week in the thymus in both sexes, as well as in the liver, spleen, and adipose tissue in the inguinal region (males only).</p> <p>Following a 12-week off-dose period, no test item related macroscopic findings.</p>
<b>Organ Weights</b>	<p>↓ in mean absolute and relative (to body and brain weight) thymus weights at 3 mg/kg/week (both sexes).</p> <p>Following a 12-week off-dose period, there were no test item-related organ weight changes.</p>

<b>Histopathology</b>	<p>At 10 mg/kg/week, adverse pathological changes were noted as follows: kidneys (tubular degeneration/regeneration and/or membranoproliferative glomerulonephritis and necrosis of the kidney urothelium); esophagus and intestinal tract, mesenteric lymph node, and thymus (minimal to moderate fibrinoid necrosis, hemorrhage and/or thrombosis in one or several blood vessels); spleen, various lymph nodes, and thymus (decreased lymphoid cellularity with or without lymphoid necrosis). Minimal hepatocellular necrosis was noted at <math>\geq 3</math> mg/kg/week. Microscopic changes at 10 mg/kg/week were no longer present following the 12-week off-dose period except for the evidence of minimal chronic vascular/perivascular inflammation in several blood vessels of the intestinal tract in one monkey that likely represents partial recovery.</p> <p>Adverse findings at 3 mg/kg/week, based on the correlation with the increases in hepatobiliary enzyme activities, was limited to the minimal hepatocellular necrosis. Non-adverse inflammatory microscopic findings included reversible increases in macrophages (with occasional increase in mitoses) in the bone marrow, red pulp of the spleen, thymus and brain (in choroid plexus only); Kupffer cell hypertrophy/hyperplasia (with occasional mitoses and/or single cell necrosis) and extramedullary hematopoiesis (EMH) in the liver; increase in mitoses in the kidney interstitial tissue and/or mesangium (10 mg/kg/week only) and minimal single cell necrosis of the kidney and/or urinary bladder urothelium; increased myeloid cellularity in the bone marrow; and an increase in mitoses in the medulla and EMH in various lymph nodes, were seen at <math>\geq 3</math> mg/kg/week. In addition, seminiferous tubule degeneration noted in the testis at 10 mg/kg/week was fully reversible after 12 weeks off-dose.</p> <p>Secondary to blood withdrawal, inguinal observations (firm swelling/mass), often accompanied by blue/red discolored skin, correlated with the moderate to marked hemorrhages (consistent with encapsulated hematomas) in the skeletal muscle of the inguinal region(s), sometimes extending into the tissues surrounding the inguinal lymph node or sciatic nerve. In addition, in the adipose tissue located in the inguinal region of one male given 3 mg/kg/week, there was a mild hemorrhage accompanied by fibrin, fibrosis and neutrophilic infiltrates, which was histopathologically consistent with an encapsulated hematoma.</p>
<b>Other evaluations (Immunogenicity/ Immunophenotyping/ Cytokines/ Complement Components)</b>	<p>One male (1 mg/kg/week), experienced a robust and specific antibody response, with an increasing titre of ADA over time, low titer ADA were also detected in all other monkeys (except one female) given <math>\geq 3</math> mg/kg/week, without evidence of reduced exposure. ADA were also detected in all monkeys in 3 or 10 mg/kg/week groups, and CIC was detected in 2 animals given 1 mg/kg/week and 3 males given 3 mg/kg/week at varying time points. Mild increases were noted for complement components Bb and C3a at 1 mg/kg/week (only dose evaluated). There was evidence for persisting immunogenic response in 4 animals during the off-dose phase at <math>\geq 3</math> mg/kg/week.</p>

Abbreviations: ADA = Anti-drug antibodies; ALT = Alanine aminotransferase; ALP = Alkaline phosphatase; AST = Aspartate aminotransferase; GGT = Gamma-glutamyl transferase; GLDH = Glutamate dehydrogenase; M:E ratio = Myeloid:Erythroid ratio; UABV = Urinary albumin excretion; UTPV = Urinary total protein excretion.

### The Applicant's Position

In the rat and monkey repeat-dose toxicity studies on belantamab mafodotin, the principal

adverse findings<sup>1</sup> not considered to be related to anti-drug antibodies (ADA) were body weight loss/reduced gain, tubular degeneration/regeneration and glomerulopathy in the kidney associated with proteinuria and enzymuria (30 and 10 mg/kg in rat and monkey, respectively), increased liver enzymes associated with hepatocellular necrosis after subchronic dosing (10 and 3 mg/kg in rat and monkey, respectively), increased macrophages in several organs associated with inflammatory parameter changes (10 and 3 mg/kg in rat and monkey, respectively) and degeneration and atrophy of the seminiferous tubules (10 mg/kg in rat and monkey). In the rat, decreased cellularity of the bone marrow with toxic and adaptive effects on the hematopoietic system (10 mg/kg) and eosinophilic material in the lung (3 mg/kg), were also noted. These effects were apparent at doses of  $\geq 10$  mg/kg in the rat (apart from the lung findings which were observed at 3 mg/kg) and  $\geq 3$  mg/kg in the monkey. Although considered non-adverse, increased mitosis of corneal epithelial cells with bilateral single cell necrosis was observed in rat and rabbit at doses  $\geq 3$  and  $\geq 15$  mg/kg, respectively. The majority of findings in rats and monkeys with the exception of the histopathological changes observed in the testes and lung had recovered or were showing reversibility following a 12-week off-dose period. The nonclinical toxicology studies in rat and monkey are considered to adequately support the toxicological assessment of belantamab mafodotin for registration.

The FDA's Assessment:

Overall, the FDA agrees with the Applicant regarding the general toxicities observed in rats and monkeys. Results of the studies indicate pro-inflammatory responses in animals as shown by increases in the WBCs and/or differentials, increased fibrinogen, and multi-organ infiltrations. Pro-inflammatory responses may have contributed to findings in the lungs, blood vessels, kidneys, and liver. The review of the data by the FDA has also resulted in the following observations and conclusions. Decreased cellularity in the bone marrow with toxicity to the hematopoietic system was mainly observed at 30 mg/kg in rats and test article-related hepatocellular necrosis was only observed in monkeys. Additionally, the bilateral single cell necrosis in the corneal epithelial cells in rats was observed at doses  $\geq 3$  mg/kg with weekly dosing and  $\geq 10$  mg/kg with q3w dosing; in rabbits, it was observed at 30 mg/kg weekly. The Applicant states that the mortality in the 13-week monkey study is due to the immune complex disease. Of note, ADA or circulating immune complex (CIC) were not detected in this animal, but overall, the findings point to ADC-related inflammatory responses. In the other monkeys that were sacrificed early at 10 mg/kg/week, renal tubular degeneration, increased fibrinogen, prolonged aPTT (and localized hemorrhages in tissues), further indicating ADC-induced pro-inflammation responses, referred to the Applicant as immune complex disease. These findings were also observed in the shorter duration studies. The severe kidney toxicity and vascular effects observed in monkeys that resulted in mortality may be both ADC- and ADA-related. The FDA has added the following information to aid in interpreting and visualizing the toxicology data from the 13-week studies.

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<sup>1</sup> Lowest effect dose provided in parenthesis after each finding

**Observations and Results: changes from control (13-week rat toxicology study)**

Parameters	Major findings																																																																																												
<b>Mortality</b>	See Applicant's assessment.																																																																																												
<b>Clinical Signs</b>	30 mg/kg/dose: higher incidence of encrustation of the dorsal surface in females.																																																																																												
<b>Body Weights</b>	Body weight changes were minor: not greater than 5% when compared to controls or 1% when compared to the previous timepoint.																																																																																												
<b>Ophthalmoscopy</b>	During Week 12, all animals were negative for fluorescein stain and there was no evidence of a test item-related effect on any ocular structures. Ophthalmic findings of corneal opacities or vitreous haemorrhage were seen in all groups, including controls, and were considered not to be test item-related as they are common findings for animals of this age, breed and strain.																																																																																												
<b>Hematology</b>	<p>Percent changes compared to the control.</p> <table border="1"> <thead> <tr> <th colspan="2"></th> <th colspan="2">Males</th> <th colspan="2">Females</th> </tr> <tr> <th>Dose (mg/kg/q3w)</th> <th>Week</th> <th>10</th> <th>30</th> <th>10</th> <th>30</th> </tr> </thead> <tbody> <tr> <td rowspan="2">RDW %</td> <td>4</td> <td>2</td> <td>7</td> <td>2</td> <td>7</td> </tr> <tr> <td>12/13</td> <td>8</td> <td>27</td> <td>8</td> <td>29</td> </tr> <tr> <td>MCV fL</td> <td>12/13</td> <td>-4</td> <td>-11</td> <td>-2</td> <td>-8</td> </tr> <tr> <td>Hematocrit %</td> <td>12/13</td> <td>-2</td> <td>-11</td> <td>-4</td> <td>-9</td> </tr> <tr> <td rowspan="2">Hemoglobin g/L</td> <td>12/13</td> <td>-1</td> <td>-14</td> <td>-4</td> <td>-10</td> </tr> <tr> <td>25</td> <td>-1</td> <td>-5</td> <td>-5</td> <td>-5</td> </tr> <tr> <td>LUC</td> <td>12/13</td> <td>18</td> <td>29</td> <td>12</td> <td>113</td> </tr> <tr> <td>Monocytes</td> <td>12/13</td> <td>18</td> <td>33</td> <td>19</td> <td>114</td> </tr> <tr> <td rowspan="2">Neutrophils</td> <td>22</td> <td>12</td> <td>22</td> <td>42</td> <td>102</td> </tr> <tr> <td>12/13</td> <td>66</td> <td>76</td> <td>78</td> <td>175</td> </tr> <tr> <td>Leukocytes</td> <td>12/13</td> <td>31</td> <td>33</td> <td>15</td> <td>64</td> </tr> <tr> <td rowspan="2">Reticulocytes</td> <td>4</td> <td>0</td> <td>36</td> <td>-4</td> <td>25</td> </tr> <tr> <td>12/13</td> <td>17</td> <td>76</td> <td>1</td> <td>58</td> </tr> <tr> <td>M:E Ratio</td> <td>12/13</td> <td>-33</td> <td>-24</td> <td>-4</td> <td>-16</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>NK cell counts were reduced starting on week 4; reduction was up to 60% when compared to pre-study values. The effect was generally reversible.</li> </ul>			Males		Females		Dose (mg/kg/q3w)	Week	10	30	10	30	RDW %	4	2	7	2	7	12/13	8	27	8	29	MCV fL	12/13	-4	-11	-2	-8	Hematocrit %	12/13	-2	-11	-4	-9	Hemoglobin g/L	12/13	-1	-14	-4	-10	25	-1	-5	-5	-5	LUC	12/13	18	29	12	113	Monocytes	12/13	18	33	19	114	Neutrophils	22	12	22	42	102	12/13	66	76	78	175	Leukocytes	12/13	31	33	15	64	Reticulocytes	4	0	36	-4	25	12/13	17	76	1	58	M:E Ratio	12/13	-33	-24	-4	-16
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BLA Multi-disciplinary Review and Evaluation BLA761158

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SKIN/SUBCUTIS	Scab (s)							0/1	1/0																																																																																																																																																																																																											
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<b>Organ Weights</b>	<p>↑ splenic weights relative to body weight were present in male and female rats (+30% and +20%, respectively) and ↑ liver weights (males only) at 30 mg/kg/dose. Non-dose related ↓ in absolute testicular weights in male rats at ≥10mg/kg/dose (-50%). Liver weights relative to body weight were increased in males at 30 mg/kg/dose (+16%).</p> <p>Organ weight changes still present in the testes of males ≥10 mg/kg/dose and decreases in absolute and relative ovary weights (-20%) were present at 30 mg/kg/dose following the 12-week off-dose period.</p>																																																																																																																																																																																																																			
<b>Histopathology</b>	<table border="1"> <thead> <tr> <th colspan="2"></th> <th colspan="4">Male</th> <th colspan="4">Female</th> </tr> <tr> <th colspan="2">Dose (mg/kg/q3w)</th> <th>0</th> <th>3</th> <th>10</th> <th>30</th> <th>0</th> <th>3</th> <th>10</th> <th>30</th> </tr> <tr> <th colspan="2">No. of Terminal Animals Examined</th> <td>12</td> <td>12</td> <td>12</td> <td>12</td> <td>12</td> <td>12</td> <td>12</td> <td>12</td> </tr> <tr> <th>Organ/Tissue</th> <th>Finding</th> <th>Sev</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> </tr> </thead> <tbody> <tr> <td rowspan="6">LUNG/ BRONCHUS</td> <td rowspan="3">Alveolar Macrophages, Increased, Diffuse</td> <td>MIN</td> <td></td> <td>2</td> <td>1</td> <td>6</td> <td></td> <td>2</td> <td>8</td> <td>4</td> </tr> <tr> <td>MILD</td> <td></td> <td>1</td> <td>10</td> <td>6</td> <td></td> <td></td> <td>3</td> <td>8</td> </tr> <tr> <td>MOD</td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td>1</td> <td></td> </tr> <tr> <td rowspan="3">Eosinophilic Material, Alveoli</td> <td>MIN</td> <td></td> <td>1</td> <td>7</td> <td>5</td> <td></td> <td></td> <td>5</td> <td>5</td> </tr> <tr> <td>MILD</td> <td></td> <td></td> <td>2</td> <td>7</td> <td></td> <td></td> <td></td> <td>7</td> </tr> <tr> <td>Infiltrate, Inflammatory Cell, Perivascular Lymphocytic/ Monocytic</td> <td>MIN</td> <td></td> <td></td> <td>4</td> <td>7</td> <td></td> <td></td> <td>10</td> <td>6</td> </tr> <tr> <td></td> <td>MILD</td> <td></td> <td>1</td> <td>8</td> <td>5</td> <td></td> <td></td> <td>2</td> <td>6</td> </tr> <tr> <td></td> <td>Inflammation, Alveoli, Neutrophilic</td> <td>MILD</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td></td> </tr> <tr> <td rowspan="2">EYE, LEFT</td> <td>Increased Mitoses, Cornea</td> <td>PRES</td> <td></td> <td></td> <td>10</td> <td>12</td> <td></td> <td>1</td> <td>10</td> <td>11</td> </tr> <tr> <td>Necrosis, Single Cell, Cornea</td> <td>MIN</td> <td></td> <td></td> <td>8</td> <td>11</td> <td></td> <td></td> <td>1</td> <td>9</td> </tr> <tr> <td rowspan="2">EYE, RIGHT</td> <td>Increased Mitoses, Cornea</td> <td>PRES</td> <td></td> <td>1</td> <td>9</td> <td>12</td> <td></td> <td>2</td> <td>10</td> <td>11</td> </tr> <tr> <td>Necrosis, Single Cell, Cornea</td> <td>MIN</td> <td></td> <td></td> <td>4</td> <td>9</td> <td></td> <td></td> <td>2</td> <td>8</td> </tr> <tr> <td rowspan="3">STOMACH</td> <td>Congestion, Mucosal/ Submucosal</td> <td>PRES</td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Eosinophilic Globules</td> <td>PRES</td> <td>1</td> <td></td> <td></td> <td>2</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Erosion, Glandular Region, Focal</td> <td>MIN</td> <td></td> <td></td> <td></td> <td>2</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>EPIDIDYMIS</td> <td>Aspermia, Bilateral</td> <td>PRES</td> <td></td> <td>1</td> <td>12</td> <td>12</td> <td></td> <td></td> <td>NA</td> <td></td> </tr> </tbody> </table>											Male				Female				Dose (mg/kg/q3w)		0	3	10	30	0	3	10	30	No. of Terminal Animals Examined		12	12	12	12	12	12	12	12	Organ/Tissue	Finding	Sev								LUNG/ BRONCHUS	Alveolar Macrophages, Increased, Diffuse	MIN		2	1	6		2	8	4	MILD		1	10	6			3	8	MOD			1				1		Eosinophilic Material, Alveoli	MIN		1	7	5			5	5	MILD			2	7				7	Infiltrate, Inflammatory Cell, Perivascular Lymphocytic/ Monocytic	MIN			4	7			10	6		MILD		1	8	5			2	6		Inflammation, Alveoli, Neutrophilic	MILD							1		EYE, LEFT	Increased Mitoses, Cornea	PRES			10	12		1	10	11	Necrosis, Single Cell, Cornea	MIN			8	11			1	9	EYE, RIGHT	Increased Mitoses, Cornea	PRES		1	9	12		2	10	11	Necrosis, Single Cell, Cornea	MIN			4	9			2	8	STOMACH	Congestion, Mucosal/ Submucosal	PRES				1					Eosinophilic Globules	PRES	1			2					Erosion, Glandular Region, Focal	MIN				2					EPIDIDYMIS	Aspermia, Bilateral	PRES		1	12	12			NA	
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BLA Multi-disciplinary Review and Evaluation BLA761158  
 [TRADE NAME] belantamab mafodotin

		Eosinophilic Material, Alveoli	MIN				2 (33%)
			MILD				1 (17%)
		Infiltrate, Inflammatory Cell, Perivascular, Lymphocytic/ Mononuclear Cells	MIN	2 (33%)	2 (33%)	3 (50%)	2 (33%)
			MILD	4 (67%)	4 (67%)	2 (33%)	4 (67%)
		Inflammation, Alveoli, Focal, Granulomatous, Alveoli, Multifocal, Macrophages		2 (33%)		1 (17%)	1 (17%)
	EYE, RIGHT	Mineralization, Cornea	MIN		1 (17%)		
	EPIDIDYMS	Aspermia	PRES	6 (100%)	6 (100%)	NA	
	GLAND, PITUITARY	Increased Vacuolation, Pars Distalis	MIN	6 (100%)	6 (100%)		
	KIDNEY	Dilatation	MIN			1 (17%)	
	SPLEEN	Germinal Center Development, Increased	MILD		1 (17%)		
TESTIS	Degeneration/Atrophy, Tubular	MOD	1 (17%)		NA		
		MRK	4 (67%)	1 (17%)			
		SEV	1 (17%)	5 (83%)			

Blank cells: finding not present in group or not toxicologically significant; () = percentage of animals in group with finding.

<b>Other evaluations (skeletal troponin I, aldolase, cytokines, immunogenicity)</b>	<p>There were sTnI levels &gt;2 U/L in two males at 10 mg/kg/dose and one male at 30 mg/kg/dose.</p> <p>Changes in cytokines comprised ↑ in TNF-α levels (both sexes at 30 mg/kg/dose; 2.5X in males and 1.9X in females with female values close to the LLOQ of 5 pg/mL and male values of up to 10 pg/mL); ↑ (~2X) KC/GRO levels ≥10 mg/kg/dose (both sexes).</p> <p>ADA: See Applicant's assessment.</p>
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Abbreviations: ADA = Anti-drug antibodies; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; KC/GRO = Keratinocyte chemoattractant/growth-regulated oncogene; Chol = cholesterol; KIM-1 = Kidney injury molecule-1; TNF = Tumor necrosis factor; sTn1 = skeletal troponin I; TK = Toxicokinetic; UABV = Urinary albumin excretion; UTPV = Urinary total protein excretion; RDW = erythrocyte distribution width; MCV = mean corpuscular volume; M:E = myeloid:erythroid; LUC = large unstained cells PRES = present; MIN = minimal; MOD = moderate; MRK = marked; SEV = severe; NA = organ not present in sex.

Regarding the methods for the 13-week toxicology study in monkeys, the age range of monkeys in the study is 2 years 6 months to 3 years 2 months old. The off-dose period for the 10 mg/kg/week group began at Week 6, as opposed to Week 13 for other groups, and off-dose animals in this group were necropsied after Week 17 (Day 120) as opposed Week 25 (Day 176) for other groups.

**Observations and Results: changes from control (13-week monkey toxicology study)**

Parameters	Major findings									
Mortality	10 mg/kg/week: animals with deteriorating clinical condition also had red cell mass/morphology changes (nucleated red blood cells). Of note, the administration of lactated Ringer’s solution did not improve the clinical condition.									
	Dose (mg/kg/week)	Sex	Disposition Results	Day	Cause of Mortality/Clinical Signs					
	10	Male	MORIBUND SACRIFICE	33	The Applicant notes mortality is possibly related to immune complex disease. We agree that the pro-inflammatory condition may have contributed to the deteriorating condition of the animal). This animal had slightly lower (~30%) exposure to the ADC (AUC and Cmax) than other animals in this group during Week 4, although no ADA or CIC were detected/ clinical signs of dry or purple skin (also present in controls) beginning on Day 24; partly closed eye, weak, and the clinical signs listed below beginning on Day 33. This animal, had elevated MCP-1, IL-8, and CRP compared to pretest as did other animals in the group without early mortality.					
Clinical Signs			Males				Females			
	Dose (mg/kg/week)	0	1	3	10	0	1	3	10	
	Number of Animals Examined	5	3	5	5	5	3	3	5	
	Sign									
	Activity Decreased				7/4					
	Breathing, Deep				1/1					
	Cold to Touch				1/1					
	Dehydrated Suspected				3/3					
	Feces, Soft	17/5	6/3	18/5	2/2	22/3	19/3	27/5	36/5	
	Hunched Posture				6/4					
	Mass Present				3/1					
	Muscle Tone Decreased				1/1					
	Skin, Pallor				4/4					
	Swollen Firm, Inguinal Region, Left		2/1	2/2	11/4				15/5	
	Swollen Firm, Inguinal Region, Right		1/1	6/4	9/3			1/1	5/2	
	Swollen Firm, Tail				7/1		4/1	1/1		
	Tremors				1/1					
Data are presented as number of observations/ number of animals with sign; blank cells: sign was not present in group or not toxicologically significant. Signs were generally only observed during										

	the treatment phase, except swollen firm and soft feces continued into, but were reversible by the end of the off-dose period.																																																																																																																																																																																																																																																										
<b>Body Weights</b>	See Applicant's assessment.																																																																																																																																																																																																																																																										
<b>Ophthalmoscopy</b>	Opacity of the posterior cortex of the lens and irregular retina pigmentation were observed at low incidence in test article-treated animals. Corneal opacity was observed in one high dose male (a different male than the moribund animal), but this finding was also observed prestudy. The ophthalmologist noted these were minor and were considered incidental in origin and unrelated to treatment since they have been routinely found in comparable populations.																																																																																																																																																																																																																																																										
<b>Hematology</b>	<p>Percent changes compared to the control.</p> <table border="1"> <thead> <tr> <th colspan="2"></th> <th colspan="2">Males</th> <th colspan="2">Females</th> </tr> <tr> <th>Dose (mg/kg/week)</th> <th>Week</th> <th>1</th> <th>3</th> <th>1</th> <th>3</th> </tr> </thead> <tbody> <tr> <td>Erythrocytes</td> <td>13</td> <td></td> <td>-12</td> <td></td> <td>-2</td> </tr> <tr> <td>RDW %</td> <td>13</td> <td></td> <td>7</td> <td></td> <td>4</td> </tr> <tr> <td>Hematocrit %</td> <td>13</td> <td></td> <td>-10</td> <td></td> <td>-1</td> </tr> <tr> <td>Hemoglobin g/L</td> <td>13</td> <td></td> <td>-12</td> <td>-3</td> <td>-4</td> </tr> <tr> <td rowspan="2">LUC</td> <td>4</td> <td></td> <td>3</td> <td>67</td> <td>22</td> </tr> <tr> <td>13</td> <td>3</td> <td>76</td> <td>108</td> <td>95</td> </tr> <tr> <td rowspan="2">Monocytes</td> <td>4</td> <td>65</td> <td>128</td> <td>3</td> <td>20</td> </tr> <tr> <td>13</td> <td></td> <td>150</td> <td>48</td> <td>110</td> </tr> <tr> <td rowspan="2">Neutrophils</td> <td>4</td> <td>34</td> <td>38</td> <td>15</td> <td>71</td> </tr> <tr> <td>25</td> <td></td> <td></td> <td></td> <td>67</td> </tr> <tr> <td rowspan="3">Platelets</td> <td>4</td> <td></td> <td></td> <td></td> <td>-8</td> </tr> <tr> <td>13</td> <td></td> <td></td> <td></td> <td>-10</td> </tr> <tr> <td>25</td> <td></td> <td></td> <td></td> <td>-29</td> </tr> <tr> <td rowspan="2">Reticulocytes</td> <td>4</td> <td>26</td> <td>123</td> <td>-24</td> <td>-29</td> </tr> <tr> <td>13</td> <td></td> <td>200</td> <td></td> <td>-19</td> </tr> </tbody> </table> <p>Blank cells: group not evaluated at particular timepoint or findings not toxicologically significant.</p> <table border="1"> <thead> <tr> <th>Sex (Dose)</th> <th colspan="5">Male (10 mg/kg/week)</th> <th colspan="5">Female (10 mg/kg/week)</th> </tr> <tr> <th>Day</th> <th>Pretest</th> <th>4</th> <th>5/6</th> <th>7</th> <th>17</th> <th>Pretest</th> <th>4</th> <th>5/6</th> <th>7</th> <th>17</th> </tr> <tr> <th>Test</th> <th>mean</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> <th>mean</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> </tr> </thead> <tbody> <tr> <td>Erythrocytes</td> <td>5</td> <td>5</td> <td>-23</td> <td>-9</td> <td>4</td> <td>5</td> <td>10</td> <td>-6</td> <td>-8</td> <td>8</td> </tr> <tr> <td>RDW %</td> <td>13</td> <td>12</td> <td>44</td> <td>46</td> <td>10</td> <td>13</td> <td>7</td> <td>18</td> <td>29</td> <td>6</td> </tr> <tr> <td>MCV fL</td> <td>75</td> <td>-2</td> <td>2</td> <td>4</td> <td>2</td> <td>75</td> <td>-4</td> <td>-1</td> <td>0</td> <td>-1</td> </tr> <tr> <td>Hematocrit %</td> <td>40</td> <td>3</td> <td>-22</td> <td>-6</td> <td>6</td> <td>40</td> <td>6</td> <td>-6</td> <td>-8</td> <td>7</td> </tr> <tr> <td>Hemoglobin g/L</td> <td>135</td> <td>2</td> <td>-28</td> <td>-15</td> <td>-2</td> <td>132</td> <td>7</td> <td>-12</td> <td>-13</td> <td>3</td> </tr> <tr> <td>LUC</td> <td>0.05</td> <td>325</td> <td>268</td> <td>277</td> <td>4</td> <td>0.05</td> <td>462</td> <td>727</td> <td>793</td> <td>22</td> </tr> <tr> <td>Monocytes</td> <td>0.19</td> <td>425</td> <td>198</td> <td>251</td> <td>12</td> <td>0.26</td> <td>454</td> <td>249</td> <td>252</td> <td>21</td> </tr> <tr> <td>Neutrophils</td> <td>7</td> <td>-24</td> <td>-31</td> <td>-14</td> <td>-24</td> <td>7</td> <td>40</td> <td>-9</td> <td>10</td> <td>-25</td> </tr> <tr> <td>Basophils</td> <td>0.02</td> <td>25</td> <td>-6</td> <td>119</td> <td>88</td> <td>0.02</td> <td>45</td> <td>127</td> <td>345</td> <td>-32</td> </tr> <tr> <td>Platelets</td> <td>408</td> <td>-42</td> <td>-16</td> <td>-8</td> <td>5</td> <td>487</td> <td>-28</td> <td>-28</td> <td>-29</td> <td>4</td> </tr> <tr> <td>Reticulocytes</td> <td>70</td> <td>24</td> <td>132</td> <td>210</td> <td>-19</td> <td>74</td> <td>-13</td> <td>50</td> <td>160</td> <td>-32</td> </tr> </tbody> </table> <p>Data for high dose animals is presented separate since samples were mostly taken on different days than other groups. %Δ: percent change relative to pretest (mean of Days -14 and -4).</p>			Males		Females		Dose (mg/kg/week)	Week	1	3	1	3	Erythrocytes	13		-12		-2	RDW %	13		7		4	Hematocrit %	13		-10		-1	Hemoglobin g/L	13		-12	-3	-4	LUC	4		3	67	22	13	3	76	108	95	Monocytes	4	65	128	3	20	13		150	48	110	Neutrophils	4	34	38	15	71	25				67	Platelets	4				-8	13				-10	25				-29	Reticulocytes	4	26	123	-24	-29	13		200		-19	Sex (Dose)	Male (10 mg/kg/week)					Female (10 mg/kg/week)					Day	Pretest	4	5/6	7	17	Pretest	4	5/6	7	17	Test	mean	%Δ	%Δ	%Δ	%Δ	mean	%Δ	%Δ	%Δ	%Δ	Erythrocytes	5	5	-23	-9	4	5	10	-6	-8	8	RDW %	13	12	44	46	10	13	7	18	29	6	MCV fL	75	-2	2	4	2	75	-4	-1	0	-1	Hematocrit %	40	3	-22	-6	6	40	6	-6	-8	7	Hemoglobin g/L	135	2	-28	-15	-2	132	7	-12	-13	3	LUC	0.05	325	268	277	4	0.05	462	727	793	22	Monocytes	0.19	425	198	251	12	0.26	454	249	252	21	Neutrophils	7	-24	-31	-14	-24	7	40	-9	10	-25	Basophils	0.02	25	-6	119	88	0.02	45	127	345	-32	Platelets	408	-42	-16	-8	5	487	-28	-28	-29	4	Reticulocytes	70	24	132	210	-19	74	-13	50	160	-32
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Test	mean	%Δ	%Δ	%Δ	%Δ	mean	%Δ	%Δ	%Δ	%Δ																																																																																																																																																																																																																																																	
Erythrocytes	5	5	-23	-9	4	5	10	-6	-8	8																																																																																																																																																																																																																																																	
RDW %	13	12	44	46	10	13	7	18	29	6																																																																																																																																																																																																																																																	
MCV fL	75	-2	2	4	2	75	-4	-1	0	-1																																																																																																																																																																																																																																																	
Hematocrit %	40	3	-22	-6	6	40	6	-6	-8	7																																																																																																																																																																																																																																																	
Hemoglobin g/L	135	2	-28	-15	-2	132	7	-12	-13	3																																																																																																																																																																																																																																																	
LUC	0.05	325	268	277	4	0.05	462	727	793	22																																																																																																																																																																																																																																																	
Monocytes	0.19	425	198	251	12	0.26	454	249	252	21																																																																																																																																																																																																																																																	
Neutrophils	7	-24	-31	-14	-24	7	40	-9	10	-25																																																																																																																																																																																																																																																	
Basophils	0.02	25	-6	119	88	0.02	45	127	345	-32																																																																																																																																																																																																																																																	
Platelets	408	-42	-16	-8	5	487	-28	-28	-29	4																																																																																																																																																																																																																																																	
Reticulocytes	70	24	132	210	-19	74	-13	50	160	-32																																																																																																																																																																																																																																																	

	<ul style="list-style-type: none"> <li>The M:E ratio from bone marrow smears at the terminal necropsy was increased 53% in males at 10 mg/kg/week compared to controls; and, increased 55% in females at 3 mg/kg/week.</li> </ul>																																																																																																																														
<b>Coagulation</b>	<table border="1"> <thead> <tr> <th>Sex (Dose)</th> <th colspan="2">Male (10 mg/kg/week)</th> <th colspan="2">Female (10 mg/kg/week)</th> </tr> <tr> <th>Test</th> <th>Week</th> <th>Δmax</th> <th>Week</th> <th>Δmax</th> </tr> </thead> <tbody> <tr> <td>Activated Partial Thromboplastin Time</td> <td>7</td> <td>+2.43 sec</td> <td>5/6</td> <td>+5.63 sec</td> </tr> <tr> <td>Prothrombin Time</td> <td>4</td> <td>+0.93 sec</td> <td>5/6 + 7</td> <td>+1.37 sec</td> </tr> <tr> <td>Fibrinogen</td> <td>4</td> <td>+38%</td> <td>4</td> <td>+35%</td> </tr> </tbody> </table> <p>Δmax: maximum change relative to pretest (mean of Days -14 and -4); Week: week in which Δmax occurred.</p> <ul style="list-style-type: none"> <li>Increases of 27% (relative to concurrent controls) in fibrinogen were observed in males at 1 and 3 mg/kg/week during Week 4.</li> <li>Increases up to 32% and 15% (relative to concurrent controls) in fibrinogen were observed in males and females, respectively, at 1 or 3 mg/kg/week during Week 13.</li> </ul>	Sex (Dose)	Male (10 mg/kg/week)		Female (10 mg/kg/week)		Test	Week	Δmax	Week	Δmax	Activated Partial Thromboplastin Time	7	+2.43 sec	5/6	+5.63 sec	Prothrombin Time	4	+0.93 sec	5/6 + 7	+1.37 sec	Fibrinogen	4	+38%	4	+35%																																																																																																					
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<b>ECG</b>	See Applicant's assessment. There was large animal variability (e.g., +20 msec differences in QTc interval in controls postdose compared to pre-treatment).																																																																																																																														
<b>Clinical Chemistry</b>	<p>Percent changes compared to the control.</p> <table border="1"> <thead> <tr> <th rowspan="2">Dose (mg/kg/week)</th> <th rowspan="2">Week</th> <th colspan="2">Males</th> <th colspan="2">Females</th> </tr> <tr> <th>1</th> <th>3</th> <th>1</th> <th>3</th> </tr> </thead> <tbody> <tr> <td rowspan="2">ALT (U/L)</td> <td>4</td> <td></td> <td>64</td> <td></td> <td></td> </tr> <tr> <td>13</td> <td></td> <td>60</td> <td></td> <td>73</td> </tr> <tr> <td rowspan="2">AST (U/L)</td> <td>4</td> <td></td> <td></td> <td></td> <td>97</td> </tr> <tr> <td>13</td> <td></td> <td>125</td> <td></td> <td>263</td> </tr> <tr> <td>GGT (U/L)</td> <td>13</td> <td></td> <td></td> <td>6</td> <td>33</td> </tr> </tbody> </table> <p>Blank cells: group not evaluated at particular timepoint or findings not toxicologically significant. Note the changes in GLDH, ALP, bilirubin, phosphorus, and albumin noted by the Applicant at 3 mg/kg/week do not appear to be strongly test article related and were within the range of animal variability.</p> <table border="1"> <thead> <tr> <th>Sex (Dose)</th> <th colspan="5">Male (10 mg/kg/week)</th> <th colspan="5">Female (10 mg/kg/week)</th> </tr> <tr> <th>Week 4</th> <th>Pretest</th> <th>4</th> <th>5/6</th> <th>7</th> <th>17</th> <th>Pretest</th> <th>4</th> <th>5/6</th> <th>7</th> <th>17</th> </tr> <tr> <th>Test</th> <th>mean</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> <th>mean</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> <th>%Δ</th> </tr> </thead> <tbody> <tr> <td>ALT (U/L)</td> <td>49</td> <td>99</td> <td>83</td> <td>77</td> <td>24</td> <td>43</td> <td>99</td> <td>123</td> <td>94</td> <td>-24</td> </tr> <tr> <td>AST(U/L)</td> <td>41</td> <td>959</td> <td>1189</td> <td>583</td> <td>31</td> <td>39</td> <td>868</td> <td>1407</td> <td>824</td> <td>-5</td> </tr> <tr> <td>Chol (mmol/L)</td> <td>3</td> <td>22</td> <td>30</td> <td>29</td> <td>-8</td> <td>3</td> <td>39</td> <td>13</td> <td>21</td> <td>-12</td> </tr> <tr> <td>GGT (U/L)</td> <td>70</td> <td>88</td> <td>92</td> <td>49</td> <td>29</td> <td>44</td> <td>103</td> <td>139</td> <td>120</td> <td>25</td> </tr> <tr> <td>GLDH (U/L)</td> <td>22</td> <td>199</td> <td>198</td> <td>104</td> <td>134</td> <td>16</td> <td>276</td> <td>477</td> <td>274</td> <td>44</td> </tr> </tbody> </table> <p>Data for high dose animals is presented separate since samples were mostly taken on different days than other groups. %Δ: percent change relative to pretest (mean of Days -14 and -4).</p> <ul style="list-style-type: none"> <li>In males, there were up to 3.7- and 1.9-fold increases in MCP-1 concentrations at 1 and 3 mg/kg/week, respectively, during Week 13 and up to 6.3-fold increases in MCP-1 concentrations at 10 mg/kg week during Week 4 compared to controls.</li> </ul>	Dose (mg/kg/week)	Week	Males		Females		1	3	1	3	ALT (U/L)	4		64			13		60		73	AST (U/L)	4				97	13		125		263	GGT (U/L)	13			6	33	Sex (Dose)	Male (10 mg/kg/week)					Female (10 mg/kg/week)					Week 4	Pretest	4	5/6	7	17	Pretest	4	5/6	7	17	Test	mean	%Δ	%Δ	%Δ	%Δ	mean	%Δ	%Δ	%Δ	%Δ	ALT (U/L)	49	99	83	77	24	43	99	123	94	-24	AST(U/L)	41	959	1189	583	31	39	868	1407	824	-5	Chol (mmol/L)	3	22	30	29	-8	3	39	13	21	-12	GGT (U/L)	70	88	92	49	29	44	103	139	120	25	GLDH (U/L)	22	199	198	104	134	16	276	477	274	44
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LUNG	Abnormal consistency, firm								1																																																																																																																																																																																																																																																																					
LYMPH NODE, MANDIBULAR	Focus, dark								1																																																																																																																																																																																																																																																																					
NERVE, SCIATIC	Material accumulation, clot				2																																																																																																																																																																																																																																																																									

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 [TRADE NAME] belantamab mafodotin

	SKIN	Mass (clot)				1					
	SMALL INTESTINE, DUODENUM	Focus, pale, raised			1					1	
	SMALL INTESTINE, ILEUM	Focus, dark				1*					
	SMALL INTESTINE, JEJUNUM	Focus, dark				1*					
	LYMPH NODE	Enlargement				1*					1
		Focus, dark		1		1					1
	ADIPOSE TISSUE	Mass [a]			1						
	BODY CAVITY, ABDOMINAL	Fluid accumulation, pale				1*					
		Mass [a]									1
BODY CAVITY, PERICARDIAL	Fluid accumulation, pale				1*						
Blank cells: finding was not present in group or not toxicologically significant.											
<b>Organ Weights</b>	Percent changes compared to control.										
				Males		Females					
Dose (mg/kg/week)				1	3	1	3				
Organ/ Tissue	Test										
KIDNEY	Weight(g)			3	-4	9	20				
	Organ to Body Weight Ratio %			9	4	5	12				
	Organ to Brain Weight Ratio %			-1	4	20	23				
THYMUS	Weight(g)			-48	-55	15	-57				
	Organ to Body Weight Ratio %			-45	-53	13	-59				
	Organ to Brain Weight Ratio %			-50	-52	25	-55				
Organ weights were not reported for the animal with early mortality. Organ weights were not compared for the 10 mg/kg/week animals since the group was sacrificed 8 weeks prior to the other groups, including controls.											
<b>Histopathology</b>											
Sex		Male				Female					
Dose (mg/kg/week)		0	1	3	10	0	1	3	10		
Organ/ Tissue	Finding	Sev									
LIVER	Angiectasis, multifocal	MILD							2		
	Hypertrophy/ hyperplasia, multifocal, Kupffer cell	MIN		2	1			2	2		
		MILD			2*				1		
	Increased mitoses, multifocal, sinusoid	MIN		1	2			1	2		
		MILD							1		
Necrosis, hepatocellular, focal	MIN			2	1*			1			

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		Single cell necrosis, multifocal sinusoid	MIN				1			1	3
KIDNEY	Degeneration/ regeneration, tubular, bilateral, multifocal		MIN				1				2
			MILD				1				
			SEVR				1*				
	Glomerulonephritis, membranoproliferative; bilateral, multifocal		MIN				1				2
			MILD				1				
			MRK				1*				
		Increased mitoses, interstitial, bilateral, multifocal; mesangial, bilateral, multifocal	MIN				1				2
	Necrosis, urothelial, bilateral, multifocal	MILD				1					
	Single cell necrosis, urothelial, bilateral, multifocal	MIN			1	1*					
SPLEEN	Decreased cellularity, lymphoid, multifocal germinal center		MIN		1	1					1
			MILD			1					1
	Hyperplasia, lymphoid, nodular, focal and multifocal	MIN		1	1			2	1		
	Necrosis, lymphoid, multifocal, germinal center		MIN				1*				
		MILD				1				1	
LYMPH NODE, MANDIBULAR	Decreased cellularity, lymphoid, multifocal germinal center		MIN			1					2
			MILD			1*					
	Increased mitoses, medullary, bilateral, multifocal	MIN			2	1			1	3	
	Necrosis, lymphoid, multifocal, germinal center	MIN									1
LYMPH NODE, MESENTERIC	Decreased cellularity, lymphoid, multifocal, germinal center	MIN				3*					1
	Increased mitoses, medullary	MIN			1	1					1
	Necrosis, vascular, focal	MIN				1*					
LYMPH NODE, INGUINAL	Decreased cellularity, lymphoid; bilateral, multifocal, germinal center		MIN			2*					1
			MILD								1
	Hemorrhage, bilateral and unilateral, regionally extensive	MILD				1					1

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		Increased mitoses, medullary, bilateral and unilateral	MIN			1	1			1	1
	LYMPH NODE	Ectopic splenic tissue	MIN				1				
		Increased mitoses, medullary, multifocal	MIN								1
		Sinus histiocytosis	MIN				1*				
	SITE, INJECTION	Granuloma, focal	MILD							1	
		Hemorrhage, perivascular	MILD		1		1*		1		2
		Inflammation, vascular/perivascular	MIN	1	2	3		2	2	3	1
			MILD		1			1			2
	SMALL INTESTINE, ILEUM	Hemorrhage, multifocal	MIN				1*				
		Necrosis, vascular, multifocal	MILD				1*				
		Thrombus, focal	MIN				1*				
	SMALL INTESTINE, JEJUNUM	Hemorrhage, multifocal	MILD				1*				
		Necrosis, vascular, multifocal	MOD				1*				
		Thrombus, multifocal	MIN				1*				
	SMALL INTESTINE, DUODENUM	Diverticulum, focal	MIN								1
		Necrosis, vascular, multifocal	MILD				1*				
	TESTIS	Degeneration, bilateral, multifocal, seminiferous tubule	MIN				1	NA			
			MILD					1*			
	THYMUS	Decreased cellularity, lymphoid	MIN			1				3	1
			MILD				1*				
			MOD				1				1
			MRK				1				1
		Necrosis, vascular, focal	MIN				1*				
	ESOPHAGUS	Hemorrhage, multifocal	MILD				1*				
		Thrombus, focal	MIN				1*				
	GLAND, ADRENAL	Hemorrhage, cortical, bilateral, multifocal	MILD				1*				
		Mineralization, cortical, unilateral, multifocal	MIN			1					
	GLAND, SALIVARY, PAROTID	Mineralization, ductular, focal	MIN			1					
	LARGE INTESTINE, CECUM	Necrosis, vascular, multifocal	MILD				1*				

	LARGE INTESTINE, COLON	Hemorrhage, multifocal	MILD				1*				
		Necrosis, vascular, multifocal	MILD				1*				
	LARGE INTESTINE, RECTUM	Hemorrhage, multifocal	MILD				1*				
		Necrosis, vascular, multifocal	MOD				1*				
	LUNG	Infiltration, histiocytic, alveolar, multifocal	MIN		1		3*				1
		Inflammation, bronchioloalveolar, multifocal	MILD								1
		Thrombus, focal	MIN				1*				
	URINARY BLADDER	Single cell necrosis, urothelial, multifocal	MIN			2	1				1
	EYE	Rosette, unilateral, focal, retina	MIN				1*				
	HEART	Hemorrhage, focal and multifocal	MIN				1*				1
	MUSCLE, SKELETAL	Hemorrhage, focal	MOD								1
		Hemorrhage, multifocal	MRK				1				
	NERVE, SCIATIC	Hemorrhage, unilateral, focal	MIN				1				
		Hemorrhage, bilateral, multifocal	MILD				1				
	PANCREAS	Degeneration, acinar, multifocal	MIN								1
	ADIPOSE TISSUE	Hemorrhage, multifocal	MILD			1					
BODY CAVITY, ABDOMINAL	Ectopic splenic tissue, focal	MILD								1	
Blank cells: finding not present in group or not toxicologically significant.											
<ul style="list-style-type: none"> <li>Mainly at doses <math>\geq 3</math> mg/kg/week, there was minimal to mild multifocal mononuclear cell infiltrates in the liver, kidney, meninges of the brain, skeletal muscle, lumbar spinal cord and parathyroid gland. At 10 mg/kg/week, there was minimal to mild mixed cell infiltration in the lymph nodes, adrenal gland, seminal vesicle, rectum and pancreas. See Applicant's assessment for other non-adverse findings.</li> <li>Minimal mononuclear cell infiltrates were not reversible and were still present in one 10 mg/kg/week male following the recovery phase. As noted by the Applicant, minimal chronic vascular/perivascular inflammation was observed in several blood vessels of the intestinal tract in one monkey at 10 mg/kg/week, which may represent partial recovery of this finding.</li> </ul>											
<b>Other evaluations (Immunogenicity/ Immunophenotyping/</b>		Percent changes compared to control.									
		Males			Females						
Dose (mg/kg/week)	Week	1	3	1	3						

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<b>Cytokines/Complement Components</b>	IgM (g/L)	4	-5	-37	-22	-45		
		13		-52	-46	-54		
		25				-46		

Blank cells: group not evaluated at particular timepoint or findings not toxicologically significant.

Sex (Dose)	Male (10 mg/kg/week)				Female (10 mg/kg/week)			
Week	Pretest	4	7	17	Pretest	4	7	17
Test	mean	%Δ	%Δ		mean	%Δ	%Δ	%Δ
IgM (g/L)	0.6	-36	-50	-38	1	-24	-34	-21

Data for high dose animals is presented separate since samples were mostly taken on different days than other groups. %Δ: percent change relative to pretest (mean of Days -14 and -4).

**ADA**  
 The onset of ADA was generally between Weeks 4 and 7, with Week 4 being the first timepoint measured for ADA. Across all dose levels, 21 of 36 monkeys tested positive for ADA, 12 of 36 monkeys were positive for circulating immune complexes CIC (none were positive in 10 mg/kg/week groups) and 7 monkeys had detectable free ADA.

**Complement Components**  
 Complement protein Bb increased up to 1.9-fold and Complement protein C3a increased up to 1.8-fold at 1 mg/kg/week, one hour postdose on Week 13.

Abbreviations: ADA = Anti-drug antibodies; ALT = Alanine aminotransferase; ALP = Alkaline phosphatase; AST = Aspartate aminotransferase; Chol = Cholesterol; GGT = Gamma-glutamyl transferase; GLDH = Glutamate dehydrogenase; LUC = Large Unstained Cells; RDW = Erythrocytes Distribution Width; MCV = Erythrocyte Mean Corpuscular Volume; M:E ratio = Myeloid: Erythroid ratio; UABV = Urinary albumin excretion; UTPV = Urinary total protein excretion; [a] = Adjacent to skeletal muscle; \* = Gross or microscopic finding was observed in animal with early mortality; Sev = Severity MIN = Minimal; MOD = Moderate; MRK = Marked; SEVR = severe; NA = organ not present in sex. Erythrocytes values are in 10<sup>12</sup>/L units and all other absolute values are in 10<sup>9</sup>/L units.

**General toxicology; additional studies**

**Data:**

No further studies.

**The FDA's Assessment:**

The FDA notes that the 3-week (IND-enabling) and 13-week toxicology studies conducted in monkeys with weekly dosing for belantamab mafodotin had comparable toxicities and exposures. Every three week (q3w) dosing, modeling the clinical dosing regimen, was used for the 13-week rat study. In agreement with the Applicant's assessment, toxicities were overall comparable between the 3-week weekly dosing rat (IND-enabling) study and the 13-week q3w rat study, except there were more pronounced reductions in hemoglobin and larger elevations in liver enzymes, aldolase, and cytokines observed at ≥ 10 mg/kg in the 3-week rat study than the 13-week q3w rat study. Additionally, Femoro-Tibial Joint bone remodeling was present and more pronounced ovarian toxicity (luteinized nonovulatory follicle, multifocal) was observed at 30 mg/kg with weekly dosing but not q3w dosing in the rat.

Fertility studies have not been conducted with belantamab mafodotin. Results of repeat-dose toxicity studies with intravenous administration of belantamab mafodotin in rats indicate the potential for impaired male and female reproductive function and fertility. In rats, weekly dosing for 3 weeks at doses greater than or equal to 10 mg/kg (approximately 4 times the exposure at the maximum recommended human dose [MRHD] of 2.5 mg/kg, based on the area under curve [AUC] of belantamab mafodotin) resulted in degeneration and atrophy of seminiferous tubules in the testes and luteinized nonovulatory follicles in the ovaries. Findings in females were reversible; findings in the testes were not reversible at the end of the 12-week recovery period with weekly dosing or when given every 3 weeks for 13 weeks at doses greater than or equal to 10 mg/kg. In male monkeys, the highest dose tested of 10 mg/kg (approximately 4 times the AUC exposure of the MRHD), given weekly for 13 weeks, resulted in seminiferous tubules degeneration in the testes that was fully reversed following the 12-week recovery period.

### 5.5.2. Genetic Toxicology

Definitive genetic toxicology studies with belantamab mafodotin have not been conducted as it would be expected to be genotoxic based on its mechanism of action. Belantamab mafodotin was genotoxic in an in vitro micronucleus screening assay in human lymphocytes. Genotoxicity assessments of cys-mcMMAF showed it was not mutagenic in the Ames test or genotoxic in the in vitro mouse lymphoma assay, consistent with findings for monomethyl auristatin E (MMAE) and vinca alkaloids (e.g., vinblastine), which were also negative in the Ames test and mouse lymphoma assays [IARC vinblastine sulphate monograph, 1981; Lee, 2003; ADCETRIS USPI]. Although cys-mcMMAF was not genotoxic in the rat bone marrow micronucleus assay, this is considered to reflect the low cell permeability of MMAF (due to its charged C terminal phenylalanine), because freely permeable MMAE was genotoxic in this assay [ADCETRIS, USPI].

#### Other Genetic Toxicity Studies

No other genetic toxicity studies have been conducted to support the development of belantamab mafodotin. The following sections are not applicable: In Vitro Reverse Mutation Assay in Bacterial Cells (Ames), In Vitro Assays in Mammalian Cells, In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay), Other Genetic Toxicity Studies (For API only; does not refer to impurities).

#### The FDA's Assessment:

FDA disagrees with the Applicant's statement that the genetic toxicology studies are not applicable, but agrees with the Applicant that the data indicate that MMAF is genotoxic based on an aneugenic mechanism and that the genetic toxicology studies conducted, given the class of drug and the proposed indication, are sufficient to communicate a genotoxic risk in the product labeling. Specifically, the in vitro micronucleus screening assay in human lymphocytes with belantamab mafodotin showed positive results. In the absence of cytotoxicity, a statistically significant increase ( $p < 0.05$ ) in micronucleated (MN) binucleate cells that exceeded

the laboratory historical control range was observed at 577 µg/mL belantamab mafodotin (1.42% MN cells or 2.7-fold increase compared to control buffer; 95% reference range 0.26-0.75% MN cells) following treatment for 24 hours in the absence of S9-mix with a 24-hour recovery.]

### 5.5.3. Carcinogenicity

Data:

No carcinogenicity studies have been conducted to support the development of belantamab mafodotin.

The FDA's Assessment:

FDA concurs.

### 5.5.4. Reproductive and Developmental Toxicology

Reproductive and developmental studies have not been conducted since cytotoxic drugs such as belantamab mafodotin which target rapidly dividing cells, particularly in the bone marrow, are expected to be embryo/fetotoxic and teratogenic. This position is consistent with ICH S9 guidance.

An in vitro micronucleus screening assay in human lymphocytes was positive. These results are consistent with the pharmacological effect of cys-mcMMAF binding to tubulin causing microtubule disruption that would affect a developing embryo which has rapidly dividing tissue. The repeat-dose toxicology studies also indicate the potential for impairment of male/female reproductive function and fertility [see Section 5.5.1]. Adverse and progressive changes in seminiferous tubules (marked degeneration/atrophy) noted in the testes of all males rats given ≥10 mg/kg/dose associated with secondary findings in the pituitary were generally not reversible. Seminiferous tubule degeneration was also noted in monkeys following 5 weekly doses of 10 mg/kg that was fully reversible following a 12-week off-dose period. Luteinized nonovulatory follicles were observed in the ovaries of rats at doses of 10 mg/kg and above.

No embryo-fetal or pre/postnatal development studies have been conducted to support the development of belantamab mafodotin. Therefore, the corresponding Embryo-Fetal Development and Prenatal and Postnatal Development sections are not applicable.

The FDA's Assessment:

FDA concurs that belantamab mafodotin is anticipated to be embryo/feto toxic and teratogenic based on the mechanism of action belantamab mafodotin, which targets rapidly dividing cells, and the fact that the payload (MMAF) conjugated to belantamab mafodotin is aneugenic. This risk for embryofetal development will be conferred in the labeling. FDA notes that there was

ovarian toxicity in rats and the testicular toxicity in rats and monkeys . The testicular toxicity in rats was observed with both the weekly dosing (3-week study) and the q3w (13-week study) schedule; follicular toxicity was only observed with weekly dosing (3-week study). The testicular finding in monkeys was observed with weekly dosing (13-week study). The adverse testicular and ovarian findings in the animals suggest the potential for the ADC to impair fertility and the information will be communicated in the product labeling. The testicular findings were reversible in monkeys but not in rats. The follicular findings were reversible in rats (not detected in monkeys). Recommendations that women wait to breastfeed for at least 3 months (or 5 x T<sub>1/2</sub> of the ADC in humans of 14 days, rounded up to the next month) after the last dose were also conveyed in labeling.

### 5.5.5. Other Toxicology Studies

#### **In vitro Evaluation of Cytokine Release [2013N173704 (V70385N)]**

Conducting laboratory and location:  
GlaxoSmithKline  
709 Swedeland Road, King of Prussia,  
PA 19406, USA  
GLP compliance: **No**

#### The Applicant's Position:

In vitro GSK2857914 resulted in interferon gamma (IFN- $\gamma$ ), TNF- $\alpha$ , and interleukin (IL)-8 release in a concentration responsive fashion when human PBMCs were co-cultured with NCI-H929 cells. In this in vitro assay, IFN- $\gamma$  and TNF- $\alpha$  were produced predominantly by the natural killer (NK) cells, and IL-8 was produced by monocytes. Since cytokine release was dependent on both target engagement and activation of effector cells, there is an increased risk of cytokine release in participants who will have higher levels of BCMA target due to the expression on the surface of MM cells. However, when GSK2857914 is cross-linked in vitro with anti-human IgG, BCMA signaling in NCI-H929 cells as measured by increased nuclear factor-kappaB (NF- $\kappa$ B) activation was observed indicating GSK2857914 can impart agonist activity on BCMA.

#### **Cytotoxicity in Primary Human Renal Proximal Tubule Epithelial and Corneal Epithelial Cells [Report 2019N410330 (N70517-1)]**

Conducting laboratory and location:  
GlaxoSmithKline Research & Development (GSK R&D),  
Ware, Hertfordshire, UK  
GLP compliance: **No**

Experiments conducted in monolayers of human primary human corneal epithelial cells (HCEC) and renal proximal tubule epithelial cells (RPTEC) indicate that belantamab mafodotin exposure results in significant concentration-dependent increases in apoptosis in vitro. The effects were observed in multiple donors for each cell type and there is a trend for HCECs being slightly more sensitive than RPTECs when assessing the lowest tested concentrations that caused a significant increase in apoptosis over concurrent vehicle controls at 48 hours post treatment (belantamab mafodotin concentration of 30 µg/mL in HCECs and 100 µg/mL in RPTECs). Given the lack of significant BCMA expression confirmed in HCEC and RPTECs, a non-specific pathway of belantamab mafodotin uptake is likely involved in this cytotoxicity. Based on the clear trend for a reduction belantamab mafodotin-mediated apoptosis with EIPA (5-(N-ethyl-N-isopropyl)amiloride) pre/co-treatment, evidence indicates that macropinocytosis plays a role in this non-specific uptake in HCEC and RPTECs in vitro.

### **Investigative Intravenous Tolerability and Ocular Toxicity Study in New Zealand White Rabbits [Report 2018N385412 (L32295N)]**

Conducting laboratory and location:  
GlaxoSmithKline Research & Development (GSK R&D),  
Ware, Hertfordshire, UK  
GLP compliance: **No**

#### The Applicant's Position:

Female NZW rabbits (n=3/group) were given belantamab mafodotin at 0 [vehicle], 15, or 30 mg/kg/week by IV (bolus) injection for 2 (0 or 30 mg/kg/week) or 4 weeks (0, 15 or 30 mg/kg/week). Animals were euthanized 7 days (Phase I) or 8 days (Phase II) following the last dose (Days 15 and 30, respectively).

No observations were noted after 2 weekly administrations up to 30 mg/kg/week. After 4 doses of 30 mg/kg/week, corneal epithelial single cell necrosis (minimal or mild) in all 3 rabbits, potentially associated with superficial corneal haze in 1 rabbit on Days 27 and 30, was observed. Increased mitoses (minimal) in the corneal epithelium in 2 of 3 rabbits given 15 mg/kg/week for 4 weeks, was also seen. There was no belantamab mafodotin-related effect on tear production (measured using Schirmer tear test strips) when compared to vehicle control. Following ophthalmologic examination (indirect and slit-lamp biomicroscopy and fluorescein staining), bilateral striations observed in the retina of a single animal, administered 15 mg/kg/week for 4 weeks, were of uncertain relationship to treatment; this observation did not correlate with any microscopic findings in the retina following examination of multiple (n=6) sections containing the retina from this animal. Animals given 30 mg/kg/week showed a reduction in group mean body weight gain following dosing for 2 weeks (X0.82) or 4 weeks (X0.65).

**Cross Reactivity Assessment with a Selected Panel of Human Tissues [Report 2013N176627]**

Conducting laboratory and location



GLP compliance: **Yes**

An ex vivo tissue cross-reactivity study was conducted assessing specific and non-specific binding of belantamab mafodotin with human tissues. The results of this immunohistochemical analysis demonstrated antigen-specific staining of belantamab mafodotin in human spleen since belantamab mafodotin binds the BCMA receptor which has expression on B cells at later stages of differentiation. Specific positive staining was also observed in a number of tissues generally associated with individual or focal groups of the cells, blood vessel walls/perivascular tissue and connective tissue. Nonetheless, the majority of this staining was cytoplasmic, although the possibility of membranous staining cannot definitively be excluded. Tissue binding *per se* does not indicate biological activity in vivo and according to ICH S6(R1) and other references [Hall, 2008; Leach, 2010], mAb binding to membrane has more potential toxicologic significance than binding to cytoplasm or other tissue/cellular sites. No binding of belantamab mafodotin to human eye was observed.

**The FDA's Assessment:**

FDA concurs with the Applicant's assessment of the cytokine release data and the following was added to convey findings from Study No. 2013N173704.

**Cytokine Release of Human PBMCs Treated for 24 Hours With GSK2857914**

GSK2857914	Fold Δ Compared to Unstimulated			+ control
Concentration (µg/mL)	0.1	1	10	10
IL-8	18	22	21	46
IFNγ	29	39	40	140
TNFα	17	23	24	116

Positive (+) control = anti-CD3 or anti-CD28 stimulation; PBMCs and IgG crosslinking were needed for cytokine release. Cytokine induction by the Fc disabled anti-BCMA and non-binding Potelligent (afucosylated) negative control antibodies were not detected, with the exception of increased IL-8 in monocytes (up to 1.9X and 2.1X, respectively, unstimulated control). MCP-1 levels were increased 5.9X with 1 µg/mL GSK2857914 compared to unstimulated control in a different run.

- Also, in Study No. 2013N173704, NFκB activation occurred in the presence of human IgG crosslinking with GSK2857914 and the anti-BCMA Fc disabled antibody, but not with a nonspecific fucosylated (Potelligent) antibody, indicating the BCMA binding and IgG crosslinking were needed for NFκB activation to occur.

FDA concurs with the Applicant that the data from Study No. 2019N410330 support that the

macropinocytosis inhibitor EIPA reduces belantamab mafodotin-induced markers of apoptosis in HCECs or RPTECs. HCECs or RPTECs were treated with belantamab mafodotin at concentrations up to 100 µg/mL and 300 µg/mL, respectively, for 48 hours. For both HCECs (1 donor) and RPTECs (3 donors), there were significant increases in markers of apoptosis (Caspase 3/7) after 48 hours of treatment with belantamab mafodotin concentrations of ≥50 and 150 µg/mL, respectively, when compared to concurrent control. The apoptosis was reduced with 6 and 25 µM EIPA pretreatment (30 minutes). These experiments included the negative control (GSK2857914) and vinblastine sulphate (comparator tubulin inhibitor).

FDA concurs with the Applicant's overall conclusion that belantamab mafodotin caused eye toxicity in rabbits at doses ≥15 mg/kg/week for 4 weeks, but added the following information that was not included in the Applicant's assessment of Study No. L22295N:

- In Study No. L22295N, minimal focal corneal erosion was also observed in 2 out of 3 rabbits given 30 mg/kg for 2 weeks and 1 out of 3 rabbits given 15 mg/kg for 4 weeks. Additionally, the rabbit given 15 mg/kg for 4 weeks with bilateral striations also had minimal increased mitoses. In this study, mean body weight gains were 8% lower than controls after 2 weeks administration of 30 mg/kg and 47% lower than controls after administration of 30 mg/kg for 4 weeks.]

Overall, the FDA concurs with the Applicant's conclusion regarding human tissue cross-reactivity (Study No. 2013N176627) and notes that minimal to moderate membranous staining was observed in the perivascular areas and scattered mononuclear cells in the lung (1/3 samples). Specific positive cytoplasmic staining, in which the Applicant stated membranous staining could not be excluded, was observed in individual or focal groups of cells in the blood vessel walls/perivascular tissue and connective tissue. In a non-GLP study (Study No. 2013N169796), GSK2857914 showed membrane staining in the spleen of human and cynomolgus monkey tissue. Cytoplasmic granular staining was observed in human heart, kidney, and liver tissue, and in the monkey lymph node.

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Primary Reviewer

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Team Leader

## 6. Clinical Pharmacology

### 6.1. Executive Summary

#### The FDA's Assessment:

Belantamab mafodotin (BLENREP) is an antibody drug conjugate (ADC) with an afucosylated, humanized anti-B-cell maturation antigen (BCMA) monoclonal antibody (mAb) conjugated by a protease-resistant maleimidocaproyl (mc) linker to a microtubule disrupting agent, monomethyl auristatin F (MMAF). The Applicant is seeking approval of BLENREP (b) (4) (b) (4) for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) (b) (4).

At the proposed dosing regimen of 2.5 mg/kg every three weeks (Q3W), objective response rate (ORR), assessed by IRC, were observed in 30 of 97 patients (31% [97.5% CI: 20.8%, 42.6%]) in pivotal study DREAMM-2. However, 71% patients had corneal events of keratopathy (any grade), 44% patients had severe (Grade 3-4) keratopathy, and 19% patients had a decrease in best-corrected visual acuity (BCVA) of unilateral 20/50 or worse in DREAMM-2. Exposure-response (E-R) analyses indicates a relationship between higher exposures of belantamab mafodotin and higher incidence of Grade 2+ or Grade 3+ corneal events after adjusting for baseline disease characteristics. Although the proposed dosing regimen is supported by the ORR in a heavily treated patient population with RRMM in study DREAMM-2, the high risk of ocular toxicity warrants further investigation of the benefit-to-risk profiles of lower doses or alternative dosing regimens of BLENREP (b) (4). A PMR to investigate a dosage regimen that will minimize the serious risk of ocular toxicity without clinically significant impact on efficacy for BLENREP in this patient population will be issued.

**Recommendations:** The Office of Clinical Pharmacology has reviewed the information submitted in BLA761158. This BLA is approvable from a clinical pharmacology perspective. However, there are several key Clinical Pharmacology review issues need to be addressed by post marketing requirements (PMRs). Specific recommendations/comments are summarized in Table 3 below.

**Table 3. Key Clinical Pharmacology Review Issues by FDA**

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from the DREAMM-1 and DREAMM-2 studies. Objective responses, assessed by IRC, were observed in 30 of the 97 patients (31% [97.5% CI: 20.8%, 42.6%]) treated with belantamab mafodotin

	2.5 mg/kg every three weeks (Q3W) in pivotal study DREAMM-2. However, high rates of ocular toxicity (71% of keratopathy), associated with high belantamab exposures, were observed at the proposed dosage regimen.
General dosing	The proposed dosage is 2.5 mg/kg Q3W. Administer as an intravenous infusion over approximately 30 minutes after reconstitution and dilution.
Dosing in patient subgroups (intrinsic and extrinsic factors)	<ul style="list-style-type: none"> <li>The pharmacokinetics (PK) of belantamab mafodotin in patients with moderate and severe hepatic impairment (total bilirubin &gt;1.5 x ULN and any AST) is unknown. This will be studied as a PMR.</li> <li>The PK of belantamab mafodotin in patients with severe renal impairment (eGFR &lt; 30 mL/min/1.73 m<sup>2</sup>) and end stage renal disease (ESRD) (eGFR &lt; 15 mL/min/1.73 m<sup>2</sup>) is unknown. This will be studied as a PMR.</li> </ul>
Bridging between the to-be-marketed formulation (lyophilized powder) and clinical trial formulations (frozen liquid)	<p>A comparison of the PK, efficacy, and safety of the lyophilized and frozen formulations at dose level of 3.4 mg/kg were conducted with the following observations:</p> <ul style="list-style-type: none"> <li>PK: No significant differences in the C<sub>max</sub> and AUC<sub>0-inf</sub> of belantamab mafodotin (ADC) when given as a lyophilized powder compared to frozen liquid.</li> <li>PK: The trough concentrations (C<sub>tau</sub>) of ADC is 34% higher in the lyophilized powder cohort compared to the frozen liquid.</li> <li>Efficacy: ORR was numerically higher in the lyophilized powder cohort (48%, N=24) than that in the frozen liquid formulation (34%, N=99).</li> <li>Safety: Higher incidence of keratopathy (92% vs. 77%) was observed in the lyophilized formulation cohort compared to the frozen cohort.</li> </ul> <p>In the BE comparison, an adequate comparison of the PK exposure of cys-mcMMAF could not be conducted due to bioanalytical issue. Further, there was an imbalance in the baseline disease characteristics between the two cohorts that may contribute to the observed numeric difference in ADC C<sub>tau</sub>, ORR and corneal events at 3.5 mg/kg Q3W.</p>
Bioanalytical assay for cys-mcMMAF	The long-term storage stability data provided was not sufficient for characterizing PK of cys-mcMMAF. The long-term storage stability data to support further analysis of cys-mcMMAF should be studied in a PMR.

Labeling	The review team has specific content and formatting change recommendations for the product labeling. Significant modifications to the label made by the FDA include the addition of Section 8.6 Renal Impairment and Section 8.7 Hepatic Impairment, the request to add statement about E-R relationship in Section 12.2, and the format and content in Section 12.3.
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## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

#### The Applicant's Position:

The clinical pharmacology portion of the submission characterizes the pharmacokinetics of belantamab mafodotin, total monoclonal antibody (antibody with or without MMAF; total mAb), and cysteine maleimidocaproyl monomethyl auristatin F (cys-mcMMAF) based on data following single and repeated IV administration from 291 participants with RRMM enrolled in the FTIH study BMA117159 (DREAMM-1) and the pivotal study 205678 (DREAMM-2). The results have been combined to describe belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetics, to assess the potential impact of intrinsic and extrinsic factors on pharmacokinetics, and to perform exposure-response analyses for efficacy and safety endpoints.

Belantamab mafodotin pharmacokinetics were well described by a linear two-compartment population model with a time-varying decrease in clearance in a population pharmacokinetic analysis. Clearance and volume of distribution values were low and half-life values were long, as seen with other monoclonal antibody-based therapeutics. Based on the population pharmacokinetic analysis, belantamab mafodotin had a systemic clearance of 0.936 L/day, a steady-state volume of distribution of 10.4 L, and an elimination half-life of 11.5 days for a typical relapsed/refractory multiple myeloma participant in DREAMM-2. Over time, the clearance was reduced to 0.674 L/day with an elimination half-life of 14.3 days (time-varying clearance). The time to 50% change in clearance was approximately 50 days.

Body weight and gender had statistically significant but not clinically meaningful effects on belantamab mafodotin and cys-mcMMAF pharmacokinetics; no dose adjustment is necessary. Other factors such as age, race, mild or moderate renal impairment, mild hepatic impairment, and presentation (frozen liquid or lyophilized [lyo]) had no significant effect. Disease-related factors (baseline soluble B-cell maturation antigen [sBCMA]), baseline IgG, baseline albumin) had the most significant effects on belantamab mafodotin and/or cys-mcMMAF pharmacokinetics; the clinical relevance of these relationships is unknown.

The overall immunogenicity risk for belantamab mafodotin is low. The current clinical data are consistent with this assessment; post-belantamab mafodotin antibody responses to date have been both low in incidence (2/274 participants) and with no obvious effects on the safety, efficacy, pharmacokinetics, or pharmacodynamics of belantamab mafodotin.

The results of the exposure-QTc analysis demonstrated that belantamab mafodotin did not have a significant effect on cardiac repolarization.

The clinical efficacy results and exposure-efficacy relationships showed similar benefit in the 2 cohorts. The clinical safety results and exposure-safety relationships showed better tolerability in the 2.5 mg/kg cohort than in the 3.4 mg/kg cohort. Integrated exposure-response results (Section 6.3.1) suggested an increased probability of corneal exam findings and thrombocytopenia with higher exposure or higher dose that was not associated with a commensurate improvement in efficacy. Based on these results, the 2.5 mg/kg Q3W regimen given as an IV infusion over approximately 30 minutes is recommended as single-agent therapy in patients with RRMM.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment on pharmacology and clinical pharmacokinetics.

The Applicant's PopPK model is acceptable to characterize the PK of the ADC and total mAb (see Appendices 20.4.2.1). However, the long-term storage stability data for the cys-mcMMAF bioanalytical method is inadequate to support the quantifiable samples in DREAMM-1 and DREAMM-2. As such, there is insufficient data to characterize the PK of cys-mcMMAF or to conduct any PK-related analysis (PopPK, E-R or concentration-QTc analyses) for cys-mcMMAF.

The exposure ( $C_{max}$  and  $AUC_{0-inf}$ ) of belantamab mafodotin when given as either a frozen liquid or lyophilized powder formulations were comparable at the same dose level of 3.4 mg/kg Q3W in DREAMM-2. The geometric mean of trough concentration ( $C_{tau}$ ) of ADC was approximately 34% higher in the lyophilized cohort compared to the frozen cohort, this difference may be due to an imbalance in patient factors between the two cohorts, such as baseline sBCMA and IgG levels, which have a significant impact on the ADC PK.

The FDA notes that a low number of patients (2/247) developed antibodies against belantamab mafodotin (see detail in Table 5). Potential effects of immunogenicity on PK, efficacy and safety are unlikely.

## 6.2.2. General Dosing and Therapeutic Individualization

### 6.2.2.1. General Dosing

#### The Applicant's Position:

The recommended dose of belantamab mafodotin is 2.5 mg/kg Q3W as an IV infusion over approximately 30 minutes until disease progression or unacceptable toxicity based on data from DREAMM-2.

Although the study was not designed to compare the 2 dose levels, the 2.5 mg/kg dose was selected as the recommended dose for the submission and for future studies of single-agent belantamab mafodotin based on the comparable efficacy outcomes with a more favorable safety profile compared with the 3.4 mg/kg dose (e.g., lower incidence of thrombocytopenic and neutropenic events and less frequent dose delays or reductions).

As described in Section 6.3.1, integrated exposure-response results suggested an increased probability of corneal exam findings and thrombocytopenia with higher exposure or higher dose that was not associated with a commensurate improvement in efficacy.

Based on these results in DREAMM-2, the 2.5 mg/kg Q3W regimen given as an IV infusion over approximately 30 minutes is supported as single-agent therapy in patients with RRMM. Further details on dose selection are provided in Section 6.3.2.2.

#### The FDA's Assessment:

FDA agrees that the recommended dosing regimen of 2.5 mg/kg Q3W has comparable efficacy and a more favorable safety profile than the 3.4 mg/kg Q3W dosing regimen (see Section 6.3.2.2 and Appendices 20.4.3). However, there are significant concerns regarding the high risk of ocular toxicity at the 2.5 mg/kg Q3W dosing regimen.

The FDA notes that among 95 patients who received treatment BLENREP 2.5 mg/kg Q3W with a median follow-up of 9 months, keratopathy (any grade) occurred in 71% of patients, including 44% Grade 3 with no Grade 4 events reported. Nineteen percent of patients had decrease in best-corrected visual acuity (BCVA) of unilateral 20/50 or worse and 17% of patients had bilateral 20/50 or worse. Nearly half (47%) of the patients required at least one dose interruption and 20% of patients required at least one dose reduction due to keratopathy. Additional details about the safety of belantamab mafodotin are provided in Section 8.2.

Increasing doses and exposures ( $C_{tau}$  and  $C_{avg}$ ) of belantamab mafodotin were associated with increasing probability of Grade 2+ or 3+ corneal events (GSK scale), and limited data also suggest that higher  $C_{max}$  may be associated with an increased risk of ocular toxicity (see Section

6.3). Given the high rates of ocular toxicity observed with the 2.5 mg/kg Q3W dose, and the limited data available at lower doses or alternative regimens, additional clinical safety and efficacy information for belantamab mafodotin is needed to assess if there is an efficacious dose with less risk of ocular toxicity.

#### 6.2.2.2. Therapeutic Individualization

##### The Applicant's Position:

Therapeutic individualization of dose is not required for subpopulations based on intrinsic patient factors according to the results of population pharmacokinetic analyses. Please see Section 6.3.2.3 for more details.

##### The FDA's Assessment:

The FDA agrees with the Applicant's position that no therapeutic individualization is needed based on demographic factors (age, race, sex). Further, no dose adjustment is needed in patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 x ULN or AST greater than ULN), or in patients with mild or moderate renal impairment (eGFR  $\geq$  30 mL/min/1.73m<sup>2</sup>). No belantamab mafodotin data is available in patients with moderate or severe hepatic impairment or patients with severe renal impairment or with ESRD. Baseline sBCMA has significant impact on belantamab mafodotin PK exposure ( $C_{\tau}$ ), ORR, PFS, Grade 2+ or 3+ corneal event, visual acuity worsening. Dose adjustments based on baseline sBMCA may need to be further explored in future studies (see details in Section 6.3.2.3).

#### 6.2.2.3. Outstanding Issues

##### The Applicant's Position:

The clinical pharmacology portions of the application have data from only a limited number of patients with severe renal impairment and do not have data from patients with moderate or severe hepatic impairment; data from patients with mild or moderate renal impairment and mild hepatic impairment were included in the population pharmacokinetic analyses, with no significant effect on belantamab mafodotin or cys-mcMMAF pharmacokinetics (Section 6.3.1). Organ impairment studies to include more severe levels of impairment are planned. In the current development program of single-agent belantamab mafodotin, no clinical studies to date have assessed drug-drug interactions; assessments are planned or ongoing in combination Phase I/II studies.

##### The FDA's Assessment:

Given the high ocular toxicities of belantamab mafodotin at the current recommended dosing

regimen of 2.5 mg/kg Q3W, additional information to identify a starting dose that will minimize the risk of corneal toxicity without clinically significant impact on efficacy is needed and will be generated in a PMR.

The FDA agrees with the Applicant that organ impairment studies to include more severe levels of impairment are needed. PMRs to assess the PK and safety of belantamab mafodotin in patients with severe renal impairment and in patients with moderate or severe hepatic impairment will be needed.

The cys-mcMMAF concentration data submitted in the BLA were not fully supported by long-term storage stability assessment and are not considered reliable for safety assessment or adequate labeling. Adequate validation of the long-term storage stability assessment for cys-mcMMAF concentration data and an evaluation of its relationship with safety events (such as corneal events) will need to be addressed.

### 6.3. Comprehensive Clinical Pharmacology Review

#### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

**Absorption:** Belantamab mafodotin is administered intravenously. Maximum concentrations of belantamab mafodotin and total mAb were observed at or shortly after the end of the infusion.

In the 2.5 mg/kg cohort in DREAMM-2, geometric mean (CVb) belantamab mafodotin C<sub>max</sub> and AUC(0-τ) values were 42.5 μg/mL (26%) and 4666 μg.h/mL (46%) at Cycle 1. For cys-mcMMAF, the geometric mean C<sub>max</sub> and AUC(0-168h) values were 0.903 ng/mL (64%) and 84.3 ng.h/mL (59%) at Cycle 1; cys-mcMMAF concentrations were <0.1% of belantamab mafodotin concentrations on a molar basis. After a planned infusion duration of 0.5 h, median t<sub>max</sub> (range) values were 0.78 h (0.42-2.50 h) for belantamab mafodotin and 22.83 h (1.92-65.63 h) for cys-mcMMAF at Cycle 1.

**Distribution:** Belantamab mafodotin had a small volume of distribution (10.4 L), consistent with distribution largely in the systemic circulation. Cys-mcMMAF exhibited low protein binding in human plasma in a concentration-dependent manner, with unbound percentages ranging from 49.1 to 61.8% at 0.5 ng/mL, from 68.8 to 70.7% at 5 ng/mL, and from 80.9 to 88.7% at 50 ng/mL (to date, all cys-mcMMAF C<sub>max</sub> values were <5 ng/mL). Cys-mcMMAF was an *in vitro* substrate of organic anion transporting polypeptide (OATP) 1B1 and 1B3, multidrug resistance associated protein (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp).

**Metabolism:** The expected metabolic pathway for the monoclonal antibody portion of belantamab mafodotin is degradation to small peptides and individual amino acids by

ubiquitous proteolytic enzymes. Cys-mcMMAF has limited metabolic clearance; *in vitro* and in a preclinical study, the maleimide ring was predominantly chemically hydrolyzed and dehydrated to a cyclized isomeric form of cys-mcMMAF, with a very minor amount of Phase I/II enzymatic biotransformation.

**Excretion:** Belantamab mafodotin had an initial systemic clearance of 0.936 L/day and an elimination half-life of 11.5 days for a typical relapsed/refractory multiple myeloma participant in DREAMM-2. Over time, the clearance was reduced to 0.674 L/day with an elimination half-life of 14.3 days (time-varying clearance). The time to 50% change in clearance was approximately 50 days.

Cys-mcMMAF was detected in urine samples collected in DREAMM-1; no metabolites were seen. Following IV dosing of <sup>3</sup>H-cys-mcMMAF in animal studies, radioactivity was excreted in feces (83%) and urine (13%), predominantly as either the linear or cyclized isomers of cys-mcMMAF.

#### **Clinical Pharmacokinetics:**

Belantamab mafodotin pharmacokinetics were well described by a linear two-compartment population model with a time-varying decrease in clearance in a population pharmacokinetic analysis. Clearance and volume of distribution values were low and half-life values were long, as seen with other monoclonal antibody-based therapeutics.

- Belantamab mafodotin had a systemic clearance of 0.936 L/day, a steady-state volume of distribution of 10.4 L, and an elimination half-life of 11.5 days for a typical relapsed/refractory multiple myeloma participant in DREAMM-2.
- Over time, the clearance was reduced to 0.674 L/day with an elimination half-life of 14.3 days (time-varying clearance).

Disease-related characteristics (baseline sBCMA, baseline IgG, and baseline albumin) were the most significant factors associated with belantamab mafodotin and/or cys-mcMMAF exposure, with values at higher disease burden associated with lower belantamab mafodotin exposure.

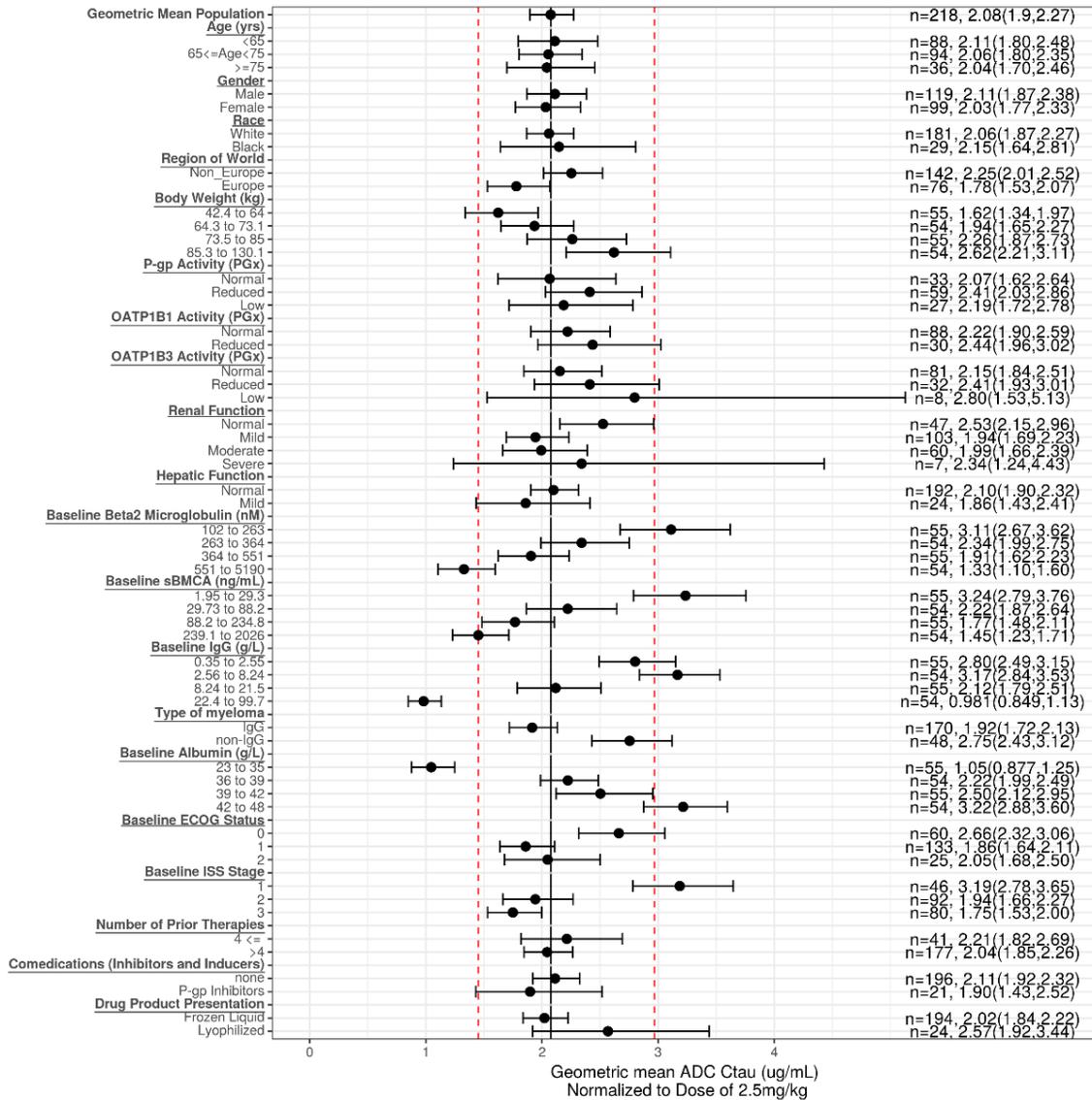
Body weight was of lesser significance with allometric exponents close to 0.5 for belantamab mafodotin CL and V1. Body weight effects were compensated for by the weight-proportional dosing regimen, resulting in largely overlapping belantamab mafodotin or cys-mcMMAF exposure ranges for body weight groups. Gender had a small effect on belantamab mafodotin central volume of distribution that was not clinically relevant. Participants receiving a dose less than 1 mg/kg (all in DREAMM-1) and participants in DREAMM-1 were found to have a higher clearance and volume of distribution for belantamab mafodotin.

Mild or moderate renal impairment, mild hepatic impairment, age, ethnicity, African American race, prior treatments, region, and belantamab mafodotin presentation (frozen liquid or lyo)

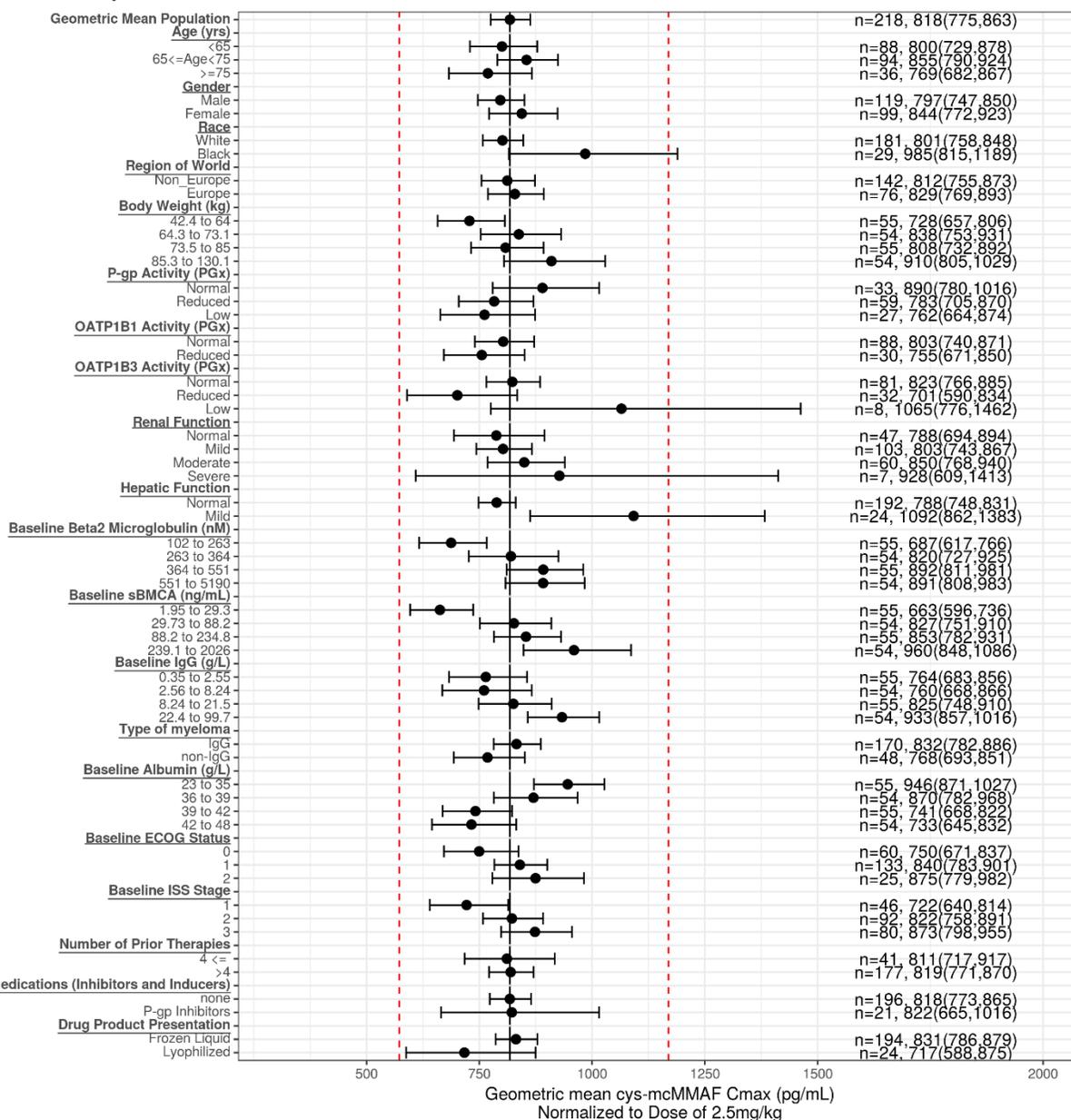
were not found to have a significant impact on the PK parameters for belantamab mafodotin or cys-mcMMAF. No dose adjustment is therefore recommended for these factors.

The forest plots in Figure 1 and Figure 2 show that there were no major differences in belantamab mafodotin  $C_{\tau}$  and cys-mcMMAF  $C_{max}$  across the important clinical covariates of age, gender, race, renal function category, hepatic function category, region, and drug product presentation. The cys-mcMMAF  $C_{max}$  was ~39% higher in participants with mild hepatic impairment, which could be explained by the presence of demographic factors associated with higher exposure (e.g., higher median baseline sBCMA and lower median baseline albumin) in that group; analysis by typical markers of hepatic function (ALT, AST, total bilirubin) saw no strong trends with cys-mcMMAF clearance in the population pharmacokinetic analysis.

**Figure 1. Forest Plot of *Post Hoc* Cycle 1 Belantamab Mafodotin C<sub>τ</sub> in Various Subgroup Populations (DREAMM-2)**



**Figure 2. Forest Plot of *Post Hoc* Cycle 1 Cys-mcMMAF Cmax in Various Subgroup Populations (DREAMM-2)**



**Frozen Liquid and Lyophilized (Lyo) Presentations:** The 2 main cohorts in DREAMM-2 (2.5 mg/kg and 3.4 mg/kg) received the frozen liquid presentation; a cohort of 24 participants received the lyo presentation at 3.4 mg/kg in order to gain clinical experience with it. In noncompartmental analyses, belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetics appeared similar between the presentations (Table 4). Presentation (frozen

liquid or lyo) was not a significant factor affecting belantamab mafodotin and/or cys-mcMMAF pharmacokinetics based on the population pharmacokinetic analysis.

**Table 4. Summary of Key Belantamab Mafodotin and Cys-mcMMAF PK Parameters (DREAMM-2)**

Parameter	Belantamab Mafodotin					
	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)		3.4 mg/kg Lyophilized (N=24)	
	n	Value	n	Value	n	Value
AUC(0- $\tau$ ) ( $\mu\text{g}\cdot\text{h/mL}$ )	30	4666 (46)	20	5678 (40)	22	5946 (37)
AUC(0- $\infty$ ) ( $\mu\text{g}\cdot\text{h/mL}$ )	26	5644 (40)	18	6495 (54)	18	6962 (51)
Cmax ( $\mu\text{g/mL}$ )	32	42.5 (26)	21	52.0 (20)	22	51.3 (18)
CL (mL/h)	26	36.1 (42)	18	38.0 (51)	18	37.1 (47)
Vss (L)	26	8.03 (30)	18	8.33 (28)	18	9.04 (26)
t $_{1/2}$ (days)	29	6.85 (46)	19	6.91 (55)	22	8.18 (41)
Cys-mcMMAF						
AUC(0-168) (ng.h/mL)	14	84.3 (59)	12	109.4 (55)	7	81.6 (58)
t $_{\text{last}}$ (days)	27	7.78 (2.78-12.89)	20	7.90 (2.64-20.96)	19	6.93 (2.91-10.89)
Cmax (ng/mL)	27	0.903 (61)	20	1.15 (65)	19	1.02 (61)
t $_{\text{max}}$ (h)	27	22.83 (1.92-65.63)	20	23.84 (17.38-72.65)	19	24.08 (0.97-69.47)

Data presented as geometric mean (%CVb), except t $_{\text{max}}$  and t $_{\text{last}}$ , presented as median (minimum-maximum)

**Cys-mcMMAF Bioanalytical Method:** The bioanalytical method used to measure cys-mcMMAF in DREAMM-1 and in DREAMM-2 (cys-mcMMAFHUPLPKB; PKB) could overestimate plasma cys-mcMMAF concentrations. A new method (cys-mcMMAFHUPLPKC; PKC) was developed and validated; it was used to measure cys-mcMMAF concentrations in DREAMM-2. All analyses using the DREAMM-2 data used the results of the PKC method. There was a strong linear relationship between the concentration results with the 2 assays ( $R^2 = 0.973$ ); this relationship was used to correct the concentration data for DREAMM-1 for pharmacokinetic analysis.

**Immunogenicity:** The assessment of the immunogenicity risk with belantamab administration is low. The current clinical data are consistent with this assessment. In DREAMM-1, there were no confirmed positive post-baseline ADA results (n=71). As of the data cut-off in DREAMM-2, there were two confirmed positive post-baseline ADA results (n=203). Both confirmed positive results occurred in participants receiving the frozen liquid presentation and had titer values near the sensitivity limit of the assay (titers = 100). One of the two confirmed positive results subsequently tested positive for neutralizing antibodies. Overall, the rate of post-dose anti-drug

antibodies in the 2 clinical trials is 2/274 participants. There were no apparent clinical consequences related to the presence of anti-belantamab antibodies, although there were too few participants with positive ADA results to reach a conclusion.

**Exposure-Response for Efficacy Endpoints:** Probability of response (defined as PR or better) was inversely related to a disease-related factor (baseline sBCMA), with no significant relationship with exposure to belantamab mafodotin for DREAMM-2. In DREAMM-1, probability of response was positively related to belantamab mafodotin C<sub>τ</sub>. No other covariates were found to be a determinant of probability of response.

Progression-free survival was significantly inversely related to disease-related factors (baseline β<sub>2</sub>-microglobulin, baseline sBCMA), and exposure to belantamab mafodotin was not found to be a significant factor for DREAMM-2. No other covariates were found to be significant. In DREAMM-1, progression-free survival was significantly related to log of belantamab mafodotin C<sub>τ</sub>, with no other covariates being found to be significant.

No exposure variable was found to significantly impact the duration of response in either DREAMM-2 or DREAMM-1.

**Exposure-Response for Safety Endpoints:** Probability of ≥Grade 2 corneal exam findings was significantly positively related to belantamab mafodotin C<sub>τ</sub> and history of dry eye and inversely related to baseline sBCMA. Probability of ≥Grade 3 corneal exam findings was significantly positively related to belantamab mafodotin C<sub>τ</sub> and inversely related to baseline sBCMA (DREAMM-2). Time to ≥Grade 2 or ≥Grade 3 corneal exam findings was inversely related to belantamab mafodotin C<sub>τ</sub>. No other covariates were found to be significant.

In DREAMM-1, probability of ≥Grade 2 corneal event using NCI-CTCAE scale was significantly related to belantamab mafodotin C<sub>τ</sub>, with time to ≥Grade 2 event being inversely related to natural log of belantamab mafodotin C<sub>τ</sub>.

Probability of any grade and ≥Grade 2 keratopathy events using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale was significantly positively related to belantamab mafodotin C<sub>τ</sub> and inversely related to baseline sBCMA (DREAMM-2). In addition, probability of ≥Grade 2 keratopathy events was higher in participants with a history of dry eye (DREAMM-2 full population only).

Probability of blurred vision events of any grade using NCI-CTCAE scale was significantly inversely related to baseline sBCMA and higher with an history of dry eye (DREAMM-2). Probability of ≥Grade 2 blurred vision events was significantly higher with presence of keratopathy at baseline (DREAMM-2) and inversely related to baseline sBCMA (DREAMM-2 full population only).

No covariates were found to explain the probability of any grade or  $\geq$ Grade 2 dry eye events using NCI-CTCAE scale except for a significant inverse relationship of baseline sBCMA with occurrence of dry eye events of any grade using the DREAMM-2 full population.

Probability of  $\geq$ Grade 3 thrombocytopenia was inversely related to baseline platelet count and positively related to natural log of cys-mcMMAF Cmax (DREAMM-2) or cys-mcMMAF Cmax (DREAMM-2 and DREAMM-1 combined).

No covariates were found to explain the probability of  $\geq$ Grade 3 neutropenia or the probability of occurrence of infusion-related reaction.

**Integrated Exposure-Response Summary:** The exposure-response analyses for Study 205678 found that both efficacy and safety endpoints were associated with disease factors and patient characteristics. Safety endpoints were most strongly associated with exposure, while efficacy endpoints had a weaker association with exposure, especially after disease factors and patient characteristics were accounted for in multivariate modeling; exposure was not retained in the final models for probability of response or progression-free survival. These results suggest an increased probability of corneal exam findings and thrombocytopenia with higher exposure or higher dose that was not associated with a commensurate improvement in efficacy.

**Concentration-QTc analysis:** No obvious relationship was found between observed and change from baseline RR, QT, QTc, and QTcF and concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF. Linear regression indicated a very slow rate of change in QTc/QTcF with increasing concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF. Consequently, the likelihood of a drug-related 10 msec increase is very low (zero and  $<0.25\%$  for QTc and QTcF, respectively) following administration of 2.5 or 3.4 mg/kg of belantamab mafodotin. The results of the exposure-QTc analysis demonstrated that belantamab mafodotin did not have a significant effect on cardiac repolarization.

#### The Applicant's Position:

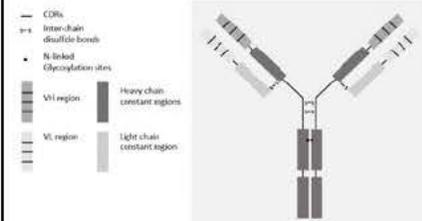
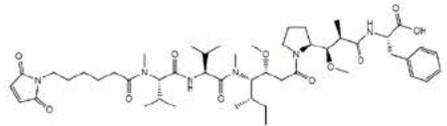
The clinical pharmacology of belantamab mafodotin, total mAb, and cys-mcMMAF has been well characterized following IV single and repeat-dose administration in the Phase I FTIH study DREAMM-1 and the Phase II pivotal study DREAMM-2.

#### The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment on general pharmacology and pharmacokinetic characteristics of belantamab mafodotin. No drug-related increase in QT greater than 10 msec is expected at the proposed dose of 2.5 mg/kg every 3 weeks.

The general overview of belantamab mafodotin ADME and clinical PK information as assessed by FDA are presented in the following Table 5.

**Table 5. Highlights of Clinical Pharmacology for Belantamab mafodotin**

Physical and Chemical Properties	
<b>Chemical Structure and Formula</b>	 <p>Schematic Representation of Belantamab</p>  <p>Chemical Structure of mcMMAF (SGD-1269)</p> <p>Belantamab mafodotin is an antibody drug conjugate (ADC), consisting of an afucosylated, humanized anti-B-cell maturation antigen (BCMA) monoclonal antibody belantamab (GSK2857914), a protease-resistant maleimidocaproyl (mc) linker, and a microtubule disrupting agent monomethyl auristatin F (MMAF).</p> <p>Molecular weight of belantamab mafodotin (GSK2857916): 152,069 Da                      Molecular weight of belantamab (GSK2857914): 148,367 Da                      Molecular weight of mcMMAF(SGD-1269, GSK3206291A): 925 Da                      Target drug-to-antibody ratio (DAR): 4</p>
Pharmacology	
<b>Mechanism of Action</b>	The mechanism of action (MOA) involves the delivery of cytotoxic microtubule disrupting agent MMAF to anti-BCMA expressing cells, antibody-dependent cellular toxicity, inducing antibody-dependent cellular phagocytosis and inducing immunogenic cell death.
<b>Active Moieties</b>	Belantamab mafodotin (GSK2857916) and unconjugated payload cys-mcMMAF
<b>QT/QTc Prolongation</b>	By-time QT analyses suggests that there is no large QTc prolongation (i.e., >20 msec) at the recommended dose of 2.5 mg/kg Q3W (see QT-IRT review).
General Information	
<b>Bioanalysis</b>	Belantamab mafodotin, total monoclonal antibody (belantamab with or without the conjugated payload) and cys-mcMMAF were measured in the plasma from Study BMA117159 and Study 205678. Cys-mcMMAF was also quantified in the urine from Study BMA117195. Belantamab mafodotin and total antibody were quantified by validated enzyme linked immunosorbent assays (ELISA). Concentrations of cys-mcMMAF in human plasma and urine were quantified using validated UHPLC-MS/MS analysis methods. However, the number of cys-mcMMAF bioanalytical samples validated by available long-term storage stability data is not sufficient to conduct PK analyses. Therefore, PK, PopPK and E-R analyses results for cys-mcMMAF were not reviewed. See Appendices 20.4.1.
<b>Healthy Volunteers vs. Patients</b>	No clinical studies were conducted in healthy volunteers.
<b>Drug exposure at steady state following the therapeutic dosing regimen</b>	In adult patients who received belantamab mafodotin 2.5 mg/kg Q3W in DREAMM-2 study, the geometric mean (CV%) of steady state $C_{max}$ was 42.4 µg/mL (26%) and $AUC_{(0-\tau)}$ was 6399 µg*h/mL (32%) for belantamab mafodotin based on noncompartmental PK analyses.

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[TRADE NAME] belantamab mafodotin

<b>Minimal effective dose or exposure</b>	Not determined.													
<b>Maximal tolerated dose or exposure</b>	In Study BMA117195, there were no formal DLTs at belantamab mafodotin at doses ranging from 0.03 to 4.6 mg/kg Q3W, and the MTD was not reached.													
<b>Dose Proportionality</b>	<p>The dose proportionality of belantamab mafodotin pharmacokinetics was examined by exploratory analyses using power models with PK parameters estimated following a single dose administration on Day 1 of Cycle 1 in Study BMA117195.</p> <p>As shown in the table below, the slope estimation for <math>C_{max}</math> was approximately 1 within the dose range of 0.12 to 4.6 mg/kg for belantamab mafodotin or total mAb and for <math>AUC_{0-inf}</math> of belantamab mafodotin or total mAb.</p> <table border="1"> <thead> <tr> <th>Analytes</th> <th>PK Parameters</th> <th>Slope Estimate (90% CI)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Belantamab mafodotin</td> <td><math>C_{max}</math></td> <td>1.05 (1.00, 1.11)</td> </tr> <tr> <td><math>AUC_{(0-inf)}</math></td> <td>0.83 (0.61, 1.04)</td> </tr> <tr> <td rowspan="2">Total mAb</td> <td><math>C_{max}</math></td> <td>1.02 (0.97, 1.06)</td> </tr> <tr> <td><math>AUC_{(0-inf)}</math></td> <td>0.97 (0.81, 1.14)</td> </tr> </tbody> </table>	Analytes	PK Parameters	Slope Estimate (90% CI)	Belantamab mafodotin	$C_{max}$	1.05 (1.00, 1.11)	$AUC_{(0-inf)}$	0.83 (0.61, 1.04)	Total mAb	$C_{max}$	1.02 (0.97, 1.06)	$AUC_{(0-inf)}$	0.97 (0.81, 1.14)
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Total mAb	$C_{max}$	1.02 (0.97, 1.06)												
	$AUC_{(0-inf)}$	0.97 (0.81, 1.14)												
<b>Accumulation</b>	<p>At the recommended dosing regimen of 2.5 mg/kg Q3W, the accumulation ratios calculated for each analyte based on <math>C_{max}</math> and AUC values at Cycle 3 compared to the values at Cycle 1, if the dose had not been changed or delayed <math>\geq 3</math> days, are shown in the table below.</p> <table border="1"> <thead> <tr> <th>Analytes</th> <th>PK Parameters</th> <th>Accumulation Ratio (CV%)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Belantamab mafodotin</td> <td><math>C_{max}</math></td> <td>1.09 (20%)</td> </tr> <tr> <td><math>AUC_{(0-tau)}</math></td> <td>1.69 (50%)</td> </tr> <tr> <td rowspan="2">Total mAb</td> <td><math>C_{max}</math></td> <td>1.20 (22%)</td> </tr> <tr> <td><math>AUC_{(0-tau)}</math></td> <td>1.94 (52%)</td> </tr> </tbody> </table>	Analytes	PK Parameters	Accumulation Ratio (CV%)	Belantamab mafodotin	$C_{max}$	1.09 (20%)	$AUC_{(0-tau)}$	1.69 (50%)	Total mAb	$C_{max}$	1.20 (22%)	$AUC_{(0-tau)}$	1.94 (52%)
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	$AUC_{(0-tau)}$	1.94 (52%)												
<b>Variability</b>	<p>After repeat dosing of 2.5 mg/kg Q3W, inter-subject variability (CV%) for belantamab mafodotin and total mAb are shown below:</p> <p>inter-subject variability (CV%) for belantamab mafodotin exposure: 26% for <math>C_{max}</math> and 32% for <math>AUC_{(0-tau)}</math>.                      Inter-subject variability (CV%) of total mAb exposure: 26% for <math>C_{max}</math> and 44% for <math>AUC_{(0-tau)}</math>.</p>													
<b>Immunogenicity</b>	A low number of patients (2/247) developed antibodies against belantamab mafodotin. One subject had positive ADA at Cycle 2 Day 1 but was negative for neutralizing Ab (nAb). None of them were positive for ADA or nAb at Cycle 6 Day 1 and Cycle 9 Day 1. The second subject was tested positive for both ADA and nAb at the end of treatment.													
<b>Absorption</b>														
<b>Bioavailability</b>	Bioavailability of belantamab mafodotin is complete, since it is administered by IV infusion.													
<b>Tmax</b>	After a planned infusion duration of 0.5 h, median $T_{max}$ (range) values were 0.78 h (0.42-2.50 h) at Cycle 1 and 0.58 h (0.47-2.03 h) at Cycle 3 for belantamab mafodotin.													
<b>Substrate transporter systems [in vitro]</b>	Cys-mcMMAF was an in vitro substrate of organic anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, and a possible substrate of bile salt export pump (BSEP) and P-glycoprotein (P-gp).													
<b>Distribution</b>														

<b>Volume of Distribution</b>	Based on the population pharmacokinetic analysis, belantamab mafodotin had a small volume of distribution (11 L).
<b>Plasma Protein Binding</b>	In vitro, cys-mcMMAF exhibited low protein binding in human plasma in a concentration-dependent manner; the unbound percentages in the three donors ranged from 49 to 62% at 0.5 ng/mL, from 69 to 71% at 5 ng/mL, and from 81 to 89% at 50 ng/mL.
<b>Blood to Plasma Ratio</b>	Not determined.
<b>Elimination</b>	
<b>Half-life</b>	The estimated elimination half-life of belantamab mafodotin ranges from 11.5 days after single dose to 14.3 days at steady state.
<b>Clearance</b>	Based on the population pharmacokinetic analysis, belantamab mafodotin had an initial systemic clearance of 0.936 L/day for a typical relapsed/refractory multiple myeloma subject in Study 205678. Over time, the clearance was reduced to 0.674 L/day at steady state.
<b>Metabolism</b>	
<b>Primary metabolic pathway(s)</b>	The monoclonal antibody portion of belantamab mafodotin is expected to be metabolized into small peptides and individual amino acids by catabolic pathways.  In vitro, cys-mcMMAF is mainly hydrolyzed and dehydrated to a cyclized isomeric form of cys-mcMMAF, which is shown to be not NADPH- nor UDPGA-dependent.
<b>Inhibitor/Inducer</b>	Cys-mcMMAF was not an inhibitor or an inducer of cytochrome P450 enzymes in vitro.
<b>Excretion</b>	
<b>Primary excretion pathways (% dose) ±SD</b>	Following IV dosing of <sup>3</sup> H-cys-mcMMAF to rats, radioactivity was excreted in feces (83%) and urine (13%), predominantly as either the linear or cyclized isomers of cys-mcMMAF.

The FDA assessment on the geometric mean ratio (GMR) and 90% confidence interval (90% CI) of belantamab mafodotin exposures between the frozen liquid (n=99) and lyophilized powder formulations (n=24) at the 3.4 mg/kg dose are shown in Table 6. The  $C_{max}$  and  $AUC_{0-inf}$  of belantamab mafodotin appear comparable between the two formulations as evidenced by the GMRs being close to 1 and the 90% CIs including 1. However, there was a trend for a higher belantamab mafodotin trough concentration ( $C_{tau}$ ) in the lyophilized powder cohort compared to the frozen liquid cohort.

The observed higher trough concentration of belantamab mafodotin in the lyophilized powder cohort may be due to differences in baseline disease characteristics of patients enrolled into lyophilized cohort compared to the frozen liquid cohort at 3.4 mg/kg. These differences include imbalances in baseline sBCMA and IgG levels in the lyophilized powder cohort (Table 7) that can significantly affect the  $C_{tau}$  of belantamab mafodotin (see Section 6.3.1).

**Table 6. Comparison of PK Parameters on Day 1 of Cycle 1 between Frozen Liquid and Lyophilized Powder Formulations at 3.4 mg/kg**

Analytes	Parameters	3.4 mg/kg Frozen liquid (N=99)	3.4 mg/kg Lyophilized powder (N=24)	GMR (90% CI) (Lyophilized/Frozen)
Belantamab mafodotin	C <sub>max</sub> (µg/mL)	52.0 (20%)	51.3 (18%)	0.99 (0.90, 1.09)
	AUC <sub>0-inf</sub> (µg*h/mL)	6496 (54%)	6962 (51%)	1.07 (0.81, 1.42)
	C <sub>tau</sub> (µg/mL)	2.54 (88%)	3.41 (76%)	1.34 (0.99, 1.81)

Note: 1. PK parameters are presented as Geometric mean and CV%. 2. The median (range) of sBCMA were 88.2 (4.9, 656) ng/mL and 61.7 (2.0, 644) ng/mL in the frozen liquid and lyophilized powder groups, respectively.

Source: FDA's analysis

**Table 7. Baseline sBCMA and IgG in the 3.4 mg/kg Frozen Liquid and Lyophilized Configuration Cohorts**

	3.4 mg/kg Frozen (N=99)	3.4 mg/kg Lyophilized (N=24)
Baseline sBCMA, ng/mL Median (min-max)	(n=96) 89 (4.93 – 656)	(n=22) 50.4 (1.95 – 644)
Baseline IgG, g/L Median (min-max)	(n=97) 12.6 (0.35 – 99.7)	(n=24) 3.83 (0.35 – 33.5)

Source: Applicant's ODAC Briefing Book

The FDA notes that the efficacy of ORR by IRC assessment was numerically higher (48% [97.5% CI: 25.5, 71.1]) in the lyophilized cohort than that in the same dose level frozen liquid cohort (34% [97.5% CI: 23.9, 46.0]), with a similar percentage of participants achieving VGFR or better (24% and 20%). The reasons for the differences in the ORR are not clear given the small sample size of the lyophilized cohort, but could be, in part, attributed to the differences in the baseline characteristics of the patients in the lyophilized cohort that were more favorable such as fewer lines of prior therapy (median of 5 in lyophilized cohort vs. 6 in frozen liquid cohort), fewer patients with high risk cytogenetics (20% in lyophilized cohort vs 32% in frozen cohort) and lower baseline sBCMA in the lyophilized cohort.

The incidence of SAEs was numerically higher in the lyophilized cohort compared to the frozen cohort (Table 8). The incidence of AE of special interest (AESI) corneal events (keratopathy, any grade) was higher in the lyophilized cohort than that in the frozen liquid cohort. However, the incidence of any grade thrombocytopenia and Grade 3/4 thrombocytopenia was lower in the lyophilized cohort compared to that in the frozen liquid cohort.

**Table 8. Comparison of AEs Including Ocular Toxicity Between Frozen Liquid and Lyophilized Powder Formulations at 3.4 mg/kg (DREAMM-2)**

AE Category	3.4 mg/kg Frozen Liquid (N=99)	3.4 mg/kg Lyophilized Powder (N=24)
All-Grade TEAEs	100%	100%
Grade 3-4 TEAEs	75.8%	83.3%
Serious TEAEs (SAEs)	47.5%	62.5%
Any-Grade Thrombocytopenia	58.6%	41.7%
Grade 3-4 Thrombocytopenia	33.3%	16.7%
All-Grade Neutropenia	26.3%	8.3%
Grade 3-4 Neutropenia	13.3%	8.3%
Dose reduction due to TEAEs	40.4%	41.7%
All-Grade Keratopathy	74.7%	91.7%
Visual acuity worsening		
Unilateral 20/50 or worse	14%	33%
Bilateral 20/50 or worse	20%	29%
Unilateral 20/200 or worse	6%	8%
Bilateral 20/200 or worse	2%	0%

Source: Study 205678 CSR Section 8.3 and Applicant's analysis on 03/13/2020

The higher incidence of SAEs and any grade keratopathy in the 3.4 mg/kg lyophilized cohort might be related to the numerically higher  $C_{tau}$  of belantamab mafodotin, which has a strong positive correlation with the incidence of SAEs and keratopathy (See Section 6.3.2.2). In addition, the imbalance in baseline disease characteristics described above may also be related to the observed difference in AEs. It should be noted that no new safety signals were observed in the lyophilized cohort (see safety in Section 8.2.4).

In summary, there are numerical difference in PK exposure ( $C_{tau}$ ), efficacy and AEs between the lyophilized powder and frozen liquid cohorts at 3.4 mg/kg. These differences may be caused by the imbalanced key baseline disease characteristics between these two cohorts, which results in a higher  $C_{tau}$  of ADC.

### 6.3.2. Clinical Pharmacology Questions

#### 6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

The FTIH study DREAMM-1 evaluated dose levels from 0.03 to 4.6 mg/kg Q3W and selected 3.4 mg/kg Q3W based on emerging efficacy, safety, and pharmacokinetic data for evaluation in Part 2 of the study. Part 2 of DREAMM-1 demonstrated a high response rate in patients with RRMM. Two dose levels, 2.5 and 3.4 mg/kg Q3W, were evaluated in the pivotal study DREAMM-2. Exposure-response analyses based on the DREAMM-2 data found that the probability of response was inversely related to a disease-related factor, baseline sBCMA level. In the univariate analysis, belantamab mafodotin ADC  $C_{\tau}$  was positively associated with the probability of response; however, it was not retained in the final model.

The Applicant's Position:

The clinical pharmacology program provides supportive evidence of effectiveness.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that the clinical pharmacology program provides supportive evidence of efficacy.

**6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Data:

The proposed dosing regimen for belantamab mafodotin as a single agent in the treatment of RRMM is 2.5 mg/kg Q3W as an IV infusion over approximately 30 minutes until disease progression or unacceptable toxicity. This dosing regimen was selected based on the clinical results of the pivotal DREAMM-2 as well as pharmacokinetics and exposure-response analyses for efficacy and safety endpoints.

**Efficacy:** The primary endpoint, ORR (as assessed by IRC) was 31% (97.5% CI: 20.8%, 42.6%) and 34% (97.5% CI: 23.9%, 46.0%) in the 2.5 mg/kg Q3W dose and 3.4 mg/kg Q3W dose, respectively; the responses were deep (18% and 20% achieving VGPR or better). Median PFS, based on IRC assessment, was 2.9 months for the 2.5 mg/kg cohort and 4.9 months for the 3.4 mg/kg cohort; however, the HR estimate of 3.4 mg/kg versus 2.5 mg/kg was 0.92 (95% CI: 0.63, 1.33), indicating that the difference between the 2 cohorts is smaller than is reflected in the median estimates. In addition, when adjusted for potential prognostic factors, the HR estimate for the 2 randomized dose cohorts became 0.99 (95% CI: 0.67, 1.46), suggesting that the numerical difference observed in PFS between the 2 dose cohorts could be mainly due to imbalance in those prognostic factors.

**Safety:** Overall, the safety data showed better tolerability in the 2.5 mg/kg cohort than in the 3.4 mg/kg cohort. The incidence of all adverse events (AEs), including Grade 3/4 AEs, was comparable between the 2.5 mg/kg and 3.4 mg/kg Q3W cohorts; however, the 3.4 mg/kg cohort had a higher frequency of AEs leading to dose delays and reductions than participants in the 2.5 mg/kg cohort (62 % vs. 54% for dose delays and 41% vs. 29% for dose reductions). The incidence of serious adverse events (SAEs) was also higher for the 3.4 mg/kg cohort than for the 2.5 mg/kg cohort (47% and 40%), as was the number of fatal SAEs (7% and 3%).

Participants in the 3.4 mg/kg cohort experienced more frequent thrombocytopenic events (59% vs. 35%), including  $\geq$ Grade 3 thrombocytopenia (34% vs. 20%), and more  $\geq$ Grade 2 bleeding events (17% vs 5%) than participants in the 2.5 mg/kg cohort.

The frequency of corneal exam findings was comparable in both cohorts, and Grade 3/4 events were also comparable. Dry eyes and blurred vision were reported more often in the 3.4 mg/kg cohort than in the 2.5 mg/kg cohort.

**Pharmacokinetics/Pharmacodynamics:** There was substantial overlap between plasma exposures of belantamab mafodotin in the 2 main cohorts, which was consistent with the difference between the dose levels and the inter-individual differences in pharmacokinetics. The median value of belantamab  $C_{\tau}$  at Cycle 1 was similar between the 2.5 and 3.4 mg/kg cohorts. Maximum and average cys-mcMMAF exposure measures in general were higher for those participants who received the 3.4 mg/kg dose than in participants in the 2.5 mg/kg cohort, although there was overlap in the distributions.

Free soluble BCMA (sBCMA) was explored as a potential marker of response. In DREAMM-1, the data suggested dose-dependent binding of belantamab mafodotin to sBCMA at end of infusion during Cycle 1, with very high binding (>90% reductions) consistently observed at doses  $\geq$ 1.92 mg/kg; free sBCMA returned to baseline levels by 7 days after dosing. There were no obvious relationships between the very high binding of sBCMA and best clinical response observed in participants.

**Integrated Exposure-Response Summary:** Exposure-response relationships for efficacy and safety endpoints are summarized in Section 6.3.1. Relationships between disease-related factors and both exposure and clinical endpoints resulted in complexity in the interpretation of the exposure-response results. The exposure-response analyses found that both efficacy and safety endpoints were associated with disease factors and patient characteristics. Safety endpoints were most strongly associated with exposure, while efficacy endpoints had a weaker association with exposure, especially after disease factors and patients characteristics were accounted for in multivariate modeling. These results suggested an increased probability of corneal exam findings and thrombocytopenia with higher exposure or higher dose that was not associated with a commensurate improvement in efficacy.

**Conclusion:** The study was not designed to compare the 2 dose levels of belantamab mafodotin, and both dose levels showed a positive benefit/risk in a heavily pretreated RRMM patient population enrolled in DREAMM-2. The clinical efficacy results and exposure-efficacy relationships showed similar benefit in the 2 main cohorts. The clinical safety results and exposure-safety relationships showed better tolerability in the 2.5 mg/kg cohort than in the 3.4 mg/kg cohort. Based on these results, the 2.5 mg/kg Q3W regimen is supported as single-agent therapy in patients with RRMM.

**The Applicant's Position:**

The proposed dosing regimen of 2.5 mg/kg Q3W administered as an IV infusion over approximately 30 minutes until disease progression or unacceptable toxicity is appropriate (b) (4) in the relapsed/refractory multiple myeloma population.

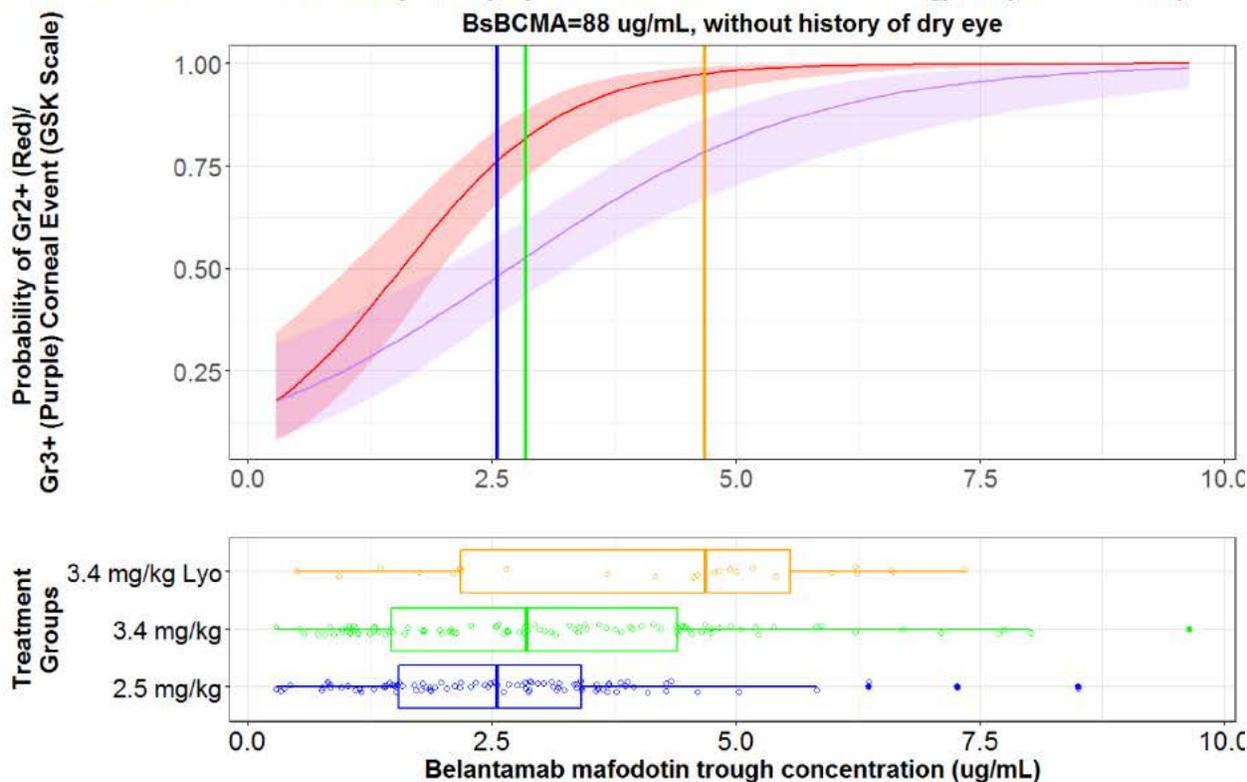
**The FDA's Assessment:**

There was no remarkable difference in ORR between 2.5 mg/kg Q3W and 3.4 mg/kg Q3W as evidenced by ORR (as assessed by IRC) of 31% (97.5% CI: 20.8%, 42.6%) for the 2.5 mg/kg dose and 34% (97.5% CI: 23.9%, 46.0%) for the 3.4 mg/kg dose. In addition, E-R analysis for efficacy also showed no clear relationship between efficacy endpoints (ORR or PFS) and exposures of belantamab mafodotin after adjusting for baseline disease characteristics, such as baseline sBCMA and  $\beta 2$  microglobulin (see Appendices 20.4.3).

The dose-response analyses for safety showed that the 2.5 mg/kg Q3W cohort had lower incidence of SAEs, serious TEAEs, fatal TEAEs and dose interruption/reduction due to AE than that in the 3.4 mg/kg Q3W cohort. However, both 2.5 mg/kg Q3W and 3.4 mg/kg Q3W cohorts with frozen liquid formulation showed high incidences of corneal adverse events in DREAMM-2 (see Section 8.2). E-R analyses indicated that increasing doses and exposures ( $C_{\tau}$  and  $C_{\text{avg}}$  at cycle 1) of belantamab mafodotin were associated with increasing probability of Grade 2+ or 3+ corneal AEs on GSK scale even after adjusting by baseline sBCMA and history of dry eye (Figure 3).

In addition, data from DREAMM-2 indicated that belantamab mafodotin  $C_{\text{max}}$  at Cycle 1 may be associated with the risk of ocular toxicity as well. The geometric mean of  $C_{\text{max}}$  was 18% higher in patients who developed Grade 2+ corneal event (GSK scale) than those who didn't in the 2.5 mg/kg cohort. However, the correlation between  $C_{\text{max}}$  and incidence of ocular toxicity is weak, due in part, to the narrow range of  $C_{\text{max}}$  in the E-R analyses.

Figure 3. Probability of Grade 2+ and Grade 3+ Corneal Event using GSK Scale by Cycle 1 ADC C<sub>tau</sub> in Patients without History of Dry Eye at a Baseline sBCMA of 88 ng/mL (Trial 205678)



Open dots and Boxes: Observed belantamab mafodotin trough concentrations at frozen liquid presentation 2.5 mg/kg Q3W (blue), 3.4 mg/kg Q3W (green) and lyophilized presentation 3.4 mg/kg Q3W (orange). Lines and areas: Logistic regression fit curves and 95% CI for grade 2+ (red) and grade 3+ (purple) corneal event.  
Source: FDA analysis.

Given the limited data available at lower doses or alternative regimens minimizing the peak concentrations, additional clinical safety and efficacy information on belantamab mafodotin with the lyophilized powder presentation (the to-be-marketed formulation) is needed to determine a dose and regimen that will minimize the risk of corneal toxicity without a clinically significant impact on efficacy.

### 6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

#### Data:

In population pharmacokinetic analyses, potential covariates influencing the pharmacokinetics of belantamab mafodotin and cys-mcMMAF have been evaluated (Section 6.3.1). Body weight and gender had statistically significant but not clinically meaningful effects on belantamab mafodotin and cys-mcMMAF pharmacokinetics; no dose adjustment is necessary. Other factors

such as age, race, mild or moderate renal impairment, mild hepatic impairment, region, and presentation (frozen liquid or lyo) had no significant effect. Disease-related factors (baseline sBCMA, baseline IgG, baseline albumin) had the most significant effects on belantamab mafodotin and/or cys-mcMMAF pharmacokinetics; the clinical relevance of these relationships is unknown.

The Applicant's Position:

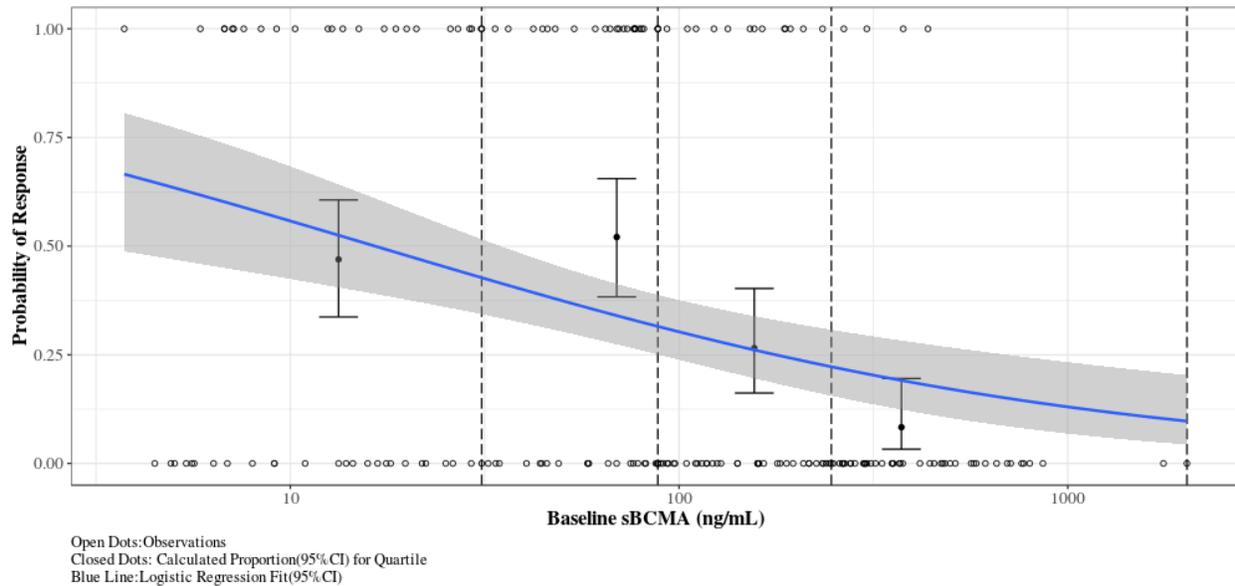
Dose adjustment is not required for subpopulations based on intrinsic patient factors (e.g., age, race, mild or moderate renal impairment, mild hepatic impairment, region) based on the results of population pharmacokinetic analyses.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. However, there is no safety and PK data of belantamab mafodotin in patients with moderate or severe hepatic impairment or patients with severe renal impairment or end stage renal disease. Additional clinical studies will be conducted, as PMRs, in these patients (see Section 14).

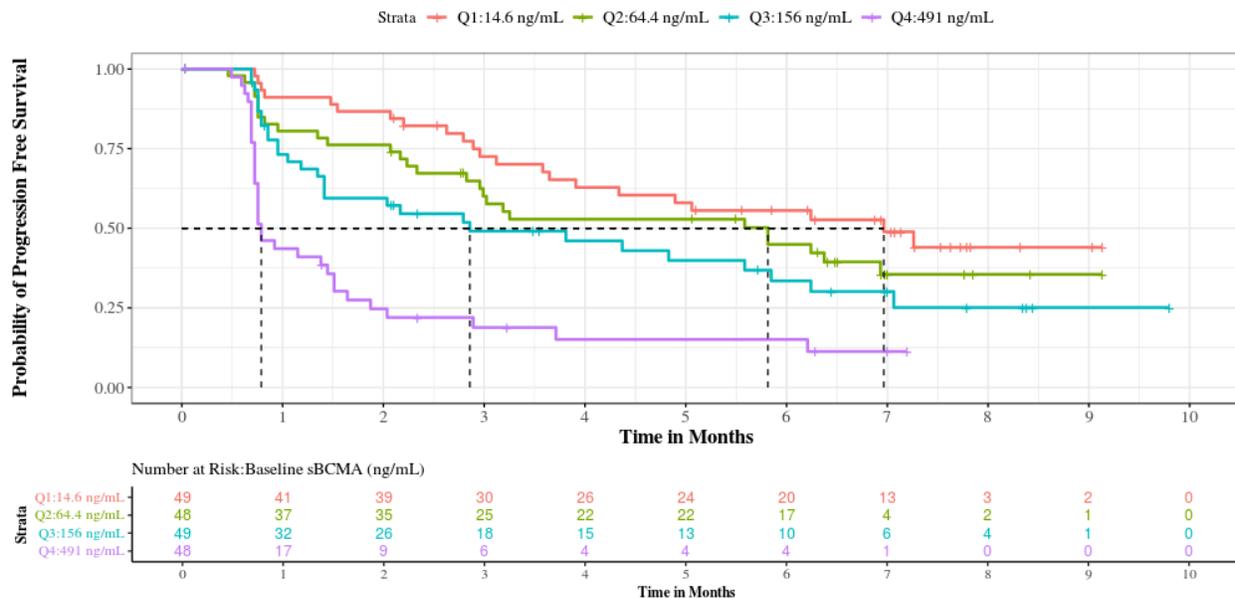
The FDA notes that there was a significant impact of baseline sBCMA on belantamab mafodotin  $C_{\tau}$  at Cycle 1 (Figure 1), ORR (Figure 4), PFS (Figure 5) and Grade 2+ or 3+ corneal event (Figure 6). In general, the groups with lower baseline sBCMA were associated with higher belantamab mafodotin exposure, higher response rate, and higher incidence of corneal AEs.

**Figure 4. Probability of ORR by Baseline sBCMA Concentrations (Trial 205678 - Frozen Liquid Presentation)**



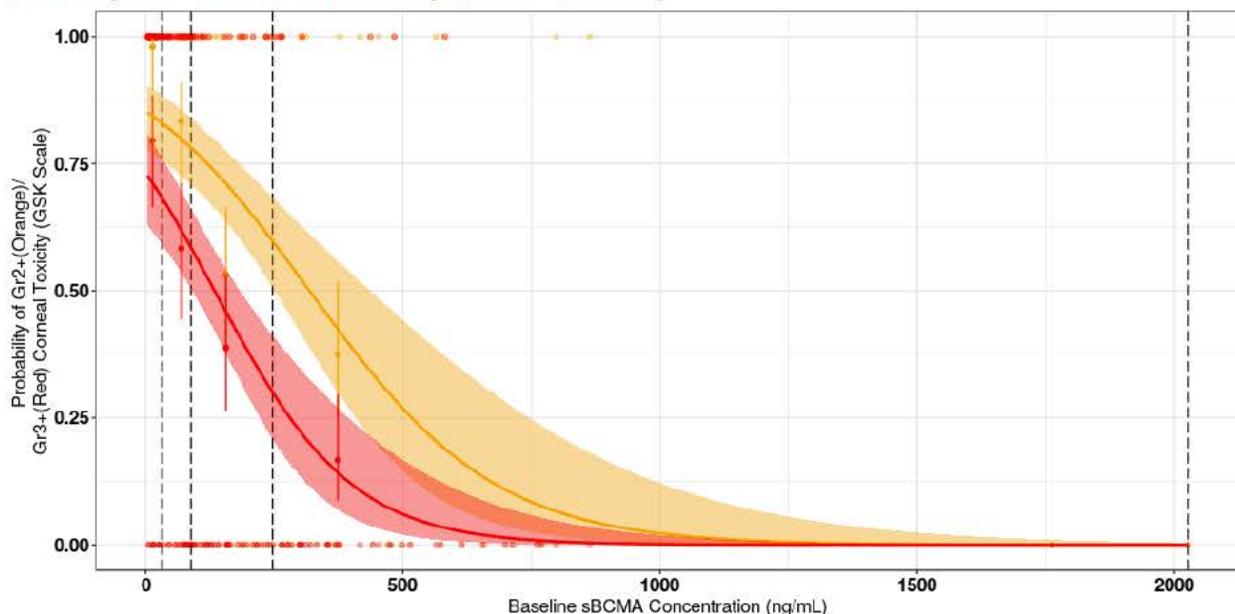
Source: Applicant’s Population PK and Exposure-Response Analyses Report, Figure 26.

**Figure 5. Progression Free Survival Stratified by Quartile of Baseline sBCMA (Trial 205678 - Frozen Liquid Presentation)**



Source: Applicant’s Population PK and Exposure-Response Analyses Report, Figure 33.

**Figure 6. Probability of Grade 2+ and Grade 3+ Corneal Event using GSK Scale by Baseline sBCMA (Trial 205678 - Frozen Liquid Presentation)**



Source: Applicant’s Population PK and Exposure-Response Analyses Report, Figure 38.

FDA conducted an independent analysis to compare the PK, efficacy and safety in patients with different baseline sBCMA at 2.5 mg/kg Q3W. The median [min, max] baseline sBCMA was 93.1 [3.7, 2026] ng/mL at 2.5 mg/kg Q3W in Trial 205678. Therefore, patients at 2.5 mg/kg Q3W group were stratified into two baseline sBCMA groups based on the median value of 93.1 ng/mL. Belantamab mafodotin PK, efficacy and safety in patients with low (19.8 [3.74, 93.1] ng/mL) and high (237 [93.1, 2026] ng/mL) baseline sBCMA are shown in Table 9.

**Table 9. Subgroup Analysis of Belantamab Mafodotin PK, Efficacy and Safety in Patients with Low and High Baseline sBCMA Administered Frozen Liquid Presentation 2.5 mg/kg Q3W in Trial 205678**

Parameters		sBCMA (ng/mL)	
		Low 19.8 [3.74, 93.1] (n = 47)	High 237 [93.1, 2026] (n = 48)
PK	GM (CV%) ADC C <sub>tau</sub> (µg/mL)	3.0 (60%)	1.6 (66%)
	GM (CV%) ADC C <sub>max</sub> (µg/mL)	43 (17%)	36 (19%)
Efficacy	ORR (sCR + CR + VGPR + PR)	45%	19%
	Median [95% CI] PFS (month)	3.7 [3.0, NA]	1.5 [0.9, 3.7]
Safety	Grade 2+ corneal events	92%	35%
	Grade 3+ corneal events	72%	23%

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 [TRADE NAME] belantamab mafodotin

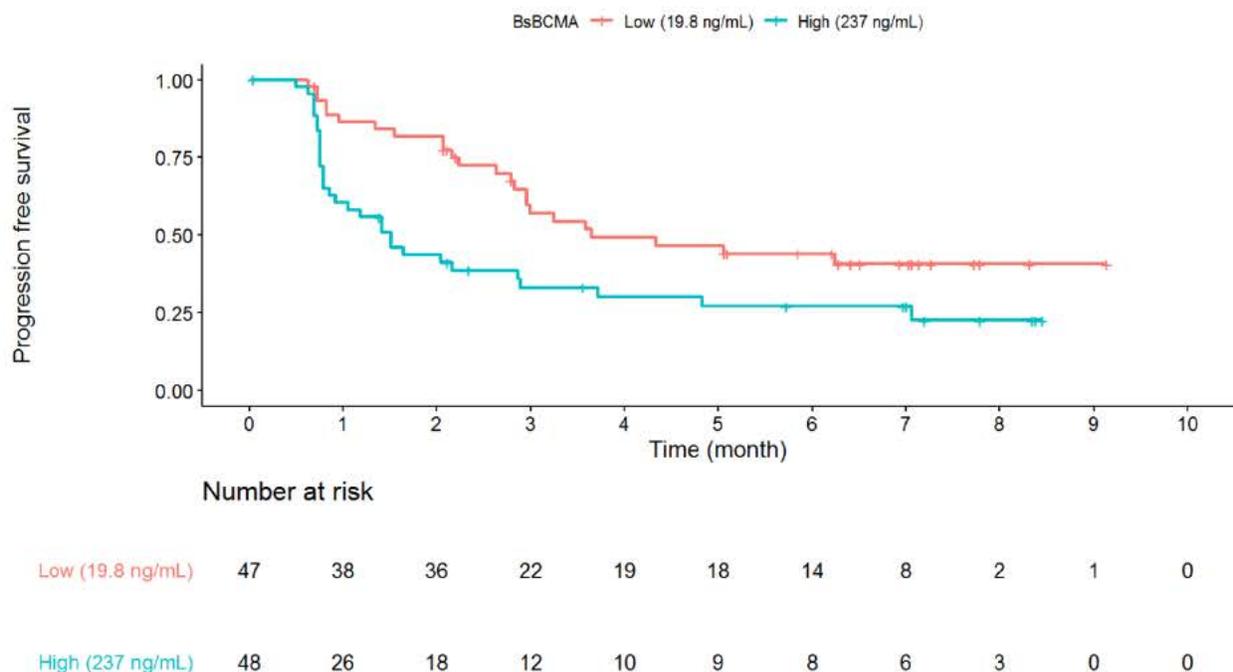
(KVA scale)	Definite worsening visual acuity in the better eye	40%	13%
	Definite worsening visual acuity in the worse eye	62%	25%
	Unilateral worsening visual acuity 20/50 or worse	32%	13%
	Bilateral worsening visual acuity 20/50 or worse	21%	6%
	Adverse events leading to dose reduction, n (%)	43%	17%

GM=geometric mean, CV=coefficient of variation, C<sub>tau</sub>=trough concentration, ORR=overall response rate, PFS=progression-free survival, sBCMA=soluble B-cell maturation antigen, Q3W=every 3 weeks

Source: Reviewer’s analysis.

As shown in the table, patients with low baseline sBCMA had 88% higher geometric mean ADC C<sub>tau</sub> at Cycle 1, 26% higher ORR and 2.2 months longer PFS as compared to patients with high baseline sBCMA. Kaplan-Meier curves of PFS (Figure 7) showed a clear separation between two subgroups at 2.5 mg/kg Q3W dosing regimen in DREAMM-2.

**Figure 7. Kaplan-Meier Analysis of PFS in Patients with RRMM and Different Levels of Baseline sBCMA Administered Frozen Liquid Presentation 2.5 mg/kg Q3W in Trial 205678**



Source: Reviewer’s analysis.

On the other hand, as shown in Table 9, patients with low baseline sBCMA also had 57% higher grade 2+ corneal events, 49% higher grade 3+ corneal events, 27% higher definite worsening visual acuity in the better eye, 37% higher definite worsening visual acuity in the worse eye, 19% higher unilateral worsening visual acuity 20/50 or worse, 15% higher bilateral worsening visual acuity 20/50 or worse, and 26% higher AEs leading to dose reduction, as compared to patients with high baseline sBCMA at 2.5 mg/kg Q3W in Trial 205678.

Version date: June 11, 2019 (ALL NDA/ BLA reviews)

**Disclaimer:** In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Given the remarkable impact of baseline sBCMA on belantamab mafodotin PK, efficacy and safety, and positive E-R relationship for corneal events after adjusting for baseline disease characteristics, the need for dose adjustment or a lower starting dose for patients with low baseline sBCMA should be further investigated for belantamab mafodotin with the lyophilized powder formulation.

**6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

Data:

As belantamab mafodotin is administered intravenously, no clinical assessment of potential food-drug interactions has been performed.

No specific clinical studies to assess potential drug-drug interactions (DDIs) have been performed.

***In vitro* victim DDI risk:** Cys-mcMMAF was not a sensitive substrate of cytochrome P450 enzymes *in vitro*. Cys-mcMMAF was an *in vitro* substrate of organic anion-transporting polypeptides (OATP) 1B1 and OATP1B3, multidrug resistance-associated proteins (MRP) 1, MRP2, and MRP3, and a borderline substrate of bile salt export pump (BSEP). Conflicting data were obtained on whether cys-mcMMAF was an *in vitro* substrate of P-glycoprotein (P-gp).

***In vitro* perpetrator DDI risk:** Cys-mcMMAF was not an inhibitor or inducer of cytochrome P450 enzymes *in vitro*. Belantamab mafodotin is unlikely to modulate the cytokines which are known to be involved in mechanisms associated with suppression of CYPs and transporters. Together these data suggest belantamab mafodotin and cys-mcMMAF have a low risk of being perpetrators of drug interactions.

The Applicant's Position:

As belantamab mafodotin is administered intravenously, no food-drug interactions are anticipated. As summarized above, the current assessment is that the risk for clinically relevant DDIs is low.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment.

X

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X

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## 7. Sources of Clinical Data

### 7.1. Table of Clinical Studies

#### The Applicant's Position:

The clinical studies to support efficacy and safety that are relevant to this BLA are summarized in Table 10.

**Table 10. Listing of Clinical Trials Relevant to this NDA/BLA**

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Primary Endpoints	Treatment Duration/ Follow Up	No. of patients	Study Population	No. of Centers and Countries
<b>Controlled Studies to Support Efficacy and Safety</b>							
Study 205678 (DREAMM-2) NCT03525678	Phase II, open-label, two-arm, randomized, multicenter study	2.5 mg/kg or 3.4 mg/kg IV Q3W.	<b>Primary:</b> ORR by IRC. <b>Secondary:</b> efficacy (CBR, DoR, TTR, PFS, TTP and OS), safety, PK, ADA, PROs (symptomatic AEs and QoL), ocular substudy and lyo cohorts.	Treat until disease progression or unacceptable toxicity / Follow until death or premature withdrawal	221 randomized, 218 dosed*	Double refractory to PI and IMiD and failed by an anti-CD38.	58 sites across 8 countries
<b>Studies to Support Safety</b>							
Study BMA117159 (DREAMM-1) NCT02064387	Phase I, Open-label, dose escalation, FTIH study	Part 1 dose escalation ranging from 0.03 to 4.9 mg/kg IV Q3W. Part 2: 3.4 mg/kg.	<b>Primary:</b> AE and changes in clinical signs and laboratory parameters <b>Secondary:</b> efficacy (ORR), PK, ADA.	Treat until disease progression or unacceptable toxicity / Follow until death or premature withdrawal from study	73 enrolled	Double- class refractory and failed by an anti- CD38.	9 centers across 3 countries
<b>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</b>							
N/A							

\*DREAMM-2 randomized 223 times, as Participants (b) (6) (first participant ID (b) (6)) and (b) (6) (first participant ID (b) (6)) were re-randomized and have been counted twice, once for each randomization.

Abbreviations: IV= intravenous; Q3W = once every 3 weeks; ORR =overall response rate; IRC= independent review committee; CBR = clinical benefit rate; DoR = duration of response; FTIH = first-time-in-human; TTR = time to response; PFS = progression free survival; TTP = time to progression; OS = overall survival; PI = proteasome inhibitor; IMiD = immunomodulatory drug; AE = adverse event; PK=pharmakokinetic; ADA = anti-drug antibodies; PROs = patient-reported outcomes; QoL = quality of life; lyo = lyophilized.

There are ongoing studies investigating belantamab mafodotin in various regimens, which are clinical studies being conducted as monotherapy or in combination with various comparators and/or investigational agents in different lines of therapy (i.e., different patient populations). The data from these studies are not considered to be relevant to the characterization of the efficacy and safety of belantamab mafodotin as monotherapy for the initial indication being sought, and therefore are not included in the original BLA.

**The FDA's Assessment:**

In general, the FDA agrees with the Applicant's description of the clinical trials used to support safety and efficacy of belantamab mafodotin in this application. However, even though patients were randomized to one of two dose levels, 2.5 mg/kg or 3.4 mg/kg, the DREAMM-2 trial is more accurately described as a single-arm trial evaluating two parallel dose cohorts. The hypothesis testing was performed for each arm separately. No hypothesis testing was performed for comparison of the overall response rate (ORR) between the two arms. There was no active comparator or placebo control, so this trial should not be classified as a randomized controlled trial.

## **8. Statistical and Clinical Evaluation**

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### **8.1. Review of Relevant Individual Trials Used to Support Efficacy**

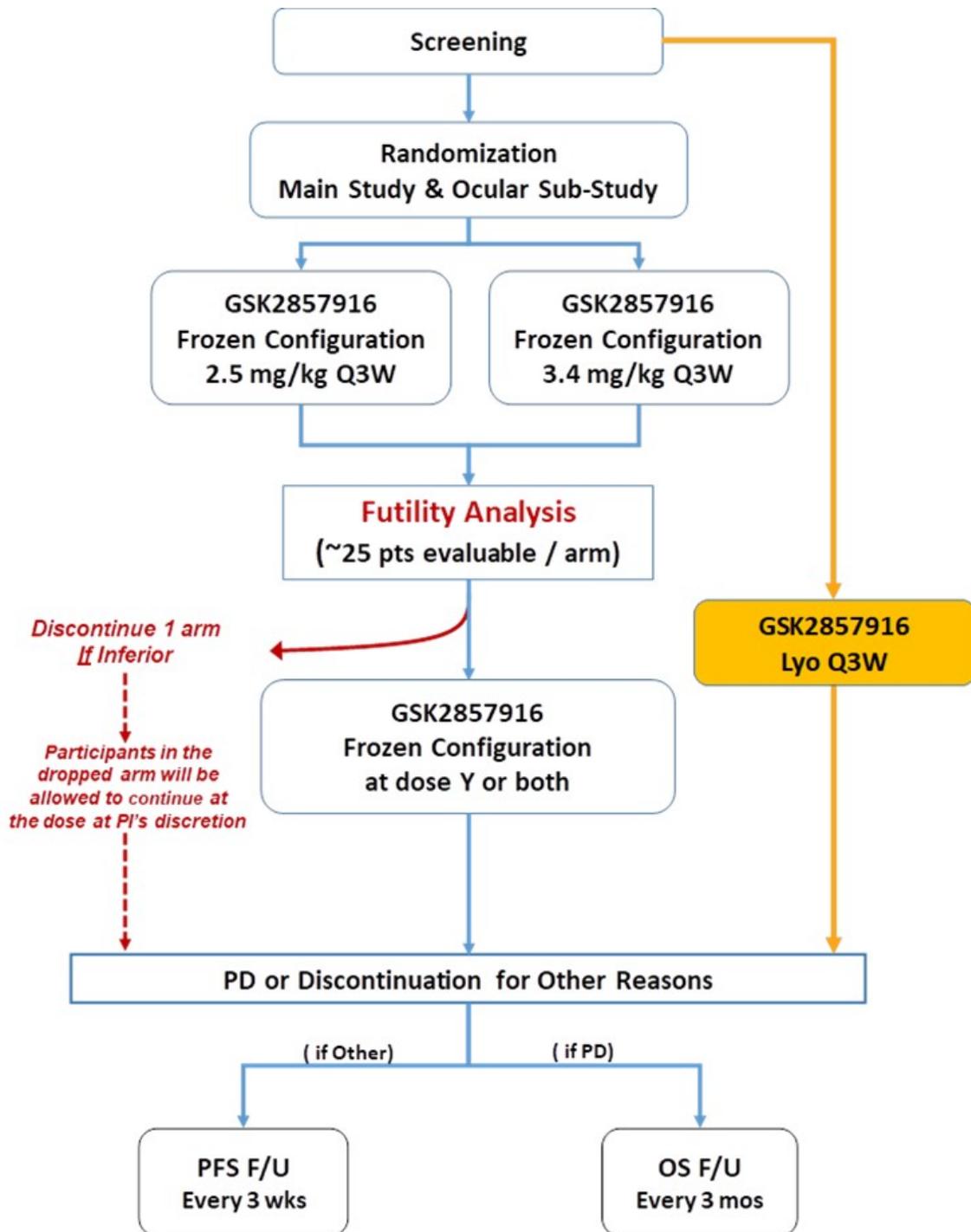
#### **8.1.1. Study 205678 (DREAMM-2)**

**The Applicant's Position:**

**Trial Design**

This is a Phase II, open-label, two-arm, randomized, multicenter study to evaluate the efficacy and safety of belantamab mafodotin monotherapy at 2 dose levels: 2.5 mg/kg or 3.4 mg/kg IV, Q3W, in participants with RRMM who received 3 or more prior therapies, were refractory to a PI and an IMiD, and had failed an anti-CD38 antibody (Figure 8). Participants are treated until disease progression or unacceptable toxicity and followed for PFS and OS. An ocular sub-study evaluated the effectiveness of steroid eye drops in approximately 30 participants (~15 on each cohort). The study also included an independent cohort of approximately 25 participants who received a lyophilized presentation (lyo) of belantamab mafodotin.

Figure 8. DREAMM-2 Schematic



Abbreviations: OS = overall survival; PD = progressive disease; PFS = progression-free survival; F/U = follow-up; lyo = lyophilized; pts = participants; PI = Principal Investigator.

**The FDA's Assessment:**

The FDA agrees with the description of the study design for the DREAMM-2 study. DREAMM-2 included an additional independent cohort of approximately 25 additional participants who received a lyophilized presentation of belantamab mafodotin at 3.4 mg/kg. The lyophilized cohort was initiated once the lyophilized presentation became available. Patients receiving lyophilized belantamab mafodotin underwent the same assessments and procedures as the main study and were analyzed separately from the patients randomized to the frozen solution.

**Trial location**

Two-hundred and twenty-one (221) participants were randomized over 58 investigational sites globally. DREAMM-2 randomized 223 times, as 2 participants were re-randomized.

**Choice of control group**

This study used a historical control for the ORR comparison with belantamab mafodotin.

DREAMM-2 was designed to enroll a subset of MM patients with the highest medical need (double-refractory and who had failed an anti-CD38 antibody either in combination or as monotherapy).

At the time DREAMM-2 was designed, there was no standard of care approved for the study population and therefore a randomized study with a globally acceptable comparator in this patient population was not feasible. The single-arm trial design comparing belantamab mafodotin to historical data was discussed previously with FDA and CHMP.

In addition, no published data on efficacy outcomes in this population were available. Indirect comparisons of available published studies conducted in a similarly heavily pretreated RRMM patient population indicated an ORR of 10-18%. A response rate of 15% was previously reported in patients at 4<sup>th</sup> relapse (ie., having relapsed after 3 prior lines of therapy) [Hájek, 2017; Kumar, 2012; Durie, 2012; Anderson, 2008]. Therefore, GSK utilized a comparative ORR of 15% for the historical control.

Comparison with historical control of 15% was planned for each dose level separately, with one sided type I error controlled at 0.0125 for each comparison and the overall one sided type I error controlled at 0.025, which would translate into reaching statistical significance (lower bound of two-sided 97.5% CI exceeding 15%) at a minimum observed ORR of ~24% in either cohort based on the actual number (~100 per arm) of participants randomized in the study.

Recent published literature reflects that data from a single-arm trial of selinexor in combination with dexamethasone has reported a 26% ORR with DoR of 3.8 months in a similarly heavily pretreated penta-refractory patient population [XPOVIO USPI].

**The FDA's Assessment:**

The Applicant designed and sized the study such that the lower bound of the 97.5% CI for the ORR would exclude a prespecified 15% boundary of ORR rate. The Applicant provided justification for the selection of the response rate, which was based on 4 publications [Hájek, 2017; Kumar, 2012; Durie, 2012; Anderson, 2008]. Even though patients were randomized to one of two dose levels, 2.5 mg/kg or 3.4 mg/kg, the DREAMM-2 trial was essentially a single arm trial evaluating two parallel dose cohorts with 1:1 randomization to either of the two cohorts. The hypothesis testing was performed within each arm separately. No hypothesis testing was performed for comparison of ORR between the two arms. FDA notes that for a single-arm study without a control arm, efficacy based on the ORR rate needs to be supported by an adequate ORR magnitude and a clinically meaningful DoR.

The FDA also notes that the patient population for the single-arm trial of selinexor in combination with dexamethasone, penta-refractory, was different than the patient population used in the DREAMM-2 study, triple-class refractory. Therefore, comparisons of the efficacy in the two studies should be interpreted with caution.

#### **Key inclusion/exclusion criteria**

The study population consisted of men and women aged 18 years or older with relapsed/refractory MM. Participants eligible for the study had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and met the following criteria:

1. Histologically or cytologically confirmed diagnosis of MM as defined in International Myeloma Working Group (IMWG) criteria [Rajkumar, 2014] who have undergone stem cell transplant or were considered transplant ineligible, and have failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and were refractory to an IMiD (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib).
2. Measurable disease with at least one of the following: Serum M-protein  $\geq 0.5$  g/dL ( $\geq 5$  g/L), Urine M-protein  $\geq 200$  mg/24h, Serum FLC assay: Involved FLC level  $\geq 10$  mg/dL ( $\geq 100$  mg/L) and an abnormal serum free light chain ratio ( $< 0.26$  or  $> 1.65$ ).
3. Participants with a history of autologous stem cell transplant: transplant was  $> 100$  days prior to study enrollment, there was no active infection(s), and participant met the remainder of the eligibility criteria outlined in the protocol.
4. Adequate organ system functions as defined in the protocol.
5. Participants were required to have contraceptive use consistent with local regulations.
6. Women were eligible to participate if they were not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)
  - OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of  $< 1\%$  per year), preferably with low user dependency, during the

intervention period and for at least 80 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours before the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

7. Men were eligible to participate if they agree to the following during the intervention period and for at least 140 days:
  - Refrain from donating sperm  
PLUS either:
  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.  
OR
  - Must agree to use contraception/barrier as detailed below:

Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

8. All prior treatment-related toxicities (defined by National Cancer Institute- Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.03) must be ≤Grade 1 at the time of enrollment except for alopecia and Grade 2 peripheral neuropathy.
9. (France only) A participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Participants were excluded from the study if they met any of the following criteria:

1. Systemic anti-myeloma therapy within ≤14 days or 5 half-lives, whichever is shorter, or plasmapheresis within 7 days prior to the first dose of study drug.
2. Systemic treatment with high dose steroids (equivalent to > 60 mg prednisone daily for ≥4 days) within the past 14 days if administered to treat MM or non-MM disease.
3. Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' (POEMS) syndrome, active plasma cell leukemia at the time of screening.

4. Prior allogeneic stem cell transplant.
5. Current corneal epithelial disease except mild punctate keratopathy.
6. 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 within 30 days of receiving the first dose of study drugs. Prior BCMA targeted therapy.
7. Evidence of active mucosal or internal bleeding.
8. Any major surgery within the last 4 weeks.
9. 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 fulfill the criteria for determining adequate organ system functioning as outlined in the protocol.
10. 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.
11. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.
12. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (MM). Participants with curatively treated non-melanoma skin cancer may be enrolled.
13. Evidence of cardiovascular risk including any of the following:
  - a. QTcF interval  $QTcF > 480$  msec (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF]).
  - b. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
  - c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
  - d. Class III or IV heart failure as defined by the New York Heart Association functional classification system [NYHA, 1994].
  - e. Uncontrolled hypertension.
14. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
15. Pregnant or lactating female.
16. Active infection requiring antibiotic, antiviral, or antifungal treatment.

17. Known HIV infection.
18. 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.
19. 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.

*Note:* Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

*Note:* Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

**The FDA’s Assessment:**

In addition to the criteria listed above, the full eligibility criteria also required that patients provide signed written informed consent, including compliance with the requirements and restrictions listed in the consent form.

Regarding inclusion criterion #1, the protocol included the following definitions:

- The number of prior lines of therapy will be determined according to the guidelines in Rajkumar et al., 2015.
- Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.
- Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease (PD) while on therapy (Rajkumar et al., 2011)

For inclusion criterion #4, the protocol defined adequate organ system functions as follows

System	Laboratory Values
<b>Hematologic</b>	
Absolute neutrophil count (ANC)	≥1.0 X 10 <sup>9</sup> /L
Hemoglobin	≥8.0 g/dL
Platelets	≥50 X 10 <sup>9</sup> /L
<b>Hepatic</b>	
Total bilirubin	≤1.5X ULN (Isolated bilirubin ≥1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
ALT	≤2.5 X ULN
<b>Renal</b>	
eGFR <sup>a</sup>	≥30 mL/min/ 1.73 m <sup>2</sup>
Spot urine (albumin/creatinine ratios (spot urine)	<500 mg/g (56 mg/mmol)
<b>Cardiac</b>	
LVEF (Echo)	≥45%

Source: Applicant’s DREAMM-2 Protocol (Amendment 3)

DREAMM-2 included several exclusion criteria for subjects with underlying ocular disease. Subjects with corneal epithelial disease, with the exception of mild punctate keratopathy, were excluded from this study, as were subjects with the best corrected visual acuity in the worst

seeing eye worse than 20/100 (Snellen equivalent). Participants with visual acuity worse than 20/100 due to a treatable condition (e.g., cataract) may have been enrolled on an individual basis after discussion with the medical monitor.

Apart from the additions noted above, the eligibility criteria listed by the Applicant represent the full eligibility criteria for the DREAMM-2 study.

### **Dose level selection for DREAMM-2**

At the time of DREAMM-2 was designed, the Phase I FTIH study DREAMM-1 was ongoing. There were no dose-limiting toxicities (DLTs) observed during dose escalation in Part 1 of DREAMM-1; however, there was limited tolerability of the 4.6 mg/kg dose. As a result, the dose of 3.4 mg/kg Q3W was identified as the RP2D for Part 2 (dose expansion) based on the totality of safety and tolerability data.

The clinical activity data from Part 2 of DREAMM-1 indicated an ORR of 60% (95% CI: 42.1, 76.1) in a population of 35 participants with heavily pretreated RRMM. The ORR for the study population consistent with that of DREAMM-2 (refractory to PI, IMiD, and failed by anti-CD38 therapy; N=13) was 38% (95% CI: 13.9, 68.4). Belantamab mafodotin was generally well tolerated; however, many participants treated at 3.4 mg/kg dose required a dose modification (71% had dose delays and 66% had dose reductions) due to an AE (mostly corneal events). Responders in the 3.4 mg/kg cohort in Part 2 maintained their responses with dose reductions and delays.

Based on the available DREAMM-1 data and supported by Bayesian Logistic Regression Modeling (BLRM), a lower dose level of 2.5 mg/kg was included in the DREAMM-2 study to generate additional data and determine whether tolerability would improve with fewer dose reductions and delays and with similar efficacy at a lower starting dose than 3.4 mg/kg.

### **The FDA's Assessment:**

The clinical efficacy results from Part 1 of the DREAMM-1 study showed that there were no responses at doses <0.96 mg/kg. There was one response of PR observed at the 0.96 mg/kg dose, one response of VGPR at the 1.92 mg/kg dose, and one response at the 2.50 mg/kg dose. All three subjects treated at the 3.4 mg/kg dose had a response (1 sCR, 1 CR, and 1 PR), while 3/6 (50%) patients responded at the 4.6 mg/kg dose (2 VGPR and 1 PR). Based on the results of the dose escalation portion (Part 1) of the DREAMM-1 trial, the 3.4 mg/kg dose was selected as the recommended phase 2 dose (RP2D) for further evaluation in the expansion phase (Part 2) of DREAMM-1. However, no statistical conclusions should be made due to the small sample size in the DREAMM-1 study.

During the clinical development, a maximum clinical benefit was observed at the 3.4 mg/kg dose level, but a substantial number of patients required a dose delay or dose reduction due to adverse events. Therefore, the dose of 2.5 mg/kg was selected for additional clinical

development. The FDA notes that the Applicant stated that the safety profile of the 2.5 mg/kg dose was more favorable. Although the overall safety profile of the 2.5 mg/kg dose was more favorable compared to 3.4 mg/kg dose, the incidence of ocular toxicities did not differ substantially between the two dose levels.

### **Study treatments**

Belantamab mafodotin was administered at a calculated dose of 2.5 mg/kg or 3.4 mg/kg as an IV infusion over approximately 30 minutes, via an infusion pump, on Day 1 of each cycle until disease progression or unacceptable toxicity.

### **Treatment assignment**

Interactive Response Technology (IRT) was used to randomize participants centrally in a 1:1 ratio to one of the two treatment arms: 2.5 mg/kg IV Q3W or 3.4 mg/kg IV Q3W. Randomization was stratified by the number of prior lines of therapy ( $\leq 4$  or  $>4$ ) and cytogenetic risk categories (high risk defined as t(4;14), t(14;16), and 17p13del vs non-high risk - all others).

### **Blinding**

This was an open-label, 2-arm randomized study with an additional independent lyo cohort.

In the ocular sub-study, the treating ophthalmologist remained blinded as to which eye received the prophylactic corticosteroid treatment.

### **Dose modification and dose discontinuation**

Dose modifications were managed according to guidance provided in the protocol. Adjustments due to body weight were made if the change in body weight was  $>10\%$ . Dose reductions or delays for toxicities were permitted after Cycle 1.

For a starting dose of 3.4 mg/kg, the first reduction permitted was to 2.5 mg/kg and second reduction permitted was to 1.92 mg/kg. For a starting dose of 2.5 mg/kg, only 1 dose reduction to 1.92 mg/kg was permitted. If the participant could not tolerate the drug after the allowed dose reductions, he or she was withdrawn from the study treatment for lack of tolerability. In case of full resolution of symptoms which led to dose reduction, further treatment at the previous dose was considered by the investigator.

Dosing delays were permitted in the case of medical/surgical events or for logistical reasons not related to study therapy. Resuming treatment was possible with or without dose reduction after the toxicity had resolved to Grade 1 or less.

Dose modification guidelines for treatment-related corneal events were based on ocular examination findings and BCVA change (please refer to Sections 8.2.4 and 8.2.5 for additional details).

### **The FDA's Assessment:**

The FDA agrees with the Applicant's description of the dose modifications and dose discontinuations. The protocol included specific dose modification guidelines for drug-related adverse events as well as for corneal-related adverse events. The dose modification guidelines used in the DREAMM-2 protocol are shown in Table 11 and Table 12 below.

**Table 11. DREAMM-2 Dose Modifications for Drug-Related Adverse Events**

Toxicity	Grade/description of toxicity	Recommendations for GSK2857916
Elevated serum creatinine which cannot be explained by concomitant sepsis, TLS, other severe condition with fever, or dehydration	If absolute serum creatinine increases from baseline by >0.5 mg/dL	<ul style="list-style-type: none"> <li>Repeat serum creatinine or eGFR within 48 hours</li> <li>If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution</li> <li>Discuss any further dosing with Medical Monitor<sup>a</sup></li> </ul>
Serum creatinine >Grade 3	>3.0 mg/dL from baseline or 3.0-6.0xULN	<ul style="list-style-type: none"> <li>Provide appropriate medical treatment.</li> <li>Permanently discontinue treatment with GSK2857916</li> </ul>
Spot urine (creatinine / albumin ratios)	>2000 mg/g (or 224 mg/mmol)	<ul style="list-style-type: none"> <li>Re-test (at least 7 days apart).</li> <li>If not confirmed, continue GSK2857916 at 100% dose</li> <li>If confirmed on re-test and no clear evidence of disease progression<sup>c</sup> <ul style="list-style-type: none"> <li>Interrupt treatment with GSK2857916</li> <li>Repeat testing within 4 weeks <ul style="list-style-type: none"> <li>i. If spot urine &lt;2000 mg/g (224 mg/mmol), may restart GSK2857916 with 25% dose reduction</li> <li>ii. If spot urine remains &gt;2000 mg/g (224 mg/mmol) after 4weeks, permanently discontinue GSK2857916 and withdraw subject from study; provide treatment as clinically indicated and follow for resolution<sup>a</sup></li> </ul> </li> </ul> </li> </ul>
Thrombocytopenia (on days of dosing)	3	<ul style="list-style-type: none"> <li>No bleeding: continue treatment with 25% dose reduction. Consider reversing to previous dose once thrombocytopenia recovered to G2 or less.</li> </ul>
		<ul style="list-style-type: none"> <li>With bleeding: withhold the dose, continue treatment after recovery with 25% dose reduction</li> </ul>
Thrombocytopenia (On days of dosing)	4	<ul style="list-style-type: none"> <li>Withhold the dose. Consider restarting with 25% dose reduction if recovered, or transfused to ≤G3 only if there is no active bleeding at time of treatment re-start</li> </ul>
		<ul style="list-style-type: none"> <li>If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to &gt;25x10<sup>9</sup>/L continuing treatment at 25-50% dose reduction may be considered after discussion with the GSK Medical Monitor</li> </ul>

Febrile neutropenia	3-4 (defined as: single temp of 38.3°C, or sustained 38°C for >1 hr AND ANC <1000/mm <sup>3</sup> )	<ul style="list-style-type: none"> <li>Withhold the dose</li> <li>Implement treatment with antibiotics, antivirals and antifungals, as clinically indicated, consider growth factors</li> <li>Continue treatment after resolution. Consider 25% dose reduction of GSK2857916, if neutropenia was drug related</li> </ul>
Infusion Reaction <sup>b</sup>	2	<ul style="list-style-type: none"> <li>Stop the infusion, provide medical treatment and continue at slower rate after resolution to Grade 0-1</li> </ul>
	3	<ul style="list-style-type: none"> <li>Further treatment with GSK2857916 needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with pre-</li> </ul>

Source: Applicant's DREAMM-2 Protocol (Amendment 3)

**Table 12. DREAMM-2 Dose Modification Guidelines for Corneal-Related Adverse Events**

Toxicity	Grade <sup>a</sup>	Recommendations <sup>b,c</sup>
Corneal events	G1 or presence of asymptomatic corneal findings on ophthalmic exam not observed at baseline	<ul style="list-style-type: none"> <li>Continue treatment with current dose of GSK2857916.</li> <li>Consider ophthalmology consult.</li> <li>If symptoms occur after the mandatory 7-day prophylactic treatment with steroid eye drops is complete, consider re-starting ocular steroid drops at four times daily until resolution. If topical steroid use is prolonged, i.e., &gt;7 days, consult ophthalmology.</li> <li>If symptoms occur within the 7-day prophylaxis window with steroid eye drops, consider increased frequency of steroid eye drops to 1 drop every 2-4 hours and continue until resolution. If topical steroid use is prolonged, i.e., &gt;7 days, consult ophthalmology.</li> <li>Use of preservative-free artificial tears may be increased up to every 2 hours, as needed.</li> </ul>
	G2/G3	<ul style="list-style-type: none"> <li>Hold GSK2857916 and consult ophthalmology as soon as possible</li> <li>If symptoms occur after the mandatory 7-day prophylactic treatment with steroid eye drops is complete, re-start ocular steroid drops at four times daily until resolution.</li> <li>If symptoms occur within the 7-day prophylaxis window with steroid eye drops, consider increased frequency of steroid eye drops to 1 drop every 2-4 hours and continue until resolution</li> <li>Use of preservative-free artificial tears may be increased up to every 2 hours, as needed</li> <li>If resolves to &lt;Grade 1 within 14 days consider continuing with the pre-hold dose.</li> <li>If resolves to &lt;Grade 1 after 14 days, consider 25% dose reduction.</li> <li>In case of recurring &gt;Grade 2 events, consult the MM</li> </ul>

	G4	<ul style="list-style-type: none"> <li>• Stop treatment with GSK2857916</li> <li>• Consult ophthalmology immediately</li> <li>• If symptoms occur after the mandatory 7-day prophylactic treatment with steroid eye drops is complete, re-start ocular steroid drops at four times daily until resolution</li> <li>• If symptoms occur within the 7-day prophylaxis window with steroid eye drops, consider increased frequency of steroid eye drops to 1 drop every 2-4 hours and continue until resolution</li> <li>• Preservative free artificial tears QID</li> <li>• Additional topical treatment if recommended by ophthalmologist</li> <li>• Treatment re-start at the reduced dose is only possible after discussion and agreement between the treating ophthalmologist, the GSK MM and possibly a GSK ophthalmologist</li> </ul>
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Source: Applicant’s DREAMM-2 Protocol (Amendment 3)

**Administrative structure**

An independent review committee (IRC) was utilized to assess responses in the study. All laboratory parameters and lesion measurements used to assess participant response were to be shared with the IRC. The interim analysis (IA) to assess futility was reviewed by an Independent Data Monitoring Committee (IDMC).

**Procedures and schedule**

Response assessments were performed regardless of dosing Q3W (starting Week 4) based on disease laboratory tests and imaging, if applicable. Imaging (CT, MRI or PET/CT) was only required for participants with extramedullary disease. Vital signs were assessed at screening, Cycle 1 Day 1 (C1D1), and Cycle 2 – any Cycle beyond with dosing, and at the End of Treatment (EoT) visit. Hematological and chemical laboratory tests were assessed at screening, C1D1, Q3W starting Week 4 (to be performed regardless of dosing), and at the EoT visit; serum creatinine was also assessed at PFS follow-up. Ocular exams were performed within 21 days prior to first dose, predose every 3 weeks, at the EoT visit, and at follow-up thereafter based on corneal signs as outlined in the protocol. Adverse events were recorded until the EoT visit, which occurred within 45 days of the last dose of study treatment. All related SAEs were collected from consent through OS follow-up.

**The FDA’s Assessment:**

The FDA agrees with the Applicant’s description of study procedures and the schedule of assessments. Ocular exams were done prior to the first dose, every three weeks prior to dosing, at the end-of-treatment visit, and at follow-up.

**Concurrent medications**

Participants received full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheal,

and analgesics, as appropriate. Concomitant therapy with bisphosphonates was allowed. Participants were allowed to receive local irradiation for pain or stability control.

### **Treatment compliance**

Participants received study treatment at the site directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic was recorded in the source documents and reported in the eCRF.

### **Participant completion, discontinuation, or withdrawal**

A participant was considered to have completed the study if he or she had received at least one dose of the study treatment and, had died or is still in follow-up when the study will close, and had not withdrawn consent from study participation.

The study will end when 60% of the participants have died, OR withdrawn consent, OR are lost to follow-up, AND all participants with corneal events have been followed for up to 12 months after last dose of treatment or until full resolution of ophthalmic changes, or deemed clinically stable by an ophthalmologist/optometrist, whichever comes first. At this time, end of study analyses will be performed. If a participant remains on treatment at the time end of study is achieved, they may be offered an option to extend treatment on another protocol. A participant was considered to have withdrawn from the study if:

- a. the participant has not died and is lost to follow-up,
- b. the participant has withdrawn consent,
- c. the participant is no longer being followed at the investigator's discretion, or
- d. the study is terminated prematurely.

Documentation of the cause of death in the electronic Case Report Form (eCRF) is required for all participants who die in the study regardless of the cause of death.

### **Study endpoints**

The primary endpoint of ORR was defined as percentage of participants with a confirmed PR or better, based on the assessment by the IRC. Investigator-assessed ORR was also reported. Secondary efficacy endpoints included CBR, TTR, DoR, TTP, OS, and PFS as assessed by both investigator and IRC. Other secondary endpoints included safety, PK, ADA, PROs (symptomatic AEs and QoL), and the ocular substudy and Iyo cohorts.

### **The FDA's Assessment:**

The FDA agrees with the Applicant's description of the study endpoints for DREAMM-2. In addition to above, DREAMM-2 included an ocular sub-study to evaluate the effect of topical corticosteroids on corneal findings in up to 30 participants who received monocular topical corticosteroids for the first 4 cycles. The endpoint of this study was the description of differences in corneal exam findings in each eye based on ophthalmic examinations. The study was not powered. Therefore, the analysis results from ocular sub-study were considered as

exploratory only. Additionally, the lyophilized cohort was not powered for any of the efficacy endpoints. Therefore, the analysis results from lyophilized cohort were also considered exploratory.

### Statistical Analysis Plan and Amendments

The protocol has been amended to address over-enrollment; the primary analysis was based on all randomized participants (approximately 200) enrolled into the Intent-to-Treat (ITT) Population. In addition, a sensitivity analysis based on the first 130 randomized participants was performed to account for the original study design. Please see the Protocol Amendments subsection below for further details on protocol amendments for DREAMM-2.

The Reporting and Analysis Plan (RAP) and RAP Amendment v01 were finalized prior to the unblinding of planned treatment. Please refer to Table 13 for analysis populations defined for the study and Table 14 for the number of participants per cohort in each analysis population.

**Table 13. Analysis Populations Defined for the Study**

Population	Definition / Criteria	Analyses Evaluated
<b>Intent-to-Treat (ITT) (N=196)</b>	<ul style="list-style-type: none"> <li>All participants randomized to the frozen liquid cohorts (main study) whether or not randomized treatment was administered.</li> <li>This population will be based on the treatment the participant was randomized to.</li> <li>Any participant who receives a treatment randomization number will be considered to have been randomized. Same participant receiving multiple randomization numbers will be counted only once using the last randomization number.</li> </ul>	<ul style="list-style-type: none"> <li>Study Population</li> <li>Efficacy</li> <li>EORTC QLQ-C30 and EORTC QLQ-MY20</li> </ul>
<b>Efficacy (N=130)</b>	<ul style="list-style-type: none"> <li>Efficacy Population will consist of first 130 ITT participants whether or not randomized treatment was administered. This population will be based on the treatment to which the participant was randomized and will be used for sensitivity analysis of primary and selected secondary efficacy endpoints.</li> </ul>	<ul style="list-style-type: none"> <li>Selected efficacy</li> </ul>
<b>Evaluable (N= 51)</b>	<ul style="list-style-type: none"> <li>All participants who have at least 2 doses of study treatment and have completed at least one disease assessment after the second dose, or progressed or died or discontinued treatment due to other reasons.</li> </ul>	<ul style="list-style-type: none"> <li>Futility analyses at IA</li> </ul>
<b>Safety (N=193)</b>	<ul style="list-style-type: none"> <li>All ITT participants who received at least 1 dose of study treatment.</li> <li>This population will be based on the treatment the participant actually received (first dose).</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> <li>PRO-CTCAE, NEI-VFQ-25 and OSDI.</li> </ul>
<b>Ocular Sub-Study (N=30)</b>	<ul style="list-style-type: none"> <li>All randomized participants to ocular sub-study who received at least 1 dose of study treatment.</li> <li>This population will be used to evaluate the effect of topical corticosteroids on corneal events/findings in approximately 30 participants who will receive monocular topical corticosteroids for the first 4 cycles.</li> </ul>	<ul style="list-style-type: none"> <li>Corneal events/findings</li> </ul>

Population	Definition / Criteria	Analyses Evaluated
<b>Full Analysis (N=221)</b>	<ul style="list-style-type: none"> <li>All participants included in either ITT or Iyo Population</li> <li>This population will be based on the treatment the participant was randomized to.</li> </ul>	<ul style="list-style-type: none"> <li>Study population</li> <li>Efficacy</li> <li>EORTC QLQ-C30 and EORTC QLQ-MY20</li> </ul>
<b>Full Safety (N=218)</b>	<ul style="list-style-type: none"> <li>All participants who receive at least 1 dose of study treatment (also including Iyo).</li> <li>This population will be based on the treatment the subject actually received (first dose).</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> <li>PRO-CTCAE, NEI-VFQ-25 and OSDI.</li> </ul>
<b>Full Pharmacokinetic (PK) (N=218)</b>	<ul style="list-style-type: none"> <li>All participants in the Full Safety Population who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values).</li> </ul>	<ul style="list-style-type: none"> <li>PK</li> </ul>

Note: 3 participants in the Full Analysis Population were untreated and not included in the Full Safety and Full Pharmacokinetic Populations.

Abbreviations: ITT = Intent-to-Treat; EORTC = European Organization for Research and Treatment of Cancer; QLQ-C30 = Quality of Life Questionnaire-Core 30; QLQ-MY20 = Quality of Life Questionnaire Multiple Myeloma Module; IA = Interim Analysis; PRO = Patient Reported Outcome; CTCAE = Common Terminology Criteria for Adverse Event; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire; OSDI = Ocular Surface Disease Index; Iyo = lyophilized; PK = Pharmacokinetic; NQ = Non-quantifiable.

**Table 14. Analysis Populations - DREAMM-2**

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

Data Source: Table 1.0070

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

Note: Full Analysis, Full Safety, and Full Pharmacokinetic populations also include the Iyo cohort in addition to the two cohorts presented above.

### Efficacy analysis

The efficacy analyses were based on the 'Intent-to-Treat' Population or 'Efficacy' Population and 'Full Analysis' Population also included the Iyo cohort. In addition, sensitivity analyses for ORR, DoR, and TTR as assessed by both investigator and IRC were performed using Efficacy Population. At interim analysis, investigator-assessed ORR was analyzed based on the Evaluable Population.

Participants with an unknown or a missing response were treated as non-responders, i.e., these participants were included in the denominator when calculating percentages of response. 97.5% confidence interval based on the exact method was calculated for the analysis of ORR.

For subgroup analysis, ORR estimates along with 97.5% exact confidence interval (CI) were presented using forest plot, and no hypothesis testing was performed.

Time to events endpoints were summarized based on Kaplan-Meier method. Details about censoring rules were specified in the study RAP.

### **Safety analysis**

Separate AE summaries were presented by system organ class (SOC), preferred term (PT), and maximum CTCAE grade. All AEs, Grade 3-4 AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, AEs requiring dose reduction, AEs leading to dose delay, Adverse Events of Special Interest (AESIs), death, ocular findings from the ophthalmic exam, and the number (%) of participants with worst post-baseline laboratory data, clinically notable vital sign abnormalities, and notable ECG abnormalities were summarized by treatment group. Safety summary tables included “on-treatment” events/assessments, i.e., those collected on or after the first dose of study treatment.

### **PK analysis**

Serial concentration-time data collected in Cycles 1 and 3 were analysed using standard non-compartmental methods. The concentration-time data were also combined with data from other studies and analysed in a population approach using nonlinear mixed effects modeling for separate reporting.

### **Health outcome analysis**

The EORTC QLQ-C30 (version 3.0), EORTC QLQ-MY20, and the PRO-CTCAE are 3 oncology-specific Health-Related Quality-of-Life (HRQoL) assessments that were analysed in this study.

In addition, the impact of potential corneal event on function and health-related quality-of-life was assessed with the use of 2 visual function questionnaires, the NEI-VFQ-25 and Ocular Surface Disease Index (OSDI).

The analysis population for EORTC QLQ-C30 and EORTC QLQ-MY20 followed the rule for efficacy analysis, while the analysis population for PRO-CTCAE, NEI-VFQ-25, and OSDI followed the rule for safety analysis.

### **Ocular sub-study**

The ocular sub-study analyses were based on the “Ocular Sub-study” Population. Data were analyzed for eyes randomized to receive topical corticosteroids vs. eyes not randomized to receive topical corticosteroids by dose cohort.

### **The FDA’s Assessment:**

The FDA agrees with the Applicant’s description of the protocol and SAP for the DREAMM-2 study with a focus on the key design elements relevant to this BLA application. The 2 single-arm study design with two dose levels and a futility analysis was acceptable for this population

because there were no approved comparators for the proposed treatment at the time of study initiation.

For the primary analysis, the null hypothesis would be rejected if the lower bound of the 2-sided 97.5% exact confidence interval exceeded the rate of 15%. The Applicant provided justification for selection of the response rate, which was based on 4 publications [Hájek, 2017; Kumar, 2012; Durie, 2012; Anderson, 2008]. The hypothesis testing was performed within each arm separately. No hypothesis testing for comparing the ORR between the two arms was performed. The following assumptions were made in the estimation of the required sample size:

- Normal approximation of binomial proportion
- $\leq 15\%$  for the response rate
- A 90% chance of rejecting the null hypothesis when the alternative hypothesis was true

In addition, the study also included an ocular sub-study of approximately 30 participants (approximately 15 participants at each dose) to evaluate and characterize the effect of ophthalmic topical corticosteroids on belantamab mafodotin-associated corneal findings. The participants for this sub-study were enrolled at select investigational sites that were equipped with ophthalmologists with subspecialty training and expertise in the cornea. These participants underwent additional ophthalmic examinations during the first four cycles of treatment or as clinically indicated as determined by the treating ophthalmologist.

PRO data were reviewed and were not considered part of the efficacy analysis, but were considered as supportive data for the review of safety and tolerability. There was no alpha allocated to the analyses of PRO endpoint. Therefore, no statistical inference could be drawn from the PRO analyses. All PRO analyses are considered descriptive and exploratory.

The endpoint of the ocular sub-study was the description of differences in corneal exam findings in each eye based on ophthalmic examinations. The study was not powered. Therefore, the analysis results from ocular sub-study were considered as exploratory.

### **Protocol Amendments**

The original protocol (Version 1, dated 18-Jan-2018) was amended 3 times leading up to the cut-off for primary analysis, with the most recent version (Version 3) dated 17-Dec-2018. Key protocol revisions include:

- Amendment 1, dated 02-Apr-2018: Amended to add 2.5 mg/kg dose arm and an exploratory cohort of 25 participants to receive the lyo presentation of belantamab mafodotin. To accommodate these changes, the overall sample size and related analytical methods were also changed.
- Amendment 2, dated 04-Sep-2018: Amended to add grading of ocular events by CTCAE Version 4 in addition to the GSK corneal scale. Additional PK sampling and time points

were also added. DREAMM-2

- Amendment 3, dated 17-Dec-2018: Amended to address over-enrollment in the ITT Population.

None of the implemented changes impacted the integrity of the trial or the interpretation of the results.

The FDA's Assessment:

The FDA generally agrees with the Applicant's statistical statements for efficacy. There were no major deviations to the originally planned statistical analysis specified in the protocol amendment 3.

**8.1.2. Results – Study 205678 (DREAMM-2)**

The Applicant's Position:

Data in this section are presented as from the 2.5 mg/kg group first, followed by the 3.4 mg/kg group, unless otherwise noted.

**Compliance with Good Clinical Practices**

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the ICH Good Clinical Practice (GCP).

Written informed consent was obtained from each participant prior to the performance of any study-specific procedures. The informed consent was signed and dated by the study participant and by the person who conducted the informed consent discussion.

**Financial Disclosure**

Details of financial disclosure are presented in Section 20.2.

**Patient Disposition – DREAMM-2 (ITT Population)**

A total of 196 participants were randomized and received treatment at either 2.5 mg/kg or 3.4 mg/kg Q3W IV. The first participant was randomized on June 29, 2018 and the last participant was randomized on January 2, 2019. Of the 196 randomized participants, 193 received at least 1 dose of belantamab mafodotin.

As of the data cut-off, the median time on study participants was 6.28 months (range: 0.1-10.9) and 6.87 months (range: 0.1-10.6). A total of 33% and 31% of participants had died, and 62% and 66% were still ongoing in the 2.5 mg/kg and 3.4 mg/kg arms, respectively (Table 15).

There are 23% and 25% of participants who continue to receive study treatment in the 2.5 mg/kg and 3.4 mg/kg arms, respectively.

A total of 77% and 75% of participants have discontinued treatment, and the most frequent reason for discontinuation was disease progression (62% and 57%). AEs leading to treatment discontinuation (7% and 10%) are detailed in Section 8.2.4 Safety Results.

**Table 15. Participant Status and Reason for Study Withdrawal or Discontinuation of Treatment (ITT Population) - DREAMM-2**

	Belantamab mafodotin Q3W	
	2.5 mg/kg (N=97) n (%)	3.4 mg/kg (N=99) n (%)
<b>Participant Status</b>		
Died	32 (33)	31 (31)
Ongoing	60 (62)	65 (66)
On study treatment	22 (23)	25 (25)
In follow-up	38 (39)	40 (40)
Withdrawn from study	5 (5)	3 (3)
<b>Primary reason for study withdrawal</b>		
Lost to Follow-up	1 (1)	0
Physician Decision	1 (1)	2 (2)
Withdrawal by participant	3 (3)	1 (1)
<b>Primary reason for treatment discontinuation<sup>a</sup></b>		
Progressive disease	59 (62)	56 (57)
Adverse event	7 (7) <sup>b</sup>	10 (10)
Lack of efficacy	1 (1)	1 (1)
Lost to follow-up	1 (1)	0
Physician decision	4 (4) <sup>c</sup>	4 (4) <sup>c</sup>
Withdrawal by participant	1 (1) <sup>c</sup>	3 (3) <sup>c</sup>

- Participant (b) (6) in the 3.4 mg/kg frozen presentation arm does not have information entered in the database for treatment discontinuation related to study treatment.
- Participant (b) (6) had a disease-related headache, but discontinued treatment for the primary reason of disease progression.
- Decisions were considered treatment-related for 3 participants and 2 participants in the 2.5 mg/kg and 3.4 mg/kg doses, respectively.

Data Source: Table 1.0010; Table 1.0020

Abbreviations: ITT = Intent-to-Treat; Q3W = every 3 weeks.

### Protocol Violations/Deviations

All deviations were assessed for importance by the study team. Important deviations were defined as: deviations which directly or indirectly have an impact on: participant's rights, safety, or well-being, and/or on data integrity and/or regulatory compliance, as per ICH E3. As such, the vast majority of deviations were related to the completeness or timely performance of assessments (68% and 85%), followed by incorrect study treatment administration (16% and 26%), and by failure to report safety events per protocol in a timely manner (within 24 hours; 4% and 7%). In general, the identified deviations were not considered to affect the integrity of the study results overall.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment on patient disposition. The reasons for treatment discontinuation were similar in both dose levels.

The Applicant's Position:

**Baseline Demographic and Disease Characteristics**

Demographic characteristics were similar between the 2 cohorts (Table 16). Participants were predominantly Caucasian (74% and 84%), with a median age of 65 and 67 years (13% and 17% age 75 years and older).

Disease characteristics were also similar between both cohorts, although participants in the 2.5 mg/kg dose arm had slightly more advanced disease (ISS stage III at Screening 43%, high risk cytogenetics 27%) and were more heavily pretreated with a median of 7 prior lines of therapies (Table 17).

The study population is representative of current clinical practice in terms of prior therapies (NCCN and European Society for Medical Oncology [ESMO] guidance), age, ethnicity/race and co-morbidities.

**Table 16. Demographic Characteristics (ITT Population) - DREAMM-2**

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

Data Source: Table 1.0120, Table 1.1150  
 Abbreviations: SD = Standard Deviation; ITT = Intent-to-Treat; Q3W = every 3 weeks.

**Table 17. Baseline Disease Characteristics (ITT Population) - DREAMM-2**

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

a. Participant <sup>(b) (6)</sup> was confirmed as Stage I.

b. If the participant has any of the following cytogenetics: t(4;14), t(14;16), and 17p13del.

Data Source: Table 1.0160, Table 1.11060

Abbreviations: Ig=Immunoglobulin; ITT = Intent-to-Treat.

**The FDA's Assessment:**

The FDA agrees with the Applicant's description of the baseline demographic information for the DREAMM-2 study. FDA agrees that, in general, the study population for DREAMM-2 was representative of the general population of patients with RRMM in the U.S. However, the FDA notes that DREAMM-2 enrolled a younger patient population (median age of 66 years) compared to the general population of patients with MM (median age at diagnosis in the U.S. population is 69 years, NCI SEER).

The majority of the patients entered the study with stage II or III multiple myeloma (77% and 82%, respectively). Approximately 30% of all participants enrolled in both dose levels had high risk cytogenetics. Extramedullary disease was present in approximately 23% (22/97) and 18% (18/99) of subjects enrolled in the 2.5 mg/kg and 3.4 mg/kg dose levels, respectively. Due to the small sample size in the patients with extramedullary disease at baseline, caution should be taken for the interpretation of efficacy result for this subgroup analyses.

The Applicant's Position:

**Prior and Concomitant Medications and Other Treatments**

**Prior Anti-Cancer Medications**

Per the study entry criteria, all participants were pre-treated with regimens containing IMiDs, PIs, and anti-CD38 mAbs (Table 18). In addition, 75% and 87% of participants also had prior stem cell transplantation.

**Table 18. Prior Anti-Cancer Therapy by Drug Class of Agents (ITT Population) - DREAMM-2**

Drug Class	Belantamab mafodotin		
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)	Total (N=196)
<b>Steroids, n (%)</b>	97 (100)	99 (100)	196 (100)
<b>Immunomodulator, n (%)</b>	97 (100)	99 (100)	196 (100)
Lenalidomide	97 (100)	99 (100)	196 (100)
Pomalidomide	89 (92)	84 (85)	173 (88)
Thalidomide	29 (30)	39 (39)	68 (35)
<b>Proteasome Inhibitor, n (%)</b>	97 (100)	99 (100)	196 (100)
Bortezomib	95 (98)	97 (98)	192 (98)
Carfilzomib	74 (76)	64 (65)	135 (70)
Ixazomib	22 (23)	23 (23)	45 (23)
<b>Monoclonal Antibody, n (%)</b>	97 (100)	98 (99) <sup>a</sup>	195 (>99)
Daratumumab	97 (100)	96 (97)	193 (98)
Elotuzumab	15 (15)	13 (13)	28 (14)
Isatuximab	3 (3)	2 (2)	5 (3)
Pembrolizumab	2 (2)	1 (1)	3 (2)
Blinatumomab	1 (1)	0	1 (<1)
Investigational antineoplastic agents	1 (1)	0	1 (<1)
<b>Chemotherapy, n (%)</b>	92 (95)	95 (96)	187 (95)
<b>Stem Cell Transplant, n (%)</b>	73 (75)	86 (87)	159 (81)
<b>Other, n (%)</b>	34 (35)	33 (33)	67 (34)
<b>HDAC Inhibitor, n (%)</b>	11 (11)	9 (9)	20 (10)

Data Source: Table 1.0190, Table 1.11070

a. Participant (b) (5) received an investigational anti-CD38 monoclonal antibody and is included under 'Other'.

Abbreviations: ITT = Intent-to-Treat; HDAC = Histone Deacetylase; CD38 = Cluster of Differentiation 38.

Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease (PD) while on therapy [Rajkumar, 2011]. Both cohorts had participants who were similarly refractory to different classes of prior anti-cancer therapies (Table 19). Most participants (100% and 92%) were also refractory to anti-CD38 monoclonal antibody treatment.

#### The FDA's Assessment:

The FDA agrees with the Applicant's description of the prior anti-myeloma therapies received in the ITT patient population. DREAMM-2 enrolled a heavily pre-treated patient population. The median number of prior lines of therapy for subjects who received the 2.5 mg/kg dose was 7 (range: 3-21).

**Table 19. Participants Refractory to Prior Anti-Cancer Therapy by Drug Class of Agents (ITT Population) - DREAMM-2**

Drug Class, n (%)	Belantamab mafodotin		
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)	Total (N=196)
<b>Proteasome Inhibitor</b>	95 (98) <sup>b</sup>	99 (100)	194 (99)
Bortezomib	74 (76)	74 (75)	148 (76)
Carfilzomib	63 (65)	57 (58)	120 (61)
Ixazomib	21 (22)	21 (21)	42 (21)
<b>Immunomodulator</b>	95 (98) <sup>b</sup>	98 (99) <sup>b</sup>	193 (98)
Lenalidomide	87 (90)	88 (89)	175 (89)
Pomalidomide	84 (87)	77 (78)	161 (82)
Thalidomide	13 (13)	18 (18)	31 (16)
<b>Monoclonal Antibody</b>	97 (100)	92 (93) <sup>a</sup>	189 (96)
Daratumumab	97 (100)	91 (92)	188 (96)
Elotuzumab	13 (13)	10 (10)	23 (12)
Isatuximab	3 (3)	1 (1)	4 (2)
Pembrolizumab	2 (2)	1 (1)	3 (2)
Blinatumomab	1 (1)	0	1 (<1)
Investigational antineoplastic agents	1 (1)	0	1 (<1)
<b>Steroids</b>	94 (97)	91 (92)	185 (94)
<b>Chemotherapy</b>	66 (68)	70 (71)	136 (69)
<b>Other</b>	29 (30)	28 (28) <sup>a</sup>	57 (29)
<b>Stem Cell Transplant</b>	11 (11)	13 (13)	24 (12)
<b>HDAC Inhibitor</b>	11 (11)	8 (8)	19 (10)
<b>Immunomodulator and Proteasome Inhibitor</b>	93 (96) <sup>b</sup>	98 (99) <sup>b</sup>	191 (97)

Data Source: Table 1.0200, Table 1.11080

- Participant <sup>(b) (6)</sup> received an investigational anti-CD38 monoclonal antibody and is included under 'Other'.
- Due to data entry errors, 4 participants at the 2.5 mg/kg dose and 1 participant in the 3.4 mg/kg dose were not categorized as refractory to prior IMiD and PI treatment.

Abbreviations: ITT = Intent-to-Treat; HDAC = Histone Deacetylase; CD38 = Cluster of Differentiation 38; IMiD = Immunomodulatory Drug; PI = Proteasome Inhibitor.

## Treatment Compliance, Concomitant Medications, and Rescue Medication Use

### The Applicant's Position:

#### Overall concomitant medications

The most common concomitant medications were paracetamol (58% and 69%), dexamethasone (47% and 64%), acyclovir (63% and 52%), carmellose (artificial tears) (29% and 43%), and prednisolone (53% and 42%).

The most commonly used blood products included red blood cells (22% and 27%) and platelet transfusions (15% and 20%). Granulocyte-colony stimulating factor (G-CSF) was the most frequently used growth factor in the study (2% and 5%). Erythropoietin-stimulating factors were received by 7% and 11% of participants.

### **Prophylactic medication for infusion-related reactions (IRRs)**

Prophylactic medications for IRRs was not mandated but were used by approximately a third of participants during the study (32% and 39%); 17% and 22% of participants received prophylactic steroids.

### **Ocular concomitant medications**

Medications for dry eye and steroid eye drops were used by all participants, as per protocol. The most common dry eye medications were various types of artificial tears (carmellose sodium eye drops [26% and 42%], artificial tears nos [40% and 16%], and hypromellose eye drops [12% and 22%]).

### **The FDA's Assessment:**

In general, FDA agrees that the study population for DREAMM-2 was representative of the general RRMM population in the U.S.; however, the median age of 66 years is younger than the median age at diagnosis of 69 years in the U.S. The FDA also notes that this was a heavily pre-treated patient population with a median of 7 prior lines of therapy. In addition, there were a total of 22 subjects with extramedullary disease treated at the 2.5 mg/kg dose, representing a small number of patients. It is notable that at the time of the primary analysis, based on a 6-month data cut-off, that less than a quarter (23%) of the patients enrolled in the 2.5 mg/kg cohort were still receiving treatment with belantamab mafodotin.

### **Efficacy Results**

#### **The Applicant's Position:**

#### **Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

##### **Overall Response Rate (ORR)**

The ORR by IRC assessment was 31% (97.5% CI: 20.8, 42.6) in the 2.5 mg/kg group and 34% (97.5% CI: 23.9, 46.0) in the 3.4 mg/kg group (Table 20).

The achieved responses were deep, with more than half of responders (60% and 59%) achieving a response of VGPR or better. Overall, the ORR as assessed by IRC was concordant with the assessment by investigators.

**Table 20. Best Confirmed Response Based on IRC and INV Assessments (ITT Population) - DREAMM-2**

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

Source: Table 2.0010; Table 2.0020

- NE could be due to response not confirmed (2 and 4 participants), or inadequate baseline assessment/no postbaseline assessment (5 and 7 participants) (L30.10010).
- 97.5% confidence interval refers to the 2-sided 97.5% exact confidence interval calculated using Clopper-Pearson method.

Abbreviations: ITT = Intent-to-Treat; sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; MR = minimal response; SD = stable disease; PD = progressive disease; NE = not evaluable; IRC = independent review committee; INV = investigator.

**The FDA's Assessment:**

The FDA reviewer's primary analysis results of ORR are consistent with the results presented in this section by Applicant. Based on protocol and SAP, the study was considered positive if the lower bound of the 97.5% confidence interval was greater than 15%. The study met its primary endpoint for ORR as assessed by IRC in both the 2.5 mg/kg and the 3.4 mg/kg treatment groups. The observed ORR by IRC assessment was 31% (97.5% CI: 20.8, 42.6) in the 2.5 mg/kg group and 34% (97.5% CI: 23.9, 46.0) in the 3.4 mg/kg group. Similar results were obtained by sensitivity analysis with the Efficacy Population. The observed ORR was 30% (97.5% CI: 17.6, 44.2) in the 2.5 mg/kg treatment group and 34% (97.5% CI: 18.3%, 44.6%) in the 3.4 mg/kg treatment group. Overall, the ORR as assessed by IRC was concordant with the assessment by investigators.

However, the FDA reviewer's descriptive analysis results demonstrated numerical differences for the analysis results of CR/PR between the IRC and Investigator assessments for both the 2.5 mg/kg and the 3.4 mg/kg treatment groups (Table 21). The reason for the discordance can be attributed to the high complexity of IMWG criteria and does not impact the overall assessment and reported ORR from the DREAMM-2 study.

**Table 21. Summary Efficacy Analysis Results for CR and PR**

	2.5 mg/kg N=97		3.4 mg/kg N=99	
	IRC	INV	IRC	INV
CR	1 (1)	6 (6)	0	2 (2)
PR	12 (12)	9 (9)	14 (14)	10 (10)

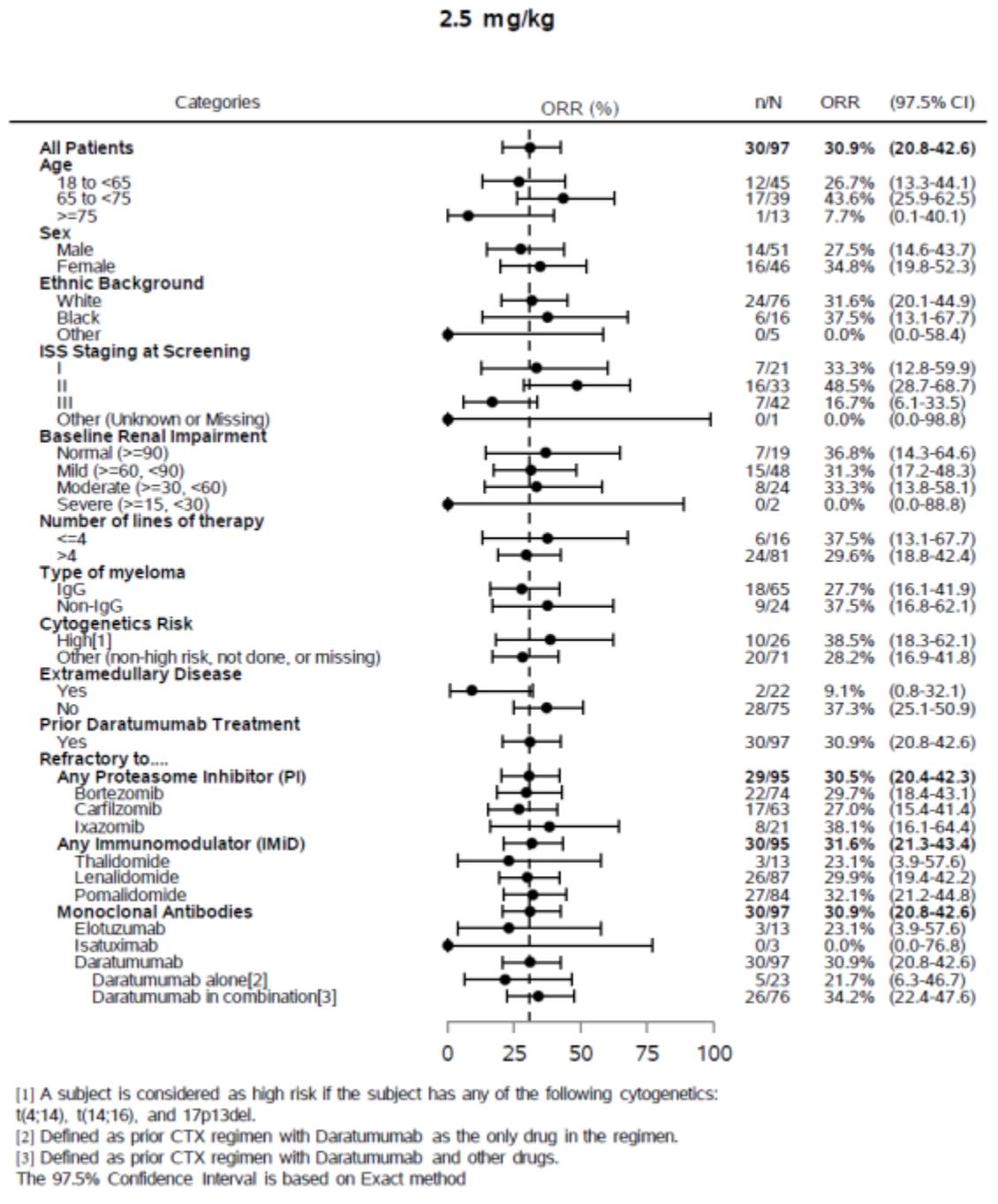
Source: FDA Reviewer's Analysis

**The Applicant's Position:**

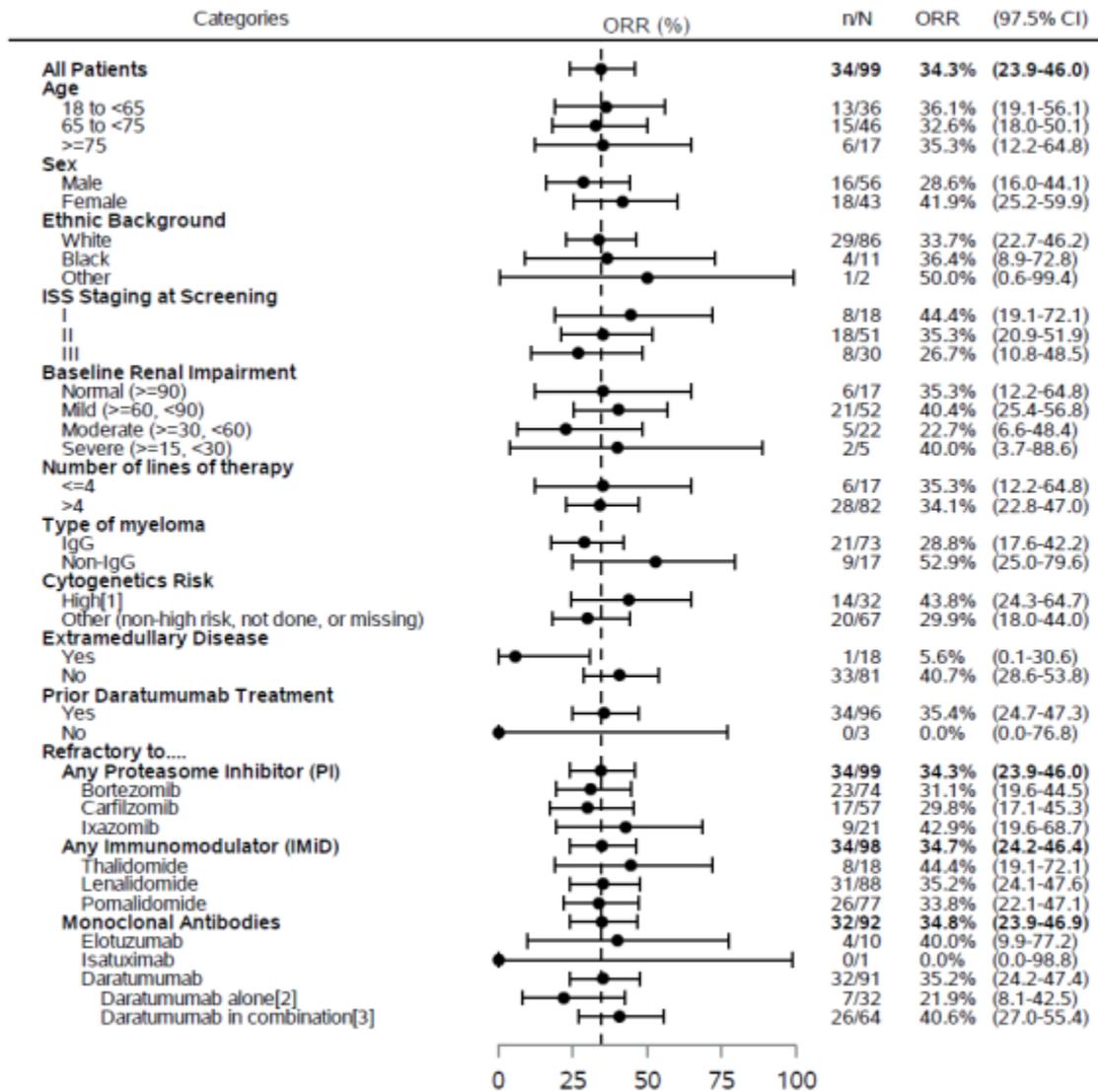
**Subgroup Analyses**

Factors potentially impacting the ORR are depicted in the forest plots below (Figure 9). There is no evidence that any subgroup is different from the overall population in ORR, except for the subgroup of participants with extramedullary disease at screening. The ORR in this subgroup appears to be worse than that in the overall population for both cohorts.

Figure 9. ORR in Demographic and Disease-based Subgroups Based on IRC Assessment



3.4 mg/kg



[1] A subject is considered as high risk if the subject has any of the following cytogenetics: t(4;14), t(14;16), and 17p13del.  
 [2] Defined as prior CTX regimen with Daratumumab as the only drug in the regimen.  
 [3] Defined as prior CTX regimen with Daratumumab and other drugs.  
 The 97.5% Confidence Interval is based on Exact method.

Source: Figure 2.10040

**The FDA’s Assessment:**

The FDA reviewer’s subgroup analysis results of ORR are consistent with the results presented in this section by Applicant. The ORR in subjects with extramedullary disease at baseline appears to be worse than that in the overall population. The observed ORR by IRC assessment

in subjects with extramedullary disease was 9.1% (97.5% CI: 0.8, 32.1) in the 2.5 mg/kg treatment group and 5.6% (97.5% CI: 0.1,30.6) in the 3.4 mg/kg treatment group. Given the small sample size of this subgroup, these results should be interpreted with caution. Additional information is needed to fully assess the efficacy of belantamab mafodotin in patients with extramedullary disease. The observed ORR by IRC assessment in the subgroup of patients aged  $\geq 75$  was 7.7% (97.5% CI: 0.1, 40.1) in the 2.5 mg/kg cohort. Given the small number of patients in this age subgroup (N=13), additional information is needed to fully assess the efficacy of belantamab mafodotin in patients aged  $\geq 75$  (see Section 14).

#### The Applicant's Position:

##### **Lyophilized (lyo) Presentation Cohort**

Supported by robust analytical comparability data discussed in the CMC Review, the lyo cohort was designed to generate clinical experience with the commercial drug product. Enrollment occurred from December 2018 – January 2019 with a median duration of follow-up of 5.3 months; therefore, the efficacy data are less mature than the same dose level cohort in the ITT Population, in which the median duration of follow-up was 6.9 months. There was also a smaller number of participants in the lyo cohort (N=24 vs. N=99 at 3.4 mg/kg). Participants in this cohort were also less heavily pretreated (median prior lines: 5 vs. 6) and less high risk cytogenetics (20% vs. 32%). These considerations should be taken into account when interpreting the results for this cohort.

ORR by IRC assessment was numerically higher (48%) than that in the same dose level cohort from the ITT Population (34%), with similar percentage of participants achieving VGPR or better (24% and 20%).

Noncompartmental pharmacokinetic analysis results for DREAMM-2 found similar belantamab mafodotin and cys-mcMMAF pharmacokinetics for the two presentations, and presentation (frozen liquid or lyophile) was not a significant factor for belantamab mafodotin, total mAb, or cys-mcMMAF pharmacokinetics in the population pharmacokinetic analysis (Section 6.3.1) .

#### The FDA's Assessment:

The FDA reviewer's analysis results from the lyophilized cohort are consistent with the results presented in this section by Applicant. Given the small sample size (N=25) in the lyophilized cohort and the observed differences in the baseline disease characteristics compared to the frozen liquid cohort, any statement regarding the comparison of efficacy endpoints between the cohorts is misleading.

The duration of response data in the lyophilized cohort is based on data from 12 patients. This implies that the DoR estimate is very unstable. Any implicit comparison with the frozen liquid cohort and interpretation of the data should be avoided.

The FDA notes that efficacy analysis from the lyophilized cohort did not control the overall type I error, and this portion of the study was not powered for efficacy endpoints. Therefore, the efficacy results from lyophilized cohort are considered exploratory.

The FDA also notes that there is no data using the lyophilized formulation at the 2.5 mg/kg dose.

The Applicant's Position:

**Data Quality and Integrity**

The Applicant does not anticipate data quality and integrity concerns.

The FDA's Assessment:

In general, the data quality for the DREAMM-2 study appears acceptable with no errors identified for the major study endpoints. The specifications on statistical analyses were provided in sufficient detail.

The Applicant's Position:

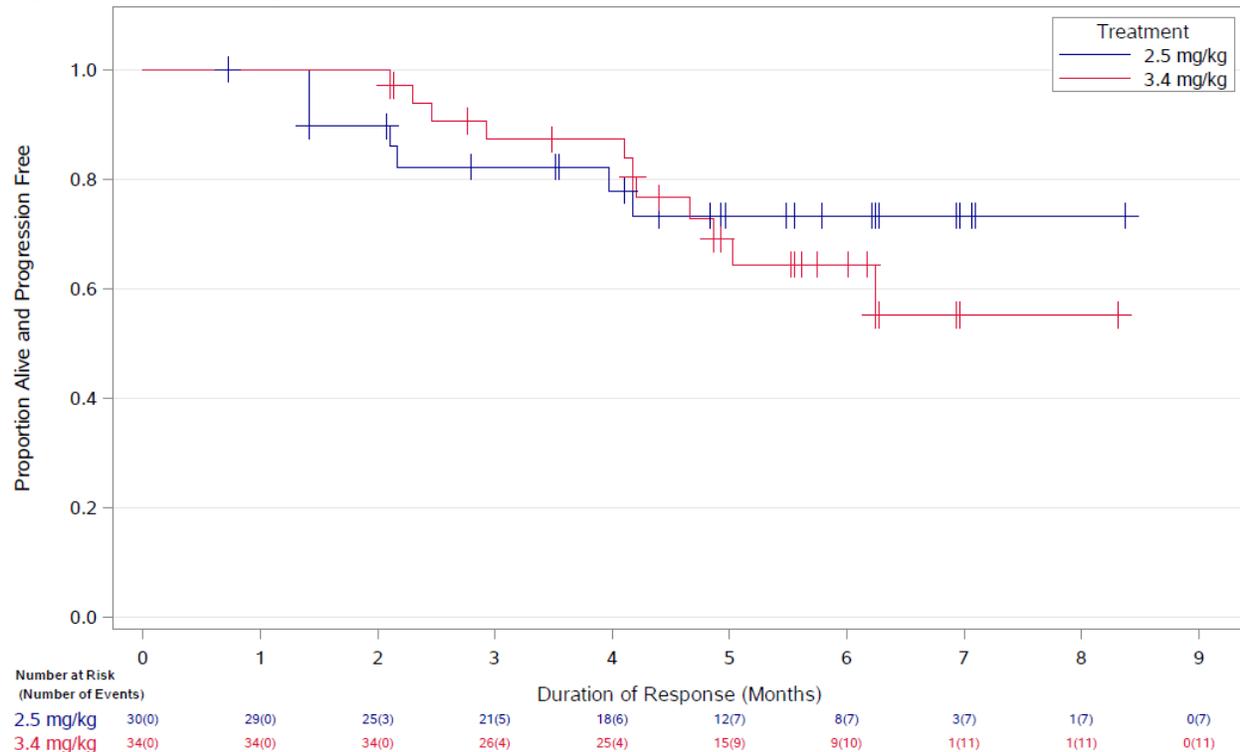
**Efficacy Results – Secondary and other relevant endpoints**

Results of secondary and exploratory outcome measures were supportive of the observed benefit in ORR.

**Durability of Response (DoR)**

The median DoR was not reached for either treatment group as of the data cut-off (Figure 10). Among responders, 23% and 32% have subsequently progressed as per IRC assessment, and the estimated probability of maintaining a response for more than 4 months was 78% and 87%.

**Figure 10. K-M Analysis of DoR Based on IRC Assessment**



Source: Figure 2.0040

**The FDA’s Assessment:**

The FDA reviewer’s analysis of the duration of response is consistent with the results presented in this section by Applicant. The estimated probability of having DoR  $\geq 6$  months was 73% in the 2.5 mg/kg treatment group. However, the FDA notes that the DoR was assessed in patients who achieved an overall response.

**The Applicant’s Position:**

**Time to Response (TTR)**

The time to response was similar between the cohorts (median 1.4 months, 95% CI: 1.0, 1.6; 1.4 months, 95% CI: 0.9, 2.1).

**The FDA’s Assessment:**

The FDA reviewer’s time to response analysis results are consistent with the results presented by the Applicant.

**The Applicant’s Position:**

**Progression-Free Survival (PFS)**

The median PFS was 2.9 months and 4.9 months, respectively. The number of PFS events (participants that died or had disease progression) was similar in the 2 cohorts (58% and 56%).

The FDA's Assessment:

The FDA reviewer's PFS analysis results are consistent with the results presented by the Applicant.

The use of single-arm studies has limitations as following: One limitation is that it is difficult to interpret time-to-event endpoints such as PFS and OS. These endpoints are unlikely to provide evidence to support efficacy because the measurements in isolation are out of context and comparisons to historical controls are prone to bias. Such biases, including variations in the eligibility criteria, clinical practice and standard of care, in addition to temporal effects, make it difficult to interpret time-to-event data from single-arm studies. These biases could be avoided if there was a concurrently sampled and randomly assigned control group. The factors listed affect the time-to-event endpoints more than the response endpoints because the time-to-event endpoints are based on time interval lengths, which can also be biased. For example, a bias can be something as simple as measuring survival from study entrance, rather than when the first dose was administered. There could also be a systematic selection of patients have certain prognostic features. Aggregating several such biases into time-to-event estimates causes those estimates to be unreliable beyond that unique situation because of the lack of a concurrent control for context. On the other hand, response endpoints directly measure the clinical impact and are easier to interpret.

The Applicant's Position:

**Overall Survival (OS)**

OS was not mature at the time of analysis. As of the data cut-off, the 6-month overall survival rate was 72% and 75%.

The FDA's Assessment:

The reviewer's OS analysis results agree with the results presented by the Applicant. The FDA reiterates the challenges with interpretation of time-to-event endpoints in single arm trials including inconsistent definitions of time intervals across studies leading to biased estimates, and bias associated with comparison to historical controls due to differences in the study population, differences in the frequency and timing of assessments, and advances in medical care over time.

The Applicant's Position:

**Minimal Residual Disease (MRD)**

MRD results were available for 6 participants. One participant per each dose arm achieved MRD negativity at the time of the data cut-off. Further sampling and analysis are ongoing for participants remaining on study, and will be reported in the future.

The FDA's Assessment:

In the DREAMM-2 study, MRD testing was done by clonoSEQ at baseline and at the time of VGPR and CR. MRD negative rate was defined as the proportion of subjects who are negative for MRD at any time point after the first dose, as determined by the protocol defined testing procedure. The FDA notes that MRD data was available for only six participants. One participant in each dose cohort achieved MRD negativity. Because of the small sample size, no statistical conclusions can be made.

The Applicant's Position:

**Dose/Dose Response**

The primary endpoint, ORR (as assessed by IRC) was 31% (97.5% CI: 20.8%, 42.6%) and 34% (97.5% CI: 23.9%, 46.0%) in the 2.5 mg/kg Q3W dose and 3.4 mg/kg Q3W dose, respectively; the responses were deep (19% and 20% achieving VGPR or better). Median DoR was not reached in either dose cohort. Median PFS, based on IRC assessment, was 2.9 months for the 2.5 mg/kg cohort and 4.9 months for the 3.4 mg/kg cohort; however, the HR estimate of 3.4 mg/kg versus 2.5 mg/kg was 0.92 (95% CI: 0.63, 1.33), indicating that the difference between the 2 cohorts is smaller than is reflected in the median estimates. In addition, when adjusted for potential prognostic factors, the HR estimate for the 2 randomized dose cohorts became 0.99 (95% CI: 0.67, 1.46), suggesting that the numerical difference observed in PFS between the 2 dose cohorts could be mainly due to imbalance in those prognostic factors. Results of exposure-response analyses for DREAMM-2 are presented in Section 6.3.1. Overall, there was no apparent evidence that the efficacy profile is different between the 2 dose cohorts.

The FDA's Assessment:

The FDA reviewer's analysis results are consistent with the results presented by the Applicant for ORR, VGPR, DoR, and PFS in the two different dose groups.

The Applicant's Position:

**Persistence of Effect**

The FTIH study DREAMM-1 results in the 13 participants that were consistent with the DREAMM-2 population demonstrated a median DoR of 6.7 months (95% CI: 5.3, NE). In DREAMM-2 as of the data cut-off of June 21, 2019, the median duration of response has not been reached. In a sensitivity analysis of DoR that assumed worst case scenario of all participants who were censored with follow-up ongoing would progress immediately at the following visit, the median estimate was 5.6 months for both arms.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

The Applicant's Position:

### **Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints**

This section is not applicable. Please refer to Section 8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability for a discussion on patient reported outcomes.

#### The FDA's Assessment:

The FDA notes that PRO data were not considered part of the efficacy analysis, but were considered as supportive data for the review of safety and tolerability. There was no alpha allocated to the analyses of PRO endpoints. Therefore, no statistical inference could be drawn from the PRO analyses. All PRO analyses are considered descriptive and exploratory.

#### The Applicant's Position:

### **Additional Analyses Conducted on the Individual Trial**

This section is not applicable.

#### The FDA's Assessment:

Not applicable.

### **8.1.3. Supportive Study for Efficacy - Study BMA117159 (DREAMM-1)**

#### The Applicant's Position:

#### **Overview of study design – Study BMA117159 (DREAMM-1)**

This was an open-label, dose-escalation plus dose-expansion Phase I FTIH study to determine the RP2D dosing regimen of belantamab mafodotin. DREAMM-1 consisted of dose escalation (Part 1) and cohort expansion (Part 2). Part 1 evaluated various dose levels from 0.03 mg/kg to 4.6 mg/kg in 38 participants. Part 2 further enrolled 35 participants at starting dose of 3.4 mg/kg. The length of each cycle was 21 days for the Q3W schedule. Participants received study treatment until disease progression, death or unacceptable toxicity or up to 16 cycles.

#### The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment regarding the DREAMM-1 trial. Additionally, the FDA notes that although the 3.4 mg/kg dose was selected as the RP2D in Part 1 (dose escalation) of DREAMM-1, there were concerns regarding the safety profile of the 3.4 mg/kg dose based on the incidence and severity of ocular toxicity and frequency of dose modifications due to ocular toxicity observed in the trial. The DREAMM-2 trial was amended to add a second cohort to evaluate the lower 2.5 mg/kg starting dose in addition to the originally planned 3.4 mg/kg dose cohort. FDA notes there were too few patients in doses lower than 3.4 mg/kg to draw any definitive conclusions regarding safety in the DREAMM-1 trial.

### **8.1.4. Efficacy Results – Study BMA117159 (DREAMM-1)**

#### The Applicant's Position:

This section refers to Part 2 of DREAMM-1 unless otherwise noted. Results from Part 2 cohort expansion of DREAMM-1 provide further supportive evidence for belantamab mafodotin as monotherapy in RRMM (the intended patient population).

DREAMM-1 (N=73; Part 1: 38; Part 2: 35) enrolled heavily pretreated (median of 5 prior lines in Part 2) MM participants. In summary, the key efficacy results from Part 2 (N=35) where participants received 3.4 mg/kg Q3W dose are as follows:

- The investigator-assessed ORR was 60% (95% CI: 42.1, 76.1)
- The median DoR was 14.3 months (95% CI: 10.6, NE)
- The median time-to response was rapid at 1.2 months (95% CI: 0.7, 1.4)
- The median PFS was 12.0 months (95% CI: 3.1, NE)

The ORR in the 13 participants that were consistent with the DREAMM-2 population was 38% (95% CI: 13.9, 68.4; median prior lines: 7). The median DoR in this subgroup of participants was 6.7 months (95% CI: 5.3, NE). Median PFS was 6.2 months (95% CI: 0.7, 7.9).

In addition, Part 1 of DREAMM-1 included 4 participants with RRMM who were refractory to PI, IMiD, and failed anti-CD38 therapy. None of these 4 participants achieved a response.

#### **8.1.5. Integrated Review of Effectiveness**

The FDA's Assessment:

Not applicable.

#### **8.1.6. Assessment of Efficacy Across Trials**

This section is not applicable.

#### **8.1.7. Integrated Assessment of Effectiveness**

The Applicant's Position:

The efficacy [REDACTED]<sup>(b) (4)</sup> was primarily based on results from the pivotal study, DREAMM-2, with supportive evidence from DREAMM-1 providing further evidence of the effectiveness of belantamab mafodotin monotherapy in RRMM participants who are refractory to PIs and IMiDs. Although the number of participants in DREAMM-1 who meet the eligibility criteria for DREAMM-2 is small, efficacy across several endpoints is consistent at the 3.4 mg/kg dose. Details of the efficacy results and exposure-response analyses of efficacy data are provided in Section 8.1.4 and Section 6.3.1, respectively.

Belantamab mafodotin at 2.5 mg/kg provided a clinically meaningful overall response rate as demonstrated by deep and durable responses in heavily pretreated RRMM participants in DREAMM-2.

ORR was 31% (97.5% CI: 20.8, 42.6) with a median follow-up of 6.3 months at the recommended dose of 2.5 mg/kg and 34% (95% CI: 26.9, 46.0) at the 3.4 mg/kg dose. The median time to response was 1.4 months (95% CI: 1.0, 1.6) at the 2.5 mg/kg dose and 1.4 months (95% CI: 0.9, 2.1) at the 3.4 mg/kg dose. Achieved responses were deep, with more than half of responders (60%) achieving a response of VGPR or better. The median DoR was not reached. OS data were not mature at the time of this primary analysis.

While the median DoR has not been reached in the DREAMM-2 study, it is noted that the FTIH study DREAMM-1 results in the 13 participants that were consistent with the DREAMM-2 population demonstrated a median DoR of 6.7 months (95% CI: 5.3, NE). In a sensitivity analysis of DoR that assumed worst case scenario of all participants who were censored with follow up ongoing would progress immediately at the following visit, the median estimate was 5.6 months for both arms, suggesting median DoR will be at least 5.6 months.

The ORR results for the 2.5- and 3.4-mg/kg cohorts in DREAMM-2 and in DREAMM-1 are presented in Table 22.

**Table 22. Best Confirmed Response for Belantamab Mafodotin (ITT Population)**

	DREAMM-1 <sup>a</sup>		DREAMM-2 <sup>b</sup>	
	2.5 mg/kg (n=4)	3.4 mg/kg (n=13)	2.5 mg/kg (n=97)	3.4 mg/kg (n=99)
<b>Best Response</b>				
sCR	0	1 (8)	2 (2)	3 (3)
CR	0	1 (8)	1 (1)	0
VGPR	0	3 (23)	15 (15)	17 (17)
PR	0	0	12 (12)	14 (14)
MR	1 (25)	0	3 (3)	5 (5)
SD	1 (25)	3 (23)	30 (31)	23 (23)
PD	2 (50)	3 (23)	27 (28)	26 (26)
NE <sup>c</sup>	0	2 (15)	7 (7)	11 (11)
<b>ORR</b>				
sCR+CR+VGPR+PR	0	5 (38)	30 (31)	34 (34)
97.5% CI	NE	NE	(20.8, 42.6)	(23.9, 46.0)
<b>CBR</b>				
sCR+CR+VGPR+PR+MR	1 (25)	5 (38)	33 (34)	39 (39)
95% CI	(0.6, 80.6)	(13.9, 68.4)	(24.7, 44.3)	(29.7, 49.7)
97.5% CI	NE	NE	(23.5, 45.8)	(28.5, 51.1)

Source: Tables 2.0180 and 2.0181 (DREAMM-1) and 2.0010 (DREAMM-2)

- The secondary endpoint (i.e., ORR) (confirmed) in DREAMM-1 was by investigator assessment; participants were refractory to both IMiDs and PIs and had received daratumumab.
- The primary endpoint (i.e., ORR) (confirmed) in DREAMM-2 was by IRC assessment; participants were refractory to both IMiDs and PIs and had received daratumumab.
- NE could be due to response not confirmed, inadequate baseline assessment, or no postbaseline assessment (5 and 7 participants) (L30.10010)

Note: All values are expressed as n (%), unless otherwise specified.

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Abbreviations: ITT = Intent-to-Treat; CI = confidence interval; CBR = clinical benefit rate; CR = complete response; IMiD = immunomodulatory drug; IRC = Independent Review Committee; MR = minimal response; NE = not evaluable; ORR = overall response rate; PI = proteasome inhibitor; PR = partial response; sCR = stringent CR; VGPR = very good PR; SD = stable disease; NE = not evaluable; ORR = overall response rate; PD = progressive disease.

In summary, belantamab mafodotin at the recommended dose delivers clinically meaningful and statistically significant benefit for heavily pretreated patients with RRMM.

**The FDA's Assessment:**

The FDA reviewer's results from the efficacy analyses are consistent with the results presented by the Applicant.

## **8.2. Review of Safety**

**The Applicant's Position:**

This safety review is based on data from a total of 291 participants across 2 clinical studies: the Phase II pivotal study DREAMM-2 and the Phase I FTIH study DREAMM-1. Safety results include data from 95 participants in the 2.5 mg/kg cohort and 99 participants in the 3.4 mg/kg cohort in DREAMM-2, and 8 participants in the 2.5 mg/kg cohort and 38 participants in the 3.4 mg/kg cohort in DREAMM-1. Safety data from patients in both cohorts across the 2 studies have been integrated. In addition, the safety database also includes data from a cohort of 24 patients treated with lyo at 3.4 mg/kg in DREAMM-2.

The size of the safety database was previously discussed at the Type B pre-BLA Meeting on May 02, 2019, and was considered acceptable to characterize the risks of belantamab mafodotin treatment in the indicated patient population. Additionally, the size is comparable to that of other recently approved monotherapy medicines in similarly heavily pretreated RRMM patients, as is the duration of follow-up.

**The FDA's Assessment:**

FDA notes that the Applicant is presenting a review of safety based on an integrated database including patients from DREAMM-1 and DREAMM-2. FDA's review of safety focused on the 95 patients who received the proposed 2.5 mg/kg dose in DREAMM-2. FDA reviewed the DREAMM-1 safety data, but, unless otherwise stated, did not independently confirm the results presented by the Applicant for the integrated DREAMM-1 and DREAMM-2 safety database. Of note, the integrated database only contains 8 additional patients from DREAMM-1 who received the proposed 2.5 mg/kg dose.

### 8.2.1. Safety Review Approach

#### The Applicant's Position:

The main safety issues identified during belantamab mafodotin drug development were ocular events, thrombocytopenia, and infusion-related reactions. Clinical experience confirmed that these events, along with neutropenia and lung infections, are some of the most frequent toxicities observed with use of belantamab mafodotin monotherapy and are manageable with dose modifications and/or supportive care.

#### The FDA's Assessment:

Safety analyses were conducted on the complete datasets provided by the Applicant for the DREAMM-1 and DREAMM-2 trials. The data cut-off dates were August 31, 2018 and June 21, 2019, respectively. FDA's review of safety focused on the DREAMM-2 trial. As discussed further in Section 8.2.5, FDA notes that ocular toxicity is a major safety concern with belantamab mafodotin and close ophthalmologic monitoring is required to ensure appropriate dose modifications are implemented to manage ocular toxicity.

### 8.2.2. Review of the Safety Database

#### The Applicant's Position:

#### **Overall Exposure**

Safety data from participants treated at the 2.5 or 3.4 mg/kg dose in DREAMM-2 (N=218) and DREAMM-1 (N=73) have been integrated. This includes a total of 103 participants at the 2.5 mg/kg dose and 161 participants at the 3.4 mg/kg dose across both studies. The safety evaluation included all participants who received at least 1 dose of study treatment, and categorizes participants based on the agent that they actually received. Data presented in this section focuses on the pooled data for the 2.5 mg/kg dose of belantamab mafodotin as the recommended monotherapy dose.

#### **Extent of Exposure**

In the 2.5 mg/kg pooled data, participants were exposed to belantamab mafodotin for a total of 28.9 participant-years. Participants received a median of 3.0 treatment cycles and spent a median of 9.1 weeks on study treatment. The median dose intensity was 2.48 mg/kg per 3-week cycle (Table 23).

**Table 23. Summary of Exposure (DREAMM-1/DREAMM-2 Safety Population)**

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

Source: Table 1.5000

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

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

Abbreviations: SD = standard deviation; Q3W = every 3 weeks.

**The FDA's Assessment:**

An overview of the patients treated at the 2.5 mg/kg and 3.4 mg/kg doses in DREAMM-1 and DREAMM-2 is shown in Table 24. In addition to the patients who were treated with either the 2.5 mg/kg or 3.4 mg/kg doses, 21 patients in DREAMM-1 received belantamab mafodotin at lower dose levels ranging from 0.03 to 1.92 mg/kg and 6 patients in DREAMM-1 received belantamab mafodotin at a higher dose level of 4.6 mg/kg. FDA's review of safety is primarily focused on the patients who received belantamab mafodotin at the proposed 2.5 mg/kg dose (N=95) in DREAMM-2. The full safety population from DREAMM-2 (N=218) was utilized for additional analyses, including analyses relating to the information presented in the Warning and Precautions section of the belantamab mafodotin USPI.

**Table 24. DREAMM-1 and DREAMM-2 Safety Populations (2.5 mg/kg and 3.4 mg/kg)**

Study	2.5 mg/kg	3.4 mg/kg	3.4 mg/kg Lyo	All Dose Cohorts
DREAMM-1	8	38	N/A	73
DREAMM-2	95	99	24	218
<b>Total</b>	<b>103</b>	<b>137</b>	<b>24</b>	<b>291</b>

Source: FDA

FDA agrees with the Applicant's summary of exposure data notes that patients in both dose cohorts received a median of 3 cycles of treatment, indicating that in general, patients received

a relatively short course of treatment with belantamab mafodotin.

The Applicant's Position:

**Relevant Characteristics of the Safety Population:**

The eligibility criteria in the pivotal study DREAMM-2 and supportive study DREAMM-1 were clinically relevant for the target population of participants who would receive belantamab mafodotin monotherapy following regulatory approval in the proposed indication. DREAMM-2 was open to enroll participants with histologically or cytologically confirmed diagnosis of MM as defined in IMWG criteria [Rajkumar, 2014] who have undergone stem cell transplant or were considered transplant ineligible, and have received at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and were refractory to an IMiD (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib). DREAMM-1 was open to enroll participants with histologically or cytologically confirmed diagnosis of MM who have undergone stem cell transplant or were considered transplant ineligible, and have been pretreated with alkylators, proteasome inhibitors and immunomodulators, and demonstrated progression on or within 60 days of completion of the last therapy.

Demographic characteristics were well balanced between the two dose arms (2.5 mg/kg and 3.4 mg/kg) in DREAMM-2, thereby providing reassurance with regard to the interpretation of the treatment comparison and the validity of the safety conclusions. Overall, the baseline characteristics were representative of the proposed indicated population (Table 15 and Table 16).

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment above. Because 95% of patients in the 2.5 mg/kg cohort received 4 or more prior lines of therapy, the proposed indication for belantamab mafodotin was revised to include patients with at least 4 prior lines of therapy. FDA also notes that patients with baseline corneal epithelial disease, with the exception of mild punctate keratopathy, were excluded from the trials. The trial enrolled a younger population of patients compared to the U.S. population of patients with MM, but otherwise the baseline demographics and disease characteristics were representative of the general population of patients with RRMM in the U.S.

The Applicant's Position:

**Adequacy of the Safety Database:**

The size of the safety database and duration of follow-up are considered adequate to characterize the risks of belantamab mafodotin treatment in the indicated population, which will be managed via labelling recommendations.

The FDA's Assessment:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may occur with treatment with belantamab mafodotin. However, the assessment of safety is limited by the DREAMM-2 trial design, and there is no randomized data comparing belantamab mafodotin to either placebo or a standard of care therapy. Apart from ocular toxicity, which requires additional risk mitigation strategies (see Sections 8.2.5, 8.2.11, and 13), FDA agrees that the remainder of risks of belantamab mafodotin treatment in the indicated population can be managed via labeling recommendations.

### **8.2.3. Adequacy of Applicant's Clinical Safety Assessments**

#### The Applicant's Position:

##### **Issues Regarding Data Integrity and Submission Quality**

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives. These were sufficiently complete to allow for a thorough review of safety.

#### The FDA's Assessment:

The quality of the safety data submitted was adequate for substantive primary review. The Applicant provided full datasets for patients enrolled in DREAMM-1 and DREAMM-2, as well as an ISS dataset. The Applicant provided patient narratives for all deaths occurring during study treatment or within 30 days of treatment discontinuation, serious adverse events (SAEs) occurring during study treatment or within 30 days of treatment discontinuation, adverse events (AEs) leading to permanent discontinuation of study treatment, and AEs of special interest (AESIs).

#### The Applicant's Position:

##### **Categorization of Adverse Event**

In the pivotal study DREAMM-2, safety assessments included the collection of adverse events (AEs), SAEs and AEs of special interest (AESIs); completion of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE); ocular examination findings; visual function questionnaires: the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) and the Ocular Surface Disease Index (OSDI); clinical laboratory tests; and analyses of vital signs, electrocardiograms (ECGs), echocardiograms and Eastern Cooperative Oncology Group (ECOG) performance status. Best Corrected Visual Acuity (BCVA) and corneal examination findings were also graded and were used to guide DREAMM-2 dose modifications.

In the supportive study DREAMM-1, safety assessments included the collection of AEs, SAEs and AESIs; ocular examination findings; clinical laboratory tests; and analyses of vital signs, ECGs and ECOG performance status. Visual function questionnaires, NEI-VFQ 25 and OSDI, were added to DREAMM 1 after all participants had been enrolled and therefore limited data are available.

For both DREAMM-2 and DREAMM-1, AEs were coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) Version 22 and grouped by SOC. AEs in DREAMM-2 were graded by the investigator according to the NCI-CTCAE Version 4.03, and AEs in DREAMM-1 were graded with CTCAE Version 4.0. The difference between the two versions was not considered significant enough to prevent pooling.

**The FDA's Assessment:**

In addition to the details regarding safety assessments presented by the Applicant above, FDA notes that a study-specific scale developed with input from FDA was used for grading of ocular toxicity and subsequent guidance of dose modifications in DREAMM-2. The scale was termed the "GSK" scale in the DREAMM-2 protocol and subsequently referred to as the "Keratopathy and Visual Acuity" ("KVA") scale in the ODAC briefing document and USPI. The overall grade for the KVA scale, based on the worst finding (corneal exam or visual acuity) in the worst affected eye, was used to guide dose modifications.

In addition to documentation of corneal exam findings and changes in best-corrected visual acuity (BCVA) in the ocular dataset ADOCGSK and grading using the GSK/KVA scale, corneal findings were also captured as an event of "microcyst-like epithelial keratopathy" on the AE form and recorded as an AE in the ADAE dataset using CTCAE grading. If a patient only had a change in visual acuity, the site may have chosen to report this as an AE of visual acuity decreased, but per the Applicant, no specific guidance was given to do so (GSK response to FDA Clinical Information Request #16 dated April 7, 2020).

FDA notes that the use of CTCAE grading for ophthalmic events, which is based in part on symptoms and interference with activities of daily living, may not be optimal because patients may not necessarily experience symptoms and interference despite findings on ophthalmic exam. Additionally, many clinically relevant ocular toxicities are not necessarily symptomatic, but may be considered serious because they will lead to irreversible sequelae, such as vision loss, if left untreated. Because the corneal epithelium normally serves as a protective barrier to injury, if keratopathy is not identified early and appropriately managed with supportive care and dose modifications, patients could go on to develop more severe corneal defects, including corneal ulcers.

Given the limitations of CTCAE for grading of ocular toxicity, FDA's analysis of ocular toxicity in DREAMM-2 is primarily based on the KVA scale because it allows for a more granular assessment. A comparison of the KVA scale and CTCAE grading for ocular toxicity is shown in Table 25.

**Table 25. Comparison of KVA Scale and CTCAE Grading for Ocular Toxicity**

Grade	KVA Scale*		CTCAE Grading
	Corneal Exam	Visual Acuity	Eye Disorders - Other
1	<ul style="list-style-type: none"> <li>Mild superficial keratopathy</li> </ul>	<ul style="list-style-type: none"> <li>Change of 1 line from baseline</li> </ul>	<ul style="list-style-type: none"> <li>Asymptomatic or mild symptoms</li> <li>Intervention not indicated</li> </ul>
2	<ul style="list-style-type: none"> <li>Moderate punctate keratopathy</li> <li>Mild/patchy microcysts</li> <li>Mild/patchy epithelial/stromal edema</li> <li>Sub-epithelial haze (peripheral)</li> <li>Active stromal opacity (peripheral)</li> </ul>	<ul style="list-style-type: none"> <li>Change of 2-3 lines from baseline, and</li> <li>Not worse than 20/200</li> </ul>	<ul style="list-style-type: none"> <li>Moderate</li> <li>Minimal intervention indicated</li> <li>Limiting IADL</li> </ul>
3	<ul style="list-style-type: none"> <li>Severe punctate keratopathy</li> <li>Diffuse microcysts</li> <li>Diffuse epithelial/stromal edema</li> <li>Sub-epithelial haze (central)</li> <li>Active stromal opacity (central)</li> </ul>	<ul style="list-style-type: none"> <li>Change of more than 3 lines from baseline, and</li> <li>Not worse than 20/200</li> </ul>	<ul style="list-style-type: none"> <li>Severe or medically significant, but not immediately sight-threatening</li> <li>Hospitalization indicated</li> <li>Disabling</li> <li>Limiting ADL</li> </ul>
4	<ul style="list-style-type: none"> <li>Corneal ulcer</li> </ul>	<ul style="list-style-type: none"> <li>Worse than 20/200</li> </ul>	<ul style="list-style-type: none"> <li>Sight-threatening consequences</li> <li>Urgent intervention indicated</li> <li>Blindness (20/200 or worse) in affected eye</li> </ul>

Source: FDA (KVA Scale information modified from DREAMM-2 Protocol (Amendment 3); CTCAE scale information modified from NCI-CTCAE v4.03)

### The Applicant’s Position

#### **Routine Clinical Tests**

Data from all sources (central and local laboratories; central ECG reads) were included. The summaries included all safety assessments collected.

The clinical monitoring of participant safety was considered adequate for the expected toxicities associated with belantamab mafodotin. Participants were questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by the participants during or between visits or through physical examination, laboratory test results, ocular exams, or other assessments. Further to the standard safety evaluations outlined above, AE categories expected to be associated with belantamab mafodotin were also analyzed. These AESIs were selected based on the mechanism of action as well as nonclinical and early clinical observations.

#### The FDA’s Assessment:

The frequency of safety monitoring was considered adequate in the context of the study. Ophthalmic exams were performed at baseline and prior to each dose of belantamab mafodotin. Although the protocol allowed a change to less frequent monitoring after Cycle 4

(Week 10), most patients continued to have ophthalmic exams every 3 weeks. FDA analysis showed that 91% of patients in the 2.5 mg/kg cohort had consecutive exams every 3 weeks.

#### 8.2.4. Safety Results

##### The Applicant's Position:

Data presented in this section focus on the pooled data for the 2.5 mg/kg dose of belantamab mafodotin, as the recommended monotherapy dose.

##### Deaths

In the 2.5 mg/kg pooled data, 32 (31%) participants died during the study (Table 26). For the majority of participants, the primary cause of death was disease under study (N=26; 25%). Fatal SAEs were reported for 3 (3%) participants. For 1 (<1%) participant, the primary cause of death was sepsis, which was considered to be possibly related to study treatment. There were 2 (2%) participants whose primary cause of death was myocardial infarction, considered unrelated to the disease under study and unrelated to study treatment. There were also 3 (3%) participants whose primary cause of death was reported as unknown, with no fatal SAEs reported for these participants.

**Table 26. Summary of Deaths (DREAMM-1/DREAMM-2 Safety Population)**

	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg All (N=161)*	All Treated (N=291)
<b>Participant status (% based on all participants), n (%)</b>			
Dead	32 (31)	39 (24)	72 (25)
Alive at the last contact, follow-up ended	10 (10)	28 (17)	64 (22)
Alive at the last contact, follow-up ongoing	61 (59)	94 (58)	155 (53)
<b>Primary cause of death, (% based on all participants) n (%)</b>			
Disease under study	26 (25)	31 (19)	58 (20)
SAE possibly related to study treatment	1 (<1)	1 (<1)	2 (<1)
Other	2 (2)	7 (4)	9 (3)
Unknown	3 (3)	0	3 (1)
<b>Time to death from last dose, (% based on all participants) n (%)</b>			
≤30 days	8 (8)	16 (10)	24 (8)
>30 days	24 (23)	23 (14)	48 (16)

\*The 3.4 mg/kg All group also includes 24 participants in the Iyo cohort.

Abbreviations: SAE = serious adverse event; Q3W = every 3 weeks.

##### The FDA's Assessment:

FDA confirmed the results presented above regarding the total numbers of deaths in the pooled safety population and breakdown of deaths occurring on or within 30 days of the last dose of study treatment versus deaths occurring more than 30 days from the last dose of study treatment. FDA agrees with the Applicant's assessment that the majority of patients died due to the disease under study. FDA does not agree with the Applicant's distinction regarding relatedness of fatal SAEs. In general, in a single-arm trial, it is not possible to distinguish

between AEs related to the underlying disease versus AEs that are due to the toxicity of study treatment. Therefore, FDA considers all treatment-emergent AEs (TEAEs) that occur on a single-arm trial. There were 3 (3.2%) fatal TEAEs in the 2.5 mg/kg cohort due to sepsis, cardiac arrest and lung infection.

An overview of the safety results from DREAMM-2 are shown in Table 27, which summarizes the categories of TEAEs observed in the trial. There were no differences in the overall TEAE rates or rates of Grade 3-4 TEAEs between the two doses.

**Table 27. Overview of TEAEs in DREAMM-2**

Adverse Event Category	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
Any Grade TEAEs	93 (98)	99 (100)
Severe (Grade 3-4) TEAEs	78 (82)	81 (82)
Fatal (Grade 5) TEAEs	3 (3)	7 (7)
Serious TEAEs (SAEs)	38 (40)	47 (48)
Discontinuation due to TEAEs	8 (8)	10 (10)
Dose interruption due to TEAEs	51 (54)	61 (62)
Dose reduction due to TEAEs	28 (29)	41 (41)

Source: FDA Analysis (ADAE dataset; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

A summary of fatal TEAEs that occurred in DREAMM-2 is shown in Table 28.

**Table 28. Summary of Fatal TEAEs in DREAMM-2**

System Organ Class/Preferred Term	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
<b>Total</b>	3 (3)	7 (7)
<b>Infections and Infestations</b>	2 (2)	3 (3)
Lung infection	1 (1)	0
Sepsis	1 (1)	0
Pneumonia	0	2 (2)
Viral infection	0	1 (1)
<b>Cardiac Disorders</b>	1 (1)	1 (1)
Cardiac arrest	1 (1)	1 (1)
<b>Immune System Disorders</b>	0	1 (1)
Hemophagocytic lymphohistiocytosis	0	1 (1)
<b>Neoplasms Benign, Malignant and Unspecified</b>	0	1 (1)
Acute myeloid leukemia	0	1 (1)
<b>Nervous System Disorders</b>	0	2 (2)
Cerebral hemorrhage	0	2 (2)

Source: FDA Analysis (ADAE dataset; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

Key details of the narratives for the 3 patients who experienced fatal TEAEs in the 2.5 mg/kg cohort are summarized below:

- Patient # (b) (6): The patient was a 74-year-old man diagnosed with MM in (b) (6), whose past medical history included cerebrovascular accident/stroke, angina pectoris, diabetes, and COPD. He had received 7 prior lines of anti-MM therapy. The patient received 2 cycles of treatment with belantamab mafodotin 2.5 mg/kg, but was noted to have only a minimal response on the Week 4 assessment. On study day 40, the patient reported increasing abdominal pain. The following day, while out running errands, he nearly passed out and was taken to an emergency medical services location, where CPR was performed, but was unsuccessful. The patient died from cardiac arrest on study day 41, 20 days after the last dose of belantamab mafodotin.
- Patient # (b) (6): The patient was a 66-year-old man diagnosed with MM in (b) (6). He had received 7 prior lines of anti-MM therapy, including ASCT twice. He received 2 cycles of belantamab mafodotin 2.5 mg/kg and was noted to have stable disease at the Week 4 assessment. He was admitted to an outside hospital on study day 33 with pulmonary infection, sepsis and acute renal failure. Broad-spectrum antibiotics were administered, and blood cultures returned positive for Escherichia coli, sensitive to the antibiotic treatment; however, the patient's condition deteriorated, and he underwent two rounds of CPR. The patient died from sepsis on study day 35, 15 days after the last dose of belantamab mafodotin.
- Patient # (b) (6): The patient was a 42-year-old man diagnosed with MM in (b) (6) with past medical history significant for a 20-pack-year smoking history. He had received 6 prior lines of anti-MM therapy, including ASCT. He received 5 cycles of treatment with belantamab mafodotin 2.5 mg/kg, but was noted to have progressive disease on all assessments, including on the most recent disease assessment on study day 85. On study day 88, he developed fever and was diagnosed with lung infection. He was started on broad-spectrum antibiotics and transferred to an intensive care unit. The patient died from lung infection on study day 96, 12 days after the last dose of belantamab mafodotin.

#### The Applicant's Position:

##### **Serious Adverse Events**

In the 2.5 mg/kg pooled data, an SAE was reported for 42 (41%) participants (Table 29). The most common SAE PT reported was pyrexia (N=6; 6%), followed by pneumonia (N=5; 5%) and IRR and hypercalcaemia (each N=4; 4%). A treatment-related SAE was reported for 12 (12%) participants. The most commonly reported treatment-related SAE PT was infusion-related reaction (N=4; 4%), followed by pyrexia and sepsis (each N=2; 2%).

**Table 29. SAEs by PT Reported for ≥3 Participants in Any Dose Group (DREAMM-1/DREAMM-2 Safety Population)**

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg All (N=161)*	All Treated (N=291)
<b>Any event</b>	<b>42 (41)</b>	<b>80 (50)</b>	<b>130 (45)</b>
Pneumonia	5 (5)	16 (10)	21 (7)
Pyrexia	6 (6)	6 (4)	14 (5)
Infusion related reaction	4 (4)	4 (2)	8 (3)
Lung infection	3 (3)	5 (3)	8 (3)
Thrombocytopenia	1 (<1)	5 (3)	7 (2)
Hypercalcaemia	4 (4)	1 (<1)	6 (2)
Febrile neutropenia	0	4 (2)	4 (1)
Pleural effusion	2 (2)	2 (1)	4 (1)
Sepsis	2 (2)	2 (1)	4 (1)
Acute kidney injury	2 (2)	1 (<1)	3 (1)
Back pain	1 (<1)	2 (1)	3 (1)
Epistaxis	1 (<1)	2 (1)	3 (1)
Hyperviscosity syndrome	0	2 (1)	3 (1)
Influenza	0	3 (2)	3 (1)
Vomiting	1 (<1)	1 (<1)	3 (1)

\* The 3.4 mg/kg All group also includes 24 participants in the lyo cohort.

**The FDA's Assessment:**

In DREAMM-2 serious TEAEs occurred in 40% of patients in the 2.5 mg/kg cohort and 47% of patients in the 3.4 mg/kg cohort. A summary of serious TEAEs that occurred in ≥3% of patients in either dose level is shown in Table 30. Serious TEAEs that occurred in ≥3% of patients in the 2.5 mg/kg cohort (using grouped terms for pneumonia and sepsis) were pneumonia (7%), pyrexia (6%), sepsis, hypercalcemia, and renal impairment (4.2%), and infusion-related reaction (3.2%).

**Table 30. Summary of Serious TEAEs in DREAMM-2 (≥3%)**

Preferred Term	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
Any serious TEAE	38 (40)	47 (47)
Pneumonia*	7 (7)	14 (14)
Pyrexia	6 (6)	5 (5)
Sepsis*	4 (4.2)	3 (3)
Hypercalcemia	4 (4.2)	0
Renal impairment	4 (4.2)	1 (1)
Infusion related reaction	3 (3.2)	2 (2)
Febrile neutropenia	0	3 (3)
Upper respiratory tract infection*	0	3 (3)

\*Includes grouped preferred terms (see Appendix Section 20.6.1)

Source: FDA Analysis (ADAE dataset; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

**The Applicant's Position:**

**Dropouts and/or Discontinuations Due to Adverse Effects**

In the 2.5 mg/kg pooled data, an AE leading to permanent discontinuation of study treatment was reported for 9 (9%) participants (Table 31). The most commonly reported AE that led to permanent discontinuation of study treatment was keratopathy (N=3; 3%). Of these 3 participants, 1 participant had recovered/resolved with sequelae and 2 participants had not recovered/resolved at the data cut-off.

**Table 31. AEs Leading to Permanent Discontinuation of Study Treatment by PT (DREAMM-1/DREAMM-2 Safety Population)**

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg All (N=161)*	All Treated (N=291)
<b>Any event</b>	<b>9 (9)</b>	<b>15 (9)</b>	<b>27 (9)</b>
Keratopathy	3 (3)	5 (3)	8 (3)
Cardiac arrest	1 (<1)	1 (<1)	2 (<1)
Cerebral hemorrhage	0	2 (1)	2 (<1)
Pneumonia	0	2 (1)	2 (<1)
Thrombocytopenia	0	1 (<1)	2 (<1)
AML	0	1 (<1)	1 (<1)
ALT increased	0	1 (<1)	1 (<1)
AST increased	0	1 (<1)	1 (<1)
Blood CPK increased	0	1 (<1)	1 (<1)
Cough	0	1 (<1)	1 (<1)
Fatigue	0	1 (<1)	1 (<1)
Foreign body sensation in eyes	0	0	1 (<1)
Hemophagocytic lymphohistiocytosis	0	1 (<1)	1 (<1)
Headache	1 (<1)	0	1 (<1)
Herpes simplex pneumonia	1 (<1)	0	1 (<1)
Hypercalcemia	0	0	1 (<1)
Infusion related reaction	1 (<1)	0	1 (<1)
Limbal stem cell deficiency	0	0	1 (<1)
Sepsis	1 (<1)	0	1 (<1)
Urine albumin/creatinine ratio increased	1 (<1)	0	1 (<1)
Viral infection	0	1 (<1)	1 (<1)

Abbreviations: AE = adverse event; PT = preferred term; Q3W = every 3 weeks; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; CPK = Creatinine Phosphokinase; AML = Acute Myeloid Leukemia.

\* The 3.4 mg/kg All group also includes 24 participants in the lyo cohort.

**The FDA's Assessment:**

FDA notes that in DREAMM-2, TEAEs leading to permanent discontinuation of belantamab mafodotin occurred in 8% of patients in the 2.5 mg/kg cohort and 10% of patients in the 3.4 mg/kg cohort. Keratopathy was the most frequent TEAE leading to discontinuation (2.1% in the

2.5 mg/kg cohort).

The Applicant's Position:

**Dose Reduction/Delay Due to Adverse Effects**

In the 2.5 mg/kg pooled data, 29 (28%) participants had an AE that led to a dose reduction (Table 32). The most commonly reported AE that led to a dose reduction was keratopathy (N=22; 21%), followed by thrombocytopenia (N=3; 3%).

**Table 32. AEs Leading to Dose Reduction by PT Reported for ≥2 Participants in Any Dose Group (DREAMM-1/DREAMM-2 Safety Population)**

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
<b>Any event</b>	<b>29 (28)</b>	<b>67 (49)</b>	<b>77 (48)</b>
Keratopathy	22 (21)	28 (20)	36 (22)
Vision blurred	2 (2)	17 (12)	19 (12)
Thrombocytopenia	3 (3)	16 (12)	18 (11)
Dry eye	0	3 (2)	4 (2)
Platelet count decreased	2 (2)	4 (3)	4 (2)
Keratitis	0	3 (2)	3 (2)
Fatigue	0	1 (<1)	2 (1)
Infusion related reaction	1 (<1)	2 (1)	2 (1)
Neutropenia	0	1 (<1)	2 (1)
Photophobia	0	2 (1)	2 (1)
Proteinuria	0	2 (1)	2 (1)
Urine albumin/creatinine ratio increased	0	2 (1)	2 (1)

Source: Table 3.2100

Abbreviations: PT = preferred term; Q3W = every 3 weeks.

In the 2.5 mg/kg pooled data, 53 (51%) participants had an AE that led to a dose delay (Table 33). The most commonly reported AE that led to a dose delay was keratopathy (N=46; 45%), followed by blurred vision (N=5; 5%).

**Table 33. AEs Leading to Dose Delay by PT Reported for  $\geq 3$  Participants in Any Dose Group (DREAMM-1/DREAMM-2 Safety Population)**

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
<b>Any event</b>	<b>53 (51)</b>	<b>89 (65)</b>	<b>108 (67)</b>
Keratopathy	46 (45)	49 (36)	65 (40)
Vision blurred	5 (5)	23 (17)	27 (17)
Pneumonia	3 (3)	8 (6)	9 (6)
Dry eye	2 (2)	6 (4)	6 (4)
Thrombocytopenia	0	7 (5)	7 (4)
Lung infection	0	5 (4)	5 (3)
Photophobia	1 (<1)	5 (4)	5 (3)
Upper respiratory tract infection	1 (<1)	5 (4)	5 (3)
Platelet count decreased	0	4 (3)	4 (2)
Blood lactate dehydrogenase increased	0	3 (2)	3 (2)
Keratitis	0	3 (2)	3 (2)
Urine albumin/creatinine ratio increased	2 (2)	3 (2)	3 (2)

Source: Table 3.2200

Abbreviations: PT = preferred term; Q3W = every 3 weeks.

**The FDA's Assessment:**

FDA notes that in DREAMM-2, dose reductions due to TEAEs occurred in 29% of patients in the 2.5 mg/kg cohort and 41% of patients in the 3.4 mg/kg cohort. The lowest dose level for dose reduction was 1.92 mg/kg (one dose level below the 2.5 mg/kg dose). TEAEs requiring a dose reduction in  $\geq 3\%$  of patients in the 2.5 mg/kg cohort were keratopathy (23%) and thrombocytopenia (5%).

Dose interruptions/delays due to TEAEs occurred in 54% of patients in the 2.5 mg/kg cohort and 62% of patients in the 3.4 mg/kg cohort in DREAMM-2. TEAEs requiring a dose interruption in  $\geq 3\%$  of patients in the 2.5 mg/kg cohort were keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Overall, the rates of dose reductions and dose interruptions due to keratopathy were high (23% and 47%, respectively). Dose modifications are the primary mitigating strategy for ocular toxicity, including keratopathy, with belantamab mafodotin, as the DREAMM-2 ocular sub-study failed to show an impact with the use of topical corticosteroids on the incidence or severity of keratopathy and no other mitigating strategies have been identified.

**The Applicant's Position:**

**Treatment-related Adverse Events**

In the 2.5 mg/kg pooled data, a treatment-related AE was reported for 91 (88%) participants (Table 34). The most common treatment-related AE PT was keratopathy (N= 66; 64%), followed

by blurred vision, nausea and AST increased (each N=15; 15%). There were 55 (53%) participants who had a Grade 3/4 treatment-related AE, and the most commonly reported Grade 3/4 treatment-related AE PT was keratopathy (N=26; 25%).

**Table 34. Treatment-Related AEs by PT Reported for ≥10% of Participants in Any Dose Group (DREAMM-1/DREAMM-2 Safety Population)**

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
<b>Any Event</b>	<b>91 (88)</b>	<b>131 (96)</b>	<b>155 (96)</b>
Keratopathy	66 (64)	72 (53)	94 (58)
Vision blurred	15 (15)	45 (33)	52 (32)
Thrombocytopenia	13 (13)	42 (31)	49 (30)
Dry eye	12 (12)	33 (24)	38 (24)
AST increased	15 (15)	25 (18)	28 (17)
Fatigue	10 (10)	22 (16)	27 (17)
Nausea	15 (15)	27 (20)	28 (17)
Pyrexia	10 (10)	22 (16)	26 (16)
Anemia	7 (7)	19 (14)	22 (14)
Platelet count decreased	8 (8)	19 (14)	21 (13)
Infusion related reaction	14 (14)	15 (11)	18 (11)
Photophobia	4 (4)	15 (11)	16 (10)

Source: Table 3.0400

Abbreviations: PT = preferred term; Q3W = every 3 weeks; AST = Aspartate aminotransferase.

**The FDA’s Assessment:**

FDA does not agree with the Applicant’s presentation of “treatment-related” TEAEs. In a single-arm trial, FDA considers all TEAEs. TEAEs occurred in 98% of patients in the 2.5 mg/kg cohort and 100% of patients in the 3.4 mg/kg cohort. The most frequent TEAEs occurring in ≥15% of patients in either dose cohort in DREAMM-2 are shown in Table 35. FDA’s analysis also differs from the Applicant’s due to FDA utilizing grouping of related preferred terms. See Table 41 for FDA’s analysis of laboratory abnormalities (e.g., thrombocytopenia and anemia) based on shift analysis of the DREAMM-2 laboratory datasets.

**Table 35. TEAEs in DREAMM-2 (≥15%)**

Adverse Event Term	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
	All Grades, n (%)	All Grades, n (%)
Any adverse event	93 (98)	99 (100)
Keratopathy <sup>†</sup>	67 (71)	76 (77)
Nausea	23 (24)	32 (32)
Pyrexia	21 (22)	25 (25)
Vision blurred*	21 (22)	30 (30)
Infusion-related reaction <sup>Δ</sup>	20 (21)	16 (16)
Fatigue*	19 (20)	34 (34)
Dry eye*	13 (14)	21 (21)
Decreased appetite	11 (12)	18 (18)
Diarrhea	12 (13)	15 (15)
Upper respiratory tract infection*	10 (11)	25 (25)
Cough*	9 (9)	19 (19)
Pneumonia*	9 (9)	18 (18)
Vomiting	7 (7)	20 (20)
Epistaxis	7 (7)	19 (19)

<sup>†</sup>Based on corneal exam findings

\*Based on grouping of related preferred terms (see Appendix Section 20.6.1)

<sup>Δ</sup>Based on AEs considered by the investigator to be part of an infusion-related reaction

Source: FDA Analysis (ADAE and ADOCGSK datasets; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

**The Applicant's Position:**

**Adverse Events by System Organ Class (SOC)**

In the 2.5 mg/kg pooled data, AEs were most frequently reported in the SOC of Eye Disorders (N=73; 71%), followed by the SOC of Investigations (N=54; 52%) (Table 36). The most commonly reported AEs in the Investigations SOC were AST increased (19%), platelet count decreased (16%) and lymphocyte count decreased (13%).

**Table 36. AEs by System Organ Class (DREAMM-1/DREAMM-2 Safety Population)**

System Organ Class	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
<b>Any event</b>	<b>101 (98)</b>	<b>137 (100)</b>	<b>161 (100)</b>
Eye disorders	73 (71)	103 (75)	125 (78)
Investigations	54 (52)	86 (63)	100 (62)
General disorders and administration site conditions	52 (50)	80 (58)	94 (58)
Gastrointestinal disorders	50 (49)	81 (59)	88 (55)
Infections and infestations	44 (43)	81 (59)	90 (56)
Blood and lymphatic system disorders	37 (36)	81 (59)	92 (57)
Metabolism and nutrition disorders	39 (38)	68 (50)	81 (50)
Musculoskeletal and connective tissue disorders	42 (41)	63 (46)	75 (47)
Respiratory, thoracic and mediastinal disorders	24 (23)	61 (45)	66 (41)
Nervous system disorders	25 (24)	42 (31)	49 (30)
Injury, poisoning and procedural complications	21 (20)	38 (28)	43 (27)

Source: Table 3.0100

Abbreviations: Q3W = every 3 weeks.

The Applicant's Position:

**Adverse Events by Incidence**

In the 2.5 mg/kg pooled data, an AE was reported for 101 (98%) participants (Table 37). The most common AE PT was keratopathy (N=68; 66%), followed by AE PTs anemia and nausea (each N=26; 25%).

**Table 37. AEs by PT Reported for  $\geq 15\%$  of Participants in Any Cohort (DREAMM-1/DREAMM-2 Safety Population)**

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
<b>Any event</b>	<b>101 (98)</b>	<b>137 (100)</b>	<b>161 (100)</b>
Keratopathy	68 (66)	77 (56)	99 (61)
Thrombocytopenia	21 (20)	55 (40)	63 (39)
Anemia	26 (25)	47 (34)	53 (33)
Vision blurred	19 (18)	46 (34)	53 (33)
Nausea	26 (25)	45 (33)	46 (29)
Fatigue	18 (17)	36 (26)	44 (27)
AST increased	20 (19)	39 (28)	43 (27)
Pyrexia	21 (20)	36 (26)	40 (25)
Dry eye	12 (12)	33 (24)	38 (24)
Cough	9 (9)	35 (26)	37 (23)
Platelet count decreased	16 (16)	28 (20)	30 (19)
Upper respiratory tract infection	8 (8)	26 (19)	29 (18)
Diarrhoea	13 (13)	26 (19)	28 (17)
Decreased appetite	13 (13)	23 (17)	27 (17)
Headache	10 (10)	20 (15)	24 (15)
Vomiting	7 (7)	23 (17)	23 (14)
Epistaxis	8 (8)	22 (16)	22 (14)
Gamma-glutamyl transferase increased	9 (9)	20 (15)	22 (14)
Neutropenia	7 (7)	21 (15)	22 (14)
Infusion related reaction	17 (17)	15 (11)	16 (10)

Source: Table 3.0200

Note: Study sites were instructed to report ocular examination findings as AEs of keratopathy in DREAMM-2, but not in DREAMM-1.

Abbreviations: PT = preferred term; Q3W = every 3 weeks; AST = Aspartate Aminotransferase.

**The FDA's Assessment:**

See Table 35 and FDA's accompanying assessment above.

**The Applicant's Position:****Adverse Events by Severity**

In the 2.5 mg/kg pooled data, a Grade 3/4 AE was reported for 80 (78%) participants (Table 38). The most commonly reported Grade 3/4 AE PT was keratopathy (N=26; 25%), followed by anemia (N=19; 18%) and thrombocytopenia (N=17; 17%).

**Table 38. Grade 3+4 AEs by PT Reported for  $\geq 10\%$  of Participants in Any Cohort (DREAMM-1/DREAMM-2 Safety Population)**

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg All (N=161)*	All Treated (N=291)
<b>Any Event</b>	<b>80 (78)</b>	<b>127 (79)</b>	<b>227 (78)</b>

Preferred Term	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg All (N=161) *	All Treated (N=291)
Thrombocytopenia	17 (17)	41 (25)	68 (23)
Anemia	19 (18)	35 (22)	60 (21)
Keratopathy	26 (25)	23 (14)	49 (17)
Lymphocyte count decreased	12 (12)	9 (6)	23 (8)
Neutropenia	4 (4)	12 (7)	21 (7)
Hypercalcemia	7 (7)	6 (4)	16 (5)

Abbreviations: AEs = adverse events; PT = preferred term; Q3W = every 3 weeks.

\*The 3.4 mg/kg All group also includes 24 participants in the lyo cohort.

### The FDA's Assessment:

Severe (Grade 3-4) TEAEs occurred in 82% of patients in both cohorts in DREAMM-2. FDA's analysis of severe TEAEs occurring in  $\geq 5\%$  of patients in either cohort using grouped preferred terms is shown in is shown in Table 39. Refer to Table 41 for the FDA analysis of laboratory abnormalities.

Of note, the incidence of Grade  $\geq 3$  keratopathy based on the KVA scale as shown below is substantially higher than the incidence of Grade  $\geq 3$  keratopathy based on the CTCAE scale (44% vs. 27%). FDA also notes that there was no substantial difference in the rates of Grade  $\geq 3$  keratopathy between the two dose levels, and the rates of Grade  $\geq 3$  keratopathy were slightly higher in the 2.5 mg/kg cohort compared to the 3.4 mg/kg cohort (44% vs. 41%).

**Table 39. Severe TEAEs in DREAMM-2 ( $\geq 5\%$ )**

Adverse Event Term	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)
Any Severe TEAE	78 (82)	81 (82)
Keratopathy <sup>†</sup>	42 (44)	41 (41)
Pneumonia*	7 (7)	13 (13)
Sepsis*	5 (5)	4 (4)
Hypertension*	2 (2)	6 (6)
Fatigue*	2 (2)	5 (5)

<sup>†</sup>Based on corneal exam findings

\*Based on grouping of related preferred terms (see Appendix Section 20.6.1)

Source: FDA Analysis (ADAE and ADOCGSK datasets; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

### The Applicant's Position:

#### **Laboratory Findings**

In the 2.5 mg/kg pooled data, the most frequent increases to any grade for clinical chemistry assessments were in AST (58%), glucose (hyperglycemia; 41%), and albumin (hypoalbuminemia; 40%). The majority of grade increases from baseline in chemistry parameters were increases to Grade 1 or Grade 2.

In the 2.5 mg/kg pooled data, the most frequent increases to any AE grade for hematology assessments were in platelets (platelets decreased; 63%), lymphocytes (lymphocyte count decreased; 50%), leukocytes (white blood cell decreased; 36%), and hemoglobin (anemia; 32%; Table 40). Increases to Grade 3 occurred in  $\leq 8\%$  of participants for any parameter, except for hemoglobin (anemia; 17%) and lymphocytes (lymphocyte count decreased; 19%).

**Table 40. Worst Case Hematology Grade Changes from Baseline Grade (DREAMM-1/DREAMM-2 Safety Population)**

Visit Category	Number (%) of Participants		
	Belantamab Mafodotin Q3W		
	2.5 mg/kg (N=103)	3.4 mg/kg Frozen (N=137)	3.4 mg/kg All (N=161)
<b>Hemoglobin (Hemoglobin increased) (g/L), n</b>	103	135	159
Any Grade Increase	1 (<1)	2 (1)	2 (1)
<b>Hemoglobin (Anemia) (g/L), n</b>	103	135	159
Any Grade Increase	33 (32)	63 (47)	69 (43)
Increase to Grade 3	17 (17)	35 (26)	39 (25)
<b>Lymphocytes (Lymphocyte count increased) (<math>10^9/L</math>), n</b>	103	135	159
Any Grade Increase	1 (<1)	4 (3)	4 (3)
<b>Lymphocytes (Lymphocyte count decreased) (<math>10^9/L</math>), n</b>	103	135	159
Any Grade Increase	51 (50)	65 (48)	74 (47)
Increase to Grade 3	20 (19)	32 (24)	38 (24)
Increase to Grade 4	5 (5)	7 (5)	7 (4)
<b>Neutrophils decreased (<math>10^9/L</math>), n</b>	103	135	159
Any Grade Increase	31 (30)	62 (46)	68 (43)
Increase to Grade 3	4 (4)	14 (10)	16 (10)
Increase to Grade 4	5 (5)	7 (5)	8 (5)
<b>Platelets decreased (<math>10^9/L</math>), n</b>	103	135	159
Any Grade Increase	65 (63)	107 (79)	124 (78)
Increase to Grade 3	8 (8)	27 (20)	28 (18)
Increase to Grade 4	12 (12)	26 (19)	28 (18)
<b>Leukocytes (Leukocytosis) (<math>10^9/L</math>), n</b>	103	135	159
Any Grade Increase	0	0	0
<b>Leukocytes (White blood cell decreased) (<math>10^9/L</math>), n</b>	103	135	159
Any Grade Increase	37 (36)	62 (46)	70 (44)
Increase to Grade 3	5 (5)	13 (10)	14 (9)
Increase to Grade 4	3 (3)	3 (2)	3 (2)

Source: Table 3.7300

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

Abbreviations: g = grams; L = liters; Q3W = every 3 weeks.

#### The FDA's Assessment:

The Applicant presented laboratory abnormality data based on a pooled safety population

which included patients in DREAMM-1 and DREAMM-2.

FDA analysis of laboratory abnormalities worsened from baseline occurring in  $\geq 20\%$  of patients in either dose cohort in DREAMM-2 is shown in Table 41. In general, the 2.5 mg/kg cohort had a lower incidence of hematology laboratory abnormalities compared to the 3.4 mg/kg cohort. Rates of thrombocytopenia, anemia, and neutropenia were significantly higher in both dose cohorts based on analysis of the laboratory dataset compared to the AE dataset.

**Table 41. FDA Analysis of Laboratory Abnormalities in  $\geq 20\%$  of Patients (DREAMM-2)**

Laboratory Parameter	All Grades, n (%)*		Grade $\geq 3$ , n (%)*	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
<b>Hematology</b>				
Platelets decreased	59 (62)	72 (74)	20 (21)	35 (36)
Lymphocytes decreased	47 (49)	45 (46)	21 (22)	29 (30)
Leukocytes decreased	36 (38)	44 (45)	8 (8)	11 (11)
Hemoglobin decreased	30 (32)	43 (44)	17 (18)	28 (29)
Neutrophils decreased	27 (28)	45 (46)	9 (9)	13 (13)
<b>Chemistry</b>				
Aspartate aminotransferase increased	53 (57)	66 (69)	2 (2)	5 (5)
Albumin decreased	40 (43)	56 (57)	4 (4)	7 (7)
Glucose increased	36 (38)	29 (31)	3 (3)	0
Creatinine increased	27 (28)	30 (31)	5 (5)	3 (3)
Alkaline phosphatase increased	24 (26)	32 (33)	1 (1)	0
Gamma-glutamyl transferase increased	23 (25)	36 (38)	5 (5)	10 (11)
Sodium decreased	20 (21)	26 (27)	2 (2)	6 (6)
Potassium decreased	19 (20)	30 (31)	2 (2)	2 (2)
Creatinine phosphokinase increased	19 (22)	25 (27)	1 (1)	0
Alanine aminotransferase increased	17 (18)	21 (22)	0	0

\*Denominators for calculation of % are based on the number of patients with at least one post-baseline laboratory value  
 Source: FDA Analysis (ADLB dataset; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

**The Applicant’s Position:**

**Vital Signs**

In the 2.5 mg/kg pooled data, 69 (67%) participants had any grade increase from baseline in systolic blood pressure, of which 32 (31%) participants had an increase to Grade 2 and 14 (14%) participants had an increase to Grade 3. Additionally, 55 (53%) participants had any grade increase from baseline in diastolic blood pressure, of which 16 (16%) participants and an increase to Grade 2 and 10 (10%) participants had an increase to Grade 3.

**The FDA’s Assessment:**

FDA reviewed the data presented by the Applicant in the DREAMM-2 Clinical Study Report

regarding vital signs, including changes from baseline through the end of treatment for heart rate, systolic blood pressure, and diastolic blood pressure. FDA notes that post-baseline decreases in heart rate to <60 bpm occurred in 13% of patients and post-baseline increases in heart rate to >100 bpm occurred in 26% of patients in the 2.5 mg/kg cohort. Grade 3 increases in systolic blood pressure occurred in 14% of patients and Grade 3 increases in diastolic blood pressure occurred in 9% of patients in the 2.5 mg/kg cohort.

The Applicant's Position:

**Electrocardiograms (ECGs) and QT**

In the 2.5 mg/kg pooled data, 15 (15%) participants had any grade increase from baseline in Fridericia's corrected Q-T (QTcF) interval during the study, of which 1 (<1%) participant had an increase to Grade 2 (481-500) and no participants had an increase to Grade 3 (>500). There were 3 (3%) participants who had an increase from baseline in QTcF interval of >60 seconds during the study. Based on these data, belantamab mafodotin had no clinically significant effect on quantitative ECG parameters or QT/QTc interval.

The results of the exposure-QTc analysis demonstrated that belantamab mafodotin, total mAb, and cys-mcMMAF did not have a significant effect on cardiac repolarisation (Section 6.3.1).

The FDA's Assessment:

The FDA Clinical Pharmacology review team assessed the ECG data for this study and stated that no drug-related increase in QT greater than 10 msec is expected at the proposed dose of 2.5 mg/kg every 3 weeks.

The Applicant's Position:

**Immunogenicity**

The assessment of the immunogenicity risk with belantamab administration is low. The current clinical data are consistent with this assessment (Section 6.3.1). Overall, the rate of post-dose anti-drug antibodies in the 2 clinical trials is 2/274 participants, with no apparent clinical consequences related to the presence of anti-belantamab antibodies.

The FDA's Assessment:

FDA's assessment of immunogenicity performed by the Clinical Pharmacology review team is discussed in Section 6.2.1.

The Applicant's Position:

**Lyophilized (lyo) Presentation Cohort of DREAMM-2**

As noted in the corresponding "Lyophilized (lyo) presentation cohort" subsection of Section 8.1.2, the lyo cohort was smaller (N=24 vs. N=99 at 3.4 mg/kg) and less heavily pretreated (median prior lines: 5 vs. 6), with less mature data compared with the same dose level cohort in

the Safety Population (median duration of follow-up: 5.3 months vs. 6.9 months). These considerations should be taken into account when interpreting the results for this cohort.

In general, the AE profile for the 3.4 mg/kg Lyo cohort was similar to that in the same dose level cohort from the Safety Population. The lyo cohort had increased reporting rates of SAEs (63% and 47%, respectively), but similar rates of AESIs compared to the Safety Population. No new safety signals were observed in the lyo cohort. The pharmacokinetics of belantamab mafodotin and cys-mcMMAF and exposure-response analyses were not impacted by the lyo presentation (Section 6.3.1).

There appears to be a higher incidence of corneal events (ocular examination findings and BCVA change; 92% and 77%), and a lower incidence of thrombocytopenic events (42% and 59%) in the lyo cohort.

Overall, AEs leading to dose modifications in the 3.4 mg/kg Lyo cohort were consistent with the results from the 3.4 mg/kg frozen dose. Keratopathy and blurred vision were the most common AEs leading to dose delays in both the lyo cohort and Safety Population.

**The FDA's Assessment:**

FDA notes that due to the small number of patients in the lyophilized cohort, definitive conclusions cannot be drawn. Safety results from the patients who received 3.4 mg/kg lyophilized presentation as compared to 3.4 mg/kg frozen presentation showed higher rates of severe TEAEs (83% vs. 76%), serious TEAEs (63% vs. 48%) and dose interruptions due to TEAEs (75% vs. 57%). Patients who received 3.4 mg/kg lyophilized presentation also had higher rates of keratopathy (92% vs. 75%) and keratopathy events leading to dose modifications (71% vs. 51%). Although the lyophilized cohort is small and there are some differences in baseline characteristics in this cohort, further data is needed to assess the safety of the lyophilized presentation of belantamab mafodotin (see Section 14).

**8.2.5. Analysis of Submission-Specific Safety Issues**

**The Applicant's Position:**

Throughout the development program, certain toxicities were determined to be adverse events of special interest (AESIs) for the compound. The following AESIs were included: corneal events, thrombocytopenia, and infusion related reactions. Neutropenia is an event of interest in patients with multiple myeloma. The data in this section are presented for DREAMM-2 in accordance with the proposed USPI with the 2.5 mg/kg dose. The 3.4 mg/kg dose is also included for completeness following the 2.5 mg/kg dose, unless stated otherwise.

**Corneal Events**

Corneal findings is a class effect reported with ADCs which have the MMAF payload and are the most frequently reported adverse events (AEs) associated with belantamab mafodotin. These

include keratopathy on eye examinations, blurred vision, dry eyes, and photophobia, and are consistent with those reported in the literature with other MMAF-conjugated ADCs in terms of manifestation and incidence [Tannir, 2014; Moskowitz, 2015; Macsai, 2016; Reardon, 2016; Thompson, 2015]. MMAF-related corneal events, including those seen in DREAMM-2 have been primarily Grades 2 and 3, and typically resolved or improved following supportive care including dose modifications and preservative-free artificial tears, thus allowing participants to continue treatment with no apparent loss of efficacy. No serious long-term sequelae have been reported to date with belantamab mafodotin or other MMAF-conjugated ADCs [Eaton, 2015; Donaghy, 2016].

Corneal examination findings (keratopathy, generally seen as changes in corneal epithelium) with or without patient-reported symptoms were frequent (71% and 75% in the 2.5 mg/kg and 3.4 mg/kg, respectively). The median time to onset was 28 (range: 9-143) days and 22 (range: 1-150) days; 54% (36/67) and 43% (32/74) recovered from the first occurrence with median duration of 101.5 days (range: 8-210) and 91.5 days (range: 8-211). The majority of participants in either cohort did not experience changes in deeper layers of the cornea. In each cohort, of the participants who had normal corneal stroma at baseline (N=89 and N=88), 6% developed an abnormal finding in their worst eye. Similarly, 1% and 9% of participants with normal corneal endothelium at baseline (N=91 and N=89) developed an abnormal finding in their worst eye. There were 4 participants (1 patient in the 2.5 mg/kg group and 3 participants in the 3.4 mg/kg group) who permanently discontinued treatment due to corneal examination findings; out of these 4 participants, 1 participants in 3.4 mg/kg cohort reported an ocular symptom.

While keratopathy rarely resulted in permanent treatment discontinuation (2% and 3%), it was the most common AE leading to dose reductions (23% and 27%) and dose delays (47% and 48%). Dose delays due to corneal exam finding started at Week 4, whereas dose reductions started later at Week 13. In the 2.5 mg/kg cohort, most participants with treatment delays due to corneal exam findings were able to re-initiate treatment (69%), with median time to re-initiation of 83 days (range: 28–146). The median time to onset of moderate to severe corneal findings was 35 days (range: 19 to 143 days), and the median time to resolution of these corneal findings was 85 days (range: 8 to 193 days).

Despite the high incidence of corneal exam findings in DREAMM-2, the extent of symptomatic corneal events was lower. The most common patient reported ocular symptoms were blurred vision events (22% and 30%), and dry eye events (14% and 23%). In the 2.5 mg/kg cohort, only 1 participant had dry eye or blurred vision without accompanying exam finding. Among participants with any exam findings in the 2.5 mg/kg cohort, 60% did not have corresponding patient-reported symptoms of blurred vision or dry eye.

The median time to onset of first blurred vision event was 48.0 days (range: 6 to 224) and 40.5 days (range: 1 to 147). The median percentage of time on treatment with any blurred vision event was 40.2% and 56.6%. 52% and 67% of participants with blurred vision events recovered

from the first occurrence and the median duration of the first occurrence was 23.0 (6-163) days and 53.5 (1-226) days.

The median time to onset of first dry eye event was 42.0 (range: 12 to 151) days and 20.0 (range 2 to 49) days. The median percentage of time on treatment with any dry eye event was 17.6% and 85.8%; 62% and 30% of participants with dry eye events recovered from the first occurrence and the median duration of the first occurrence was 28.5 (12 to 64) days and 88.0 (2 to 153) days. In the 2.5 mg/kg cohort, one participant had a significant worsening of vision in their best eye to 20/200 (visual acuity worse than 20/400 in their worst eye at baseline); however, vision recovered to baseline during follow-up. Based on limited follow-up data, vision returned to baseline or near baseline in most cases. Median time to resolution post-treatment exposure was 21.0 days. Permanent loss of vision was not reported.

For the 2.5 mg/kg cohort, participants with a definite decrease in visual acuity ( $\Delta\log\text{MAR} \geq 0.3$  as compared to baseline) had a mean time to onset of 65.9 days. The median time to onset was 63.0 days. The median duration (time from the onset of a definite change from baseline to the first measured  $\Delta\log\text{MAR} < 0.30$  for both eyes) was 23.0 days. Resolution, as defined by return to a  $\Delta\log\text{MAR}$  of  $< 0.30$ , occurred in 85% of participants for their first occurrence. Participants with definite decreases in visual acuity ( $\Delta\log\text{MAR} \geq 0.3$  as compared to baseline) include individuals with varying degrees of change to their Snellen equivalent values which can range from changes better than 20/70 in either or both eyes to values equal to or worse than 20/200.

In exposure-response analyses based on the DREAMM-2 data, the probability of  $\geq$ Grade 2 or  $\geq$ Grade 3 corneal exam findings was positively related to belantamab mafodotin  $C_{\tau}$  and inversely related to a disease-related factor, baseline sBCMA level; history of dry eye was also associated with probability of  $\geq$ Grade 2 corneal exam findings. Time to  $\geq$ Grade 2 or  $\geq$ Grade 3 corneal exam findings was inversely related to belantamab mafodotin  $C_{\tau}$ . Probability of any grade and  $\geq$ Grade 2 keratopathy events using NCI-CTCAE scale was significantly positively related to belantamab mafodotin  $C_{\tau}$  and inversely related to baseline sBCMA. Please see Section 6.3.1 for more information.

#### *Ocular sub-study*

The median time to development of corneal examination findings was similar between eyes treated with (23.5 [11-65] days) and without (26.5 [11-65] days) corticosteroid eye drops in the 2.5 mg/kg arm compared to treated with (25 [8-63] days) and without (25 [8-63] days) in the 3.4 mg/kg arm). Therefore, based on eye examinations, steroid eye drops do not prevent changes in the cornea.

#### The FDA's Assessment:

Ocular toxicity, including changes in the corneal epithelium (keratopathy) and changes in visual acuity identified on ophthalmic exam, and symptoms such as dry eye and blurred vision, is the key safety concern for belantamab mafodotin.

The mechanism by which belantamab mafodotin causes ocular toxicity is not completely understood; however, FDA agrees that ocular toxicities, including keratopathy, are a known class-effect associated with MMAF-containing ADCs. Regarding the Applicant's statement that "no serious long-term sequelae have been reported to date with belantamab mafodotin or other MMAF-conjugated ADCs," FDA notes that no other MMAF-containing ADCs have been approved to date. In addition, while the corneal changes that occur do not appear to result in permanent sequelae, this may be contingent on events being identified early and appropriately managed with supportive care and dose modifications. Because the corneal epithelium normally serves as a protective barrier, if left untreated, patients with keratopathy could go on to develop more extensive corneal defects such as corneal ulcers, which in severe cases, may require corneal transplant.

FDA notes that based on the KVA scale, the incidence of keratopathy was 71% and 77%, in the 2.5 mg/kg and 3.4 mg/kg cohorts of DREAMM-2, respectively. Severe (Grade 3-4) keratopathy occurred in 44% and 41% of patients, respectively. Therefore, the incidence and severity of keratopathy did not differ substantially between the two dose levels. Based on the KVA scale, the median time to onset for keratopathy events in the 2.5 mg/kg cohort was 36 days (range 19-143), and 39% of patients experienced more than one event of keratopathy. In the DREAMM-2 trial, resolution of keratopathy was defined as recovery to Grade  $\leq 1$ . The median time to resolution for events that resolved was 62 days (range 11-193). As of the data cut-off date for the primary analysis (median follow-up 6.3 months), among the 67 patients with keratopathy in the 2.5 mg/kg cohort, 41% of patients had resolution, and this increased to 48% with extended follow-up (median follow-up 9 months) based on the 90-day safety update. Among the patients without resolution as of the last study assessment, 27% remained on treatment or in active follow-up and 25% had keratopathy that was ongoing when follow-up ended.

FDA agrees with the rates of dose modifications presented by the Applicant and notes that dose modifications are the primary mitigating strategy for ocular toxicity with belantamab mafodotin. FDA also notes that the rates of dose modification due to keratopathy were not substantially different between the two doses levels, and even though the DREAMM-2 protocol only recommended permanent discontinuation for Grade 4 events, the patients who discontinued due to keratopathy had Grade 2 or 3 events.

FDA notes that patients with keratopathy also experienced worsening in visual acuity with 17% of patients having worsening to a Snellen score of 20/50 or worse in the better seeing eye, and one patient having worsening to 20/200 or worse in the better seeing eye in the 2.5 mg/kg cohort. Only 43% of patients with keratopathy had other ocular symptoms, raising the concern that keratopathy could go undetected in the absence of close ophthalmic monitoring.

FDA agrees with the assessment that the ocular sub-study did not demonstrate an impact on the incidence or severity of ocular toxicity in DREAMM-2, but notes the limited sample size of

the study. FDA also notes that all patients in DREAMM-2 received corticosteroid eye drops regardless of whether they were part of the ocular sub-study.

Considering the incidence and severity of ocular toxicity observed in DREAMM-2 with the proposed 2.5 mg/kg dose of belantamab mafodotin, in addition to a Warning and Precaution for ocular toxicity, additional strategies are required to mitigate the risks of ocular toxicity. The USPI will include a Boxed Warning for ocular toxicity and belantamab mafodotin will only be available through a REMS program.

Refer also to the BLA 761158 Belantamab Mafodotin Combined FDA and Applicant ODAC Briefing Document for additional analyses and discussion of ocular toxicity with belantamab mafodotin (ODAC, 2020).

#### The Applicant's Position:

##### **Thrombocytopenic Events**

Thrombocytopenic events were one of the most common  $\geq$ Grade 3 AEs reported with belantamab mafodotin and occurred more frequently at 3.4 mg/kg dose (including Grades 3-4 events) than at 2.5 mg/kg dose.

- Time-to-Onset was comparable (median: 22 d vs. 21 d) between the 2 doses with majority of the thrombocytopenic events first occurring by Cycle 4 in either arm. For participants with thrombocytopenia:
  - 16/33 (48%) and 24/58 (41%) recovered from the first occurrence.
  - Duration of first occurrence was comparable (median: approximately 21 d).
  - $\geq$  Grade 2 concomitant bleeding events (associated with Grade 3-4 thrombocytopenia) were more frequent at 3.4 mg/kg (1% vs 7%).

Exposure-response analyses based on the DREAMM-2 data found that lower baseline platelet count and higher cys-mcMMAF Cmax were associated with a higher probability of  $\geq$ Grade 3 thrombocytopenia.

#### The FDA's Assessment:

FDA notes that the incidence of thrombocytopenia was higher based on analysis of laboratory data compared to the incidence based on AE capture. Based on the analysis of laboratory abnormalities worsening from baseline in the 2.5 mg/kg cohort, 62% of patients had thrombocytopenia of any grade and 21% of patients had Grade 3-4 thrombocytopenia. In the full safety population (N=218), 69% of patients had thrombocytopenia of any grade and 6% of patients had a Grade 3-4 bleeding event. Thrombocytopenia is included as a Warning and Precaution in the belantamab mafodotin USPI and the proposed mitigation strategies appear adequate to manage the risks of this toxicity.

The Applicant's Position:

**Neutropenic Events**

Neutropenic events are frequently associated with advanced RRMM and participants with Grade  $\leq 2$  neutropenia were allowed on study. Although neutropenia was not an AESI per protocol, reports of neutropenia are of interest in this patient population.

At the recommended dose, 14% of participants experienced a neutropenic event: 6% neutropenia and 7% neutrophil count decrease. Grade 3 or higher events occurred in 9% of study participants: 4% neutropenia and 5% neutrophil count decrease. Febrile neutropenia was not reported on 2.5 mg/kg, although 3% of participants on the 3.4 mg/kg arm reported Grade  $\leq 2$  febrile neutropenia.

In exposure-response analyses, no covariates were found to explain the probability of  $\geq$ Grade 3 neutropenia.

(b) (4)

The FDA's Assessment:

FDA notes that the incidence of neutropenia was higher based on analysis of laboratory data compared to the incidences reported by the Applicant above, which are based on AE capture. Based on the analysis of laboratory abnormalities worsening from baseline in the 2.5 mg/kg cohort, 28% of patients had neutropenia of any grade and 9% of patients had Grade 3-4 neutropenia.

(b) (4)

The Applicant's Position:

**Infusion-Related Reactions**

Infusion-related reactions (IRRs) occurred in 20 (21%) and 16 (17%) participants. Among participants experiencing IRRs, IRRs were predominantly Grade 1 or 2 (17/20 and 15/16). Eighteen/20 (90%) and 14/16 (88%) participants experienced IRRs after the first infusion. Only 1 patient (2.5 mg/kg group) discontinued treatment because of an IRR; this was a Grade 3 IRR, which occurred at both Cycle 1 and Cycle 2.

In exposure-response analyses, no covariates were found to explain the probability of occurrence of infusion-related reactions.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment, and notes that in the full safety

population (N=218), IRRs occurred in 18% of patients. While most IRRs were Grade 1 or 2 in severity, Grade 3 IRRs occurred in 1.8% of patients. The USPI for belantamab mafodotin will include a Warning and Precaution for IRRs and the proposed mitigation strategies appear adequate to manage the risks of this toxicity.

### **8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

#### The Applicant's Position:

##### **Patient-Reported Outcomes**

Patient-reported outcomes (PROs) are important for evaluating the benefit of a treatment, particularly in patients with a short life-expectancy and limited effective treatment options. For heavily pretreated MM patients, maintenance of disease-related symptoms, such as fatigue and pain symptoms, can be viewed as a benefit. Ocular PROs were also used to assess the impact of belantamab mafodotin-associated corneal events. A high-level summary of PRO-related data from DREAMM-2 (N=196) is provided below:

- Disease symptoms and QOL PRO summary (using EORTC-QLQ-C30, EORTCQLQ-MY20)
  - On average, study participants at least maintained (had stable) Global Health status whilst on belantamab mafodotin.
  - A notable proportion demonstrated clinically meaningful improvements in Fatigue and Disease Symptoms (specific locations of pain) early in treatment.
- Ocular PRO summary (using 2 visual symptoms and function questionnaires NEI-VQF-25 and OSDI):
  - Ocular PROs showed clinically meaningful deteriorations in vision symptoms and functioning with onset at Week 7 and highest deteriorations at Week 13
  - Severity of symptoms and functional impairment were similar between 2.5 mg/kg and 3.4 mg/kg dose cohorts.

In summary, participants experienced a worsening in their eye symptoms and maintenance of their disease-related symptoms while on treatment with belantamab mafodotin. The severity of symptoms and ocular-related functional impairment was similar between 2.5 mg/kg and 3.4 mg/kg dose cohorts.

#### The FDA's Assessment:

Regarding the Health-Related Quality of Life (HRQoL) results from DREAMM-2, FDA notes that interpretability of the HRQoL results are significantly limited by the sample size, study design and completion rate. The EORTC QLQ-C30 completion rate was less than 70% of expected subjects in the 2.5 mg/kg cohort at all on-treatment timepoints (ranged between 59%-67% of expected). Therefore, FDA does not agree with the Applicant's assessment that GHS/QoL was maintained and stable, in the 2.5 mg/kg cohort nor the subset of patients who had ocular symptoms. DREAMM-2 was neither designed nor powered to assess maintenance of QoL. FDA

notes that patients experienced worsening in their symptoms as assessed using the 2 visual symptoms and function questionnaires.

FDA did not review the questions from the trial-embedded interview sub-study, therefore cannot comment on the satisfaction results. The patient interview analysis was based on the responses at Cycle 4. FDA notes that about half of the study patients discontinued treatment soon after the third dose (median time on study treatment was 9.1 weeks). FDA notes that if patients were continuing therapy at Cycle 4, they were likely benefiting from a response to anti-MM therapy. Presumably, patients who did not have a disease response and patients who discontinued therapy due to TEAEs were not satisfied with their treatment and were not likely captured at Cycle 4.

### 8.2.7. Safety Analyses by Demographic Subgroups

#### The Applicant's Position:

No meaningful differences in safety were observed between the age groups (<65 years, ≥65 to <75 years, ≥75 years) and genders, although some differences were observed between genders for the following safety assessments:

- AEs leading to dose reduction were reported for a higher proportion of female participants (14-18% higher across the cohorts) compared to male participants. This trend was apparent in AEs of keratopathy that led to dose reduction, which were reported for a higher proportion of female participants (15-19% higher across the cohorts) compared with male participants;
- AEs leading to dose delay were reported for a higher proportion of female participants (14-16% higher across the cohorts) compared to male participants.

No meaningful differences in safety were observed between the race groups (White, Black, Other) and regions (North America, Europe/Australia), although some differences were observed between regions for the following safety assessments:

- Deaths were reported for a higher proportion of participants in Europe/Australia (16-20% higher across the cohorts) compared with North America.
- AEs leading to dose delay were reported for a higher proportion of participants in North America (14-18% higher across the cohorts) compared with Europe/Australia.

There is no clear explanation for the differences observed between the regions of North America and Europe/Australia, other than different individual tolerance level and possibly due to differences in patient management.

In population pharmacokinetic analyses, age, ethnicity, African American race, mild or moderate renal impairment, mild hepatic impairment, prior treatments, region, and

belantamab mafodotin presentation (frozen liquid or lyophilized) were not found to be significant factors accounting for interindividual variability in belantamab mafodotin or cys-mcMMAF pharmacokinetics. Body weight and gender had statistically significant but not clinically meaningful effects on belantamab mafodotin and cys-mcMMAF pharmacokinetics. In exposure-safety analyses, age, race, gender, and region were also not found to be significant factors.

Overall, the Applicant considers the differences in these subgroup analyses not to be clinically relevant, and no dose adjustment is recommended.

**The FDA’s Assessment:**

FDA does not agree with the Applicant’s assessment that no meaningful differences in safety were observed between the age groups. FDA otherwise agrees with the Applicant’s assessment above that the differences observed in the other subgroup analyses are not clinically relevant. As discussed in Section 8.1.2, the baseline demographic characteristics of the DREAMM-2 study population was generally representative of the U.S. population of patients with RRMM, except for enrollment of a younger population in the trial (Table 42). The median age in the DREAMM-2 trial was 66 years (median age of 65 years in the 2.5 mg/kg cohort) compared to a median age of 69 years for patients with newly diagnosed MM in the U.S. Furthermore, patients with RRMM who have had multiple prior lines of therapy are likely to be older compared to the median age at diagnosis. The FDA analysis of the efficacy and safety of belantamab mafodotin based on demographic age subgroups is summarized below. FDA notes that there was an insufficient number of patients in the ≥75 years subgroup to draw any definitive conclusions regarding differences in safety or efficacy.

**Table 42. FDA Analysis of Age Demographics (DREAMM-2)**

Age	2.5 mg/kg (N=97) n (%)	3.4 mg/kg (N=99) n (%)
Median (range), years	65 (39-85)	67 (34-84)
<b>Age Subgroup</b>		
<65 years	45 (46)	36 (36)
65 to <75 years	39 (40)	46 (46)
≥75 years	13 (13)	17 (17)

Source: FDA Analysis (ADSL dataset; DREAMM-2 ITT Population; 21JUN2019 Data Cut-off)

FDA analysis of ORR by age for DREAMM-2 is shown in Table 43.

**Table 43. FDA Analysis of ORR by Age (DREAMM-2)**

Age Subgroup	2.5 mg/kg (N=97) ORR, n (%) (97.5% CI)	3.4 mg/kg (N=99) ORR, n (%) (97.5% CI)
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<65 years	12 (27) (13.3, 44.1)	13 (36) (19.1, 56.1)
65 to <75 years	17 (44) (25.9, 62.5)	15 (33) (18, 50.1)
≥75 years	1 (8) (0.1, 40.1)	6 (35) (12.2, 64.8)

Source: FDA Analysis (ADRS dataset; DREAMM-2 ITT Population; 21JUN2019 Data Cut-off)

The ORR in the 2.5 mg/kg cohort for all age subgroups combined was 31% (97.5% CI: 20.8, 42.6). In the 2.5 mg/kg cohort, the ORR in patients age <65 years and 65 to <75 years is similar to the overall ORR. Although FDA notes that the ORR data in the age ≥75 years cohort is only based on N=13 for this subgroup, only 1 out of 13 patients had a response, corresponding to an ORR of 8%.

FDA analysis of overall safety by age for DREAMM-2 is shown in Table 44.

**Table 44. FDA Analysis of Overall Safety by Age (DREAMM-2)**

Adverse Event Category Age Subgroup	2.5 mg/kg (N=95) n (%)*	3.4 mg/kg (N=99) n (%)*
All Grade TEAEs (all ages)	93 (98)	99 (100)
<65 years	42 (98)	36 (100)
65 to <75 years	39 (100)	46 (100)
≥75 years	12 (92)	17 (100)
Grade 3-4 TEAEs (all ages)	76 (80)	75 (76)
<65 years	36 (84)	30 (83)
65 to <75 years	33 (85)	35 (76)
≥75 years	9 (69)	16 (94)
Serious TEAEs (all ages)	38 (40)	47 (48)
<65 years	17 (40)	15 (42)
65 to <75 years	17 (44)	22 (48)
≥75 years	4 (31)	10 (59)
Fatal TEAEs (all ages)	3 (3)	7 (7)
<65 years	1 (2)	2 (6)
65 to <75 years	2 (5)	4 (9)
≥75 years	0	1 (6)

\*For each age subgroup, the denominator is based on the number of patients in that subgroup

Source: FDA Analysis (ADAE and ADSL datasets; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

The incidences of TEAEs appears to be similar for the age <65 years and age 65 to <75 years subgroups. Due to the small number of patients within the age ≥75 years subgroup, definitive conclusions cannot be drawn; however, there does not appear to an increased incidence of TEAEs in this subgroup.

FDA analysis of ocular toxicity by age is shown in Table 45.

**Table 45. FDA Analysis of Ocular Toxicity by Age (DREAMM-2)**

Adverse Event Age Subgroup	2.5 mg/kg (N=95) n (%)*	3.4 mg/kg (N=99) n (%)*
Keratopathy† (all ages)	67 (71)	76 (77)
<65 years	29 (67)	32 (89)
65 to <75 years	31 (79)	32 (70)
≥75 years	7 (54)	12 (71)
Change in BCVA† (all ages)	50 (53)	48 (48)
<65 years	20 (47)	17 (47)
65 to <75 years	23 (59)	19 (41)
≥75 years	7 (54)	12 (71)
Vision blurred <sup>Δ</sup> (all ages)	21 (22)	30 (30)
<65 years	8 (19)	12 (33)
65 to <75 years	11 (28)	11 (24)
≥75 years	2 (15)	7 (41)
Dry eye <sup>Δ</sup> (all ages)	13 (14)	21 (21)
<65 years	6 (14)	10 (28)
65 to <75 years	4 (10)	9 (20)
≥75 years	3 (23)	4 (24)

\*For each age subgroup, the denominator is based on the number of patients in that subgroup

†Based on KVA scale

<sup>Δ</sup>Based on grouped terms (see Appendix Section 20.6.1)

Source: FDA Analysis (ADSL, ADAE, ADOCGSK, and ADOCDVA datasets; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

There appears to be an increased incidence of ocular toxicity in the age 65 to <75 years and ≥75 years subgroups compared to the age <65 years subgroup. Due to the small number of patients within the age ≥75 years subgroup, definitive conclusions cannot be drawn. As discussed in Section 14, there will be a post-marketing requirement to further characterize the safety and efficacy of belantamab mafodotin in the age 65 to <75 years and ≥75 years subgroups.

### 8.2.8. Specific Safety Studies/Clinical Trials

#### The Applicant's Position:

This section is not applicable.

#### The FDA's Assessment:

FDA agrees that this section is not applicable.

### 8.2.9. Additional Safety Explorations

#### The Applicant's Position:

#### **Human Carcinogenicity or Tumor Development**

This section is not applicable.

The FDA's Assessment:

FDA notes that no carcinogenicity studies were conducted as this drug is a therapeutic mAb being developed for oncology indications.

One patient in the belantamab mafodotin 3.4 mg/kg cohort developed Grade 5 (fatal) acute myeloid leukemia (AML) while on treatment with belantamab mafodotin. The patient was a 69-year-old man who had received 8 prior lines of therapy, which included alkylating agents, cyclophosphamide and melphalan, as well as lenalidomide and pomalidomide, all of which are associated with a risk of secondary malignancies, including AML. The patient was diagnosed with secondary acute myeloid leukemia after presenting with a fall and occipital hematoma/bleeding 201 days after the first dose and 94 days after the last dose of belantamab mafodotin and died 19 days later.

One patient in the belantamab mafodotin 3.4 mg/kg lyophilized cohort developed a serious adverse event of Grade 2 basal cell carcinoma on study day 89, 64 days after the last dose of study treatment. The patient was a 77-year-old man with a history of non-melanoma skin cancer, who had received 7 prior lines of therapy, which included cyclophosphamide, melphalan, lenalidomide and pomalidomide.

Both cases had confounding factors of prior treatment with agents associated with a risk of second primary malignancies, therefore, it is not possible to determine whether exposure to belantamab mafodotin was a factor in these cases.

The Applicant's Position:

**Human Reproduction and Pregnancy**

No pregnancies were reported in participants in DREAMM-1 or DREAMM-2 as of the data cut-off dates. The pregnancy status of females of reproductive potential should be verified prior to initiating therapy with belantamab mafodotin. Pregnant women, or patients becoming pregnant while receiving belantamab mafodotin, should be informed of the potential risk to the fetus.

To avoid exposure to the fetus, women of reproductive potential should use highly effective contraception during treatment and for 9 months following the last dose. Males with female partners of reproductive potential should use highly effective contraception during treatment and for 6 months following the last dose.

Women are advised not to breastfeed during treatment and for 9 months following the last dose.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The belantamab mafodotin USPI will include a

Warning and Precaution for embryo-fetal toxicity.

The Applicant's Position:

**Pediatrics and Assessment of Effects on Growth**

No studies were conducted in pediatric patients, as development is currently focused on RRMM, which has no pediatric patients. Belantamab mafodotin has been granted orphan designation and is therefore exempt from current Pediatric Research Equity Act (PREA) requirements for conducting pediatric studies.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

The Applicant's Position:

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

There have been no incidents of overdose, drug abuse, withdrawal and rebound with belantamab mafodotin as of the data cut-off dates. There is no potential for abuse as administration is conducted in the hospital setting.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

**8.2.10. Safety in the Postmarket Setting**

The Applicant's Position:

**Safety Concerns Identified Through Postmarket Experience**

Not applicable as belantamab mafodotin is not currently registered or approved in the US or in any other part of the world.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

The Applicant's Position:

**Expectations on Safety in the Postmarket Setting**

Toxicities have been adequately characterized in DREAMM-2, supported with safety data in DREAMM-1. Potential safety concerns beyond the risks conveyed in the proposed labeling with associated management recommendations are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:

FDA does not agree with the Applicant's assessment that potential safety concerns beyond the

risks conveyed in the proposed labeling with associated management recommendations are not expected. Given the frequency and severity of ocular toxicity observed in DREAMM-2, there is a concern that patients could develop serious ocular toxicity if not monitored closely with ophthalmic exams at baseline and while on treatment with belantamab mafodotin. A risk evaluation and mitigation strategy (REMS) is needed to ensure the risks of ocular toxicity associated with belantamab mafodotin can be adequately managed in the post-marketing setting (see Section 13).

### **8.2.11. Integrated Assessment of Safety**

#### The Applicant's Position:

Belantamab mafodotin has a manageable safety profile in patients with RRMM, an unmet medical need patient population. The main safety issues identified during drug development were ocular events, thrombocytopenia, and infusion-related reactions. Clinical experience confirm that these events, along with neutropenia and lung infections/pneumonia, are some of the most frequent toxicities observed.

In the pivotal study DREAMM-2, the most common AEs were changes to the corneal epithelium (observed on ophthalmic examination (71% reported as keratopathy), thrombocytopenic events (35%) and anemia (24%). Neutropenic events of any grade were reported in 14% of participants.

The most common Grade 3 or 4 AEs were changes to the corneal epithelium found on ophthalmic examination (27%), thrombocytopenic events (20%) and Anemia (20%), as graded by CTCAE criteria v4.

Serious AEs were reported in 40% of participants at the 2.5 mg/kg dose. One death was considered potentially related to study treatment by the investigator: one case of sepsis.

Approximately half (54%) of participants experienced an AE leading to dose delay and 29% of participants a dose reduction. AEs leading to permanent treatment discontinuation occurred in 8% of participants.

There was consistency in the AEs observed across subgroups, such as age and gender; therefore, therapeutic individualization is not required on the basis of AEs.

The safety profile observed in the pivotal study DREAMM-2 is supported by and consistent with the safety data from Phase I FTIH study DREAMM-1, as no new safety signals were identified. Please refer to Section 8.2.4 for additional details on safety results from both studies and Section 8.2.5 for additional details on the analysis of submission-specific safety issues. Details of the exposure-response analyses of safety data are provided in Section 6.3.1.

Overall, the safety profile of belantamab mafodotin in heavily pretreated RRMM patients is adequately characterized and manageable, with dose modifications and/or supportive care therapies. The label provides comprehensive information to prescribers and patients to ensure eye disorders and thrombocytopenia are promptly identified and managed. No additional risk management strategies beyond labelling are required.

The FDA's Assessment:

FDA agrees that keratopathy was the most frequent TEAE in DREAMM-2, occurring in 71% of patients in the 2.5 mg/kg cohort, with severe (Grade 3-4) keratopathy in 44% of patients.

Based on the analysis of laboratory data from DREAMM-2, the rates of cytopenias were higher than the rates reported above by the Applicant based on AE capture. Based on laboratory shift analysis, in the 2.5 mg/kg cohort, 62% of patients had thrombocytopenia, 32% had anemia, and 28% had neutropenia. Grade 3-4 hematology abnormalities included severe thrombocytopenia in 21% of patients, severe anemia in 18% of patients, and severe neutropenia in 9% of patients.

Because DREAMM-2 was a single-arm trial, FDA considers all TEAEs and does not agree with the Applicant's distinction between AEs and AEs related to study treatment. There were 3 fatal TEAEs in the 2.5 mg/kg cohort due to cardiac arrest, sepsis, and pneumonia.

FDA agrees with the overall numbers presented above regarding dose modifications due to TEAEs. FDA notes that 47% of patients in the 2.5 mg/kg cohort required a dose modification due to keratopathy, including 47% of patients with at least one dose interruption and 23% of patients with a dose reduction due to keratopathy.

Regarding the Applicant's assessment of safety across subgroups, FDA notes that while the overall incidences of TEAEs appear to be similar for the age <65 and 65 to <75 years subgroups, due to the small number of patients within the age ≥75 years subgroup, definitive conclusions cannot be drawn; however, there does not appear to be an increased incidence of TEAEs in this subgroup. There does, however, appear to be an increased incidence of ocular toxicity (keratopathy, decreased visual acuity and blurred vision) in patients age ≥65 years compared to younger patients in the 2.5 mg/kg cohort. As discussed in Section 14, a PMC will be issued to further characterize the ocular toxicity with belantamab mafodotin in the age 65 to <75 and ≥75 years subgroups.

Given the higher rates of keratopathy, including severe keratopathy, observed in the cohort of patients who received the lyophilized presentation of belantamab mafodotin at the 3.4 mg/kg dose and lack of data with the lyophilized presentation at the 2.5 mg/kg dose, a PMR will be issued to further characterize the safety of the lyophilized presentation of belantamab mafodotin.

Overall, ocular toxicity, including keratopathy, decreased visual acuity, and ocular symptoms, is

the key safety concern for belantamab mafodotin. FDA does not agree with the Applicant's assessment that no additional risk management strategies beyond labeling are required. As discussed, the USPI will include a Boxed Warning for ocular toxicity and a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is required to ensure that the risks of ocular toxicity with belantamab mafodotin can be adequately managed in the post-marketing setting.

## 9. SUMMARY AND CONCLUSIONS

### 9.1. Statistical Issues

#### The FDA's Assessment:

There were no major statistical issues that could impact the interpretation of the efficacy of belantamab mafodotin. However, the following caveats may need to be taken into account in the final decision in the efficacy of belantamab mafodotin:

- For subgroup analysis, the ORR in extramedullary disease at baseline appears to be worse than that in the overall population. The observed ORR by IRC assessment with extramedullary disease at baseline was 9.1% (97.5% CI: 0.8, 32.1) in the 2.5 mg/kg group and 5.6% (97.5% CI: 0.1,30.6) in the 3.4 mg/kg group. Given the small sample size in the subgroups, caution should be taken in the interpretation of the subgroup analysis results.
- Time-to-event endpoints such as PFS and OS are difficult to interpret in single-arm studies. These endpoints are unlikely to provide evidence to support efficacy because the measurements in isolation are out of context and comparisons to historical controls are prone to bias. Such biases include inconsistent definitions of time intervals across studies leading to biased estimates, and bias associated with comparison to historical controls due to differences in the study population, differences in the frequency and timing of assessments, and advances in medical care over time. In addition, the OS data was not mature at the time of primary efficacy analysis which limits the interpretation of the data.
- Efficacy analysis from the lyophilized cohort did not control the overall type I error, and this portion of the study was not powered for efficacy endpoints. Therefore, the efficacy results from lyophilized cohort are considered exploratory. The DoR data in the lyophilized cohort is based on data from 12 patients. This implies that the DoR estimate is very unstable. Any implicit comparison with the frozen liquid cohort and interpretation of the data should be avoided.
- The reviewer's descriptive analyses results showed that there were numerical differences for CR/PR between IRC and Investigator assessments for both the 2.5 mg/kg and 3.4 mg/kg cohorts (Table 21). The reasons for discordance can be attributed to the high complexity of IMWG criteria and this does not impact the overall assessment and reported ORR in the study.

## 9.2. Conclusions and Recommendations

The FDA's Assessment:

Based on the benefit for belantamab mafodotin in conjunction with the REMS with ETASU to mitigate the risk of ocular toxicity, the clinical and statistical reviewers recommend approval of:

*BLENREP for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.*

X

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X

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Primary Statistical Reviewer

Statistical Team Leader

X

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Andrea Baines

X

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Primary Clinical Reviewer

Clinical Team Leader

## 10. Advisory Committee Meeting and Other External Consultations

### The FDA's Assessment:

The application was presented to the Oncologic Drug Advisory Committee (ODAC) on July 14, 2020. FDA requested discussion of (1) whether the risk of ocular toxicity has been adequately characterized in Study 205678 (DREAMM-2) to allow for an assessment of the benefit-risk profile, and (2) the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

Specific issues presented to the ODAC were as follows:

- The high incidence of ocular toxicity, including severe events, with keratopathy in 71% of patients in the 2.5 mg/kg cohort experiencing keratopathy of any grade and 44% having severe (Grade 3-4) keratopathy. The incidence and severity were similar in the 2.5 mg/kg and 3.4 mg/kg cohorts.
- Patients experienced decreased visual acuity, including severe vision loss in some patients. Any change in visual acuity ( $\geq 1$ -line decrease) occurred in 53% of patients in the 2.5 mg/kg cohort and 26% of patients had a  $>3$ -line decrease. In addition, 17% had worsening to  $\geq 20/50$  in the better eye (not able to legally drive) and 1 patient had worsening to  $\geq 20/200$  in the better eye (consistent with legal blindness). Based on patient reported outcomes, a substantial proportion of patients reported severe visual symptoms with significant interference in their usual/daily activities.
- Ocular symptoms were only present in 43% of patients with keratopathy. The absence of ocular symptoms despite findings on exam raises concerns that keratopathy may not be identified in absence of close ophthalmic monitoring.
- There was a frequent need for dose modifications due to ocular toxicity with dose interruptions/delays due to keratopathy in 47% of patients in the 2.5 mg/kg cohort and dose reduction due to keratopathy in 23% of patients.
- Despite dose modifications and evaluation of the lower dose, some patients had recurrent and unresolved events of ocular toxicity. In the 2.5 mg/kg cohort, 39% of patients had more than 1 event of keratopathy. As of the last assessment (based on 9-month data from the safety update), of the 60 patients with Grade 2 or higher keratopathy in the 2.5 mg/kg cohort, 52% had ongoing keratopathy. Of those, 27% (16/60) remained on treatment or in active follow-up and 25% (15/60) had ongoing keratopathy when follow-up ended.
- Additional uncertainties include the acceptability of the proposed 2.5 mg/kg dosage regimen, the efficacy and safety in older patients, and the safety of the 2.5 mg/kg lyophilized presentation of belantamab mafodotin.
- The Applicant presented the REMS with ETASU proposal to address the ocular toxicity with belantamab mafodotin, which requires certification of healthcare facilities and prescribers, patient enrollment, and ocular examinations at baseline and prior to each dose of belantamab mafodotin.

The voting question was: “Does the demonstrated benefit of belantamab mafodotin outweigh the risks in the proposed patient population with multiple myeloma?” The final vote was 12 votes Yes, 0 votes No.

## 11. Pediatrics

### The Applicant’s Position:

This section is not applicable.

### The FDA’s Assessment:

No pediatric studies have been conducted and there is no data regarding the use of belantamab mafodotin in pediatric patients. (b) (4)

## 12. Labeling Recommendations

### The Applicant’s Position:

The final USPI for belantamab mafodotin reflects several changes from the version originally submitted by the Applicant.

### The FDA’s Assessment:

The table below summarizes changes to the proposed prescribing information made by the FDA. See the final approved prescribing information of BLENREP accompanying the approval letter for more information.

Section	Applicant’s Proposed Labeling	FDA’s Proposed Labeling
Full Prescribing Information		
Boxed Warning	...	BLENREP causes changes in corneal epithelium, which results in changes in vision and BLENREP will only be available through a restricted program under a REMS. Added Boxed Warning, because the prescribing information should discuss the risks that the REMS programs intends to mitigate in a Boxed Warning if a REMS program includes ETASU.
Dosage and Administration	Included (b) (4) considerations	(b) (4)

	<p>prior to dosing and supportive care.</p> <p>Included a 2-column table to describe dosage modifications for adverse reactions.</p>	<p>summarize important safety information regarding ophthalmic exams, lubricant eye drops and contact lenses.</p> <p>Created two 3-column tables to describe the dosage modifications for ocular toxicities separate from other adverse reactions. Revised recommendations for infusion-related reactions.</p>
<p>Warnings and Precautions</p>	<p>Included Warnings and Precautions for (b) (4) thrombocytopenia, and infusion-related reactions. Focused on the recommended dosage.</p>	<p>Used a pooled safety population to inform the Warnings and Precautions subsections (W&amp;P).</p> <p>Broadened the first W&amp;P (b) (4) to ocular toxicity and described the incidence and severity of keratopathy and visual acuity based on the report and grading in the ADOCGSK dataset.</p> <p>Added a W&amp;P for REMS program, because the specific subsection that discusses the risks that the REMS is trying to mitigate should be followed immediately by the subsection that discusses the REMS.</p> <p>Revised the W&amp;P for thrombocytopenia to include the incidence of thrombocytopenia based on the lab dataset. The incidence appears underreported in the AE dataset as compared to the lab dataset. Included a description of dose interruptions, reductions and discontinuation for bleeding and thrombocytopenia.</p> <p>Revised the W&amp;P for infusion-related reactions to include recommended dosage modifications for these reactions.</p>
<p>Adverse Reactions, Clinical Trials Experience</p>	<p>Described adverse events in DREAMM-2 trial at the recommended dosage.</p>	<p>Minimized description of study and study population because information found in section 14.</p> <p>Added description of serious adverse reactions and fatal adverse reactions and modified reasons for permanent</p>

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		<p>discontinuation. Added information regarding dosage interruptions and dose reductions.</p> <p>Revised adverse reactions to group similar adverse reactions and report the incidence and severity of keratopathy based on the ADOCGSK dataset.</p> <p>Revised table to include adverse reactions <math>\geq 10\%</math> and describe lab abnormalities that occurred in <math>\geq 20\%</math> in a separate table.</p>
Adverse Reactions, Immunogenicity	...	<p>Added a statement that the few number of patients with antibodies limited the ability to determine their effects on pharmacokinetics, efficacy and safety.</p>
Use in Specific Populations	<p>Recommended not to breastfeed for months following the last dose. (b) (4)</p> <p>Recommended to use contraception for (b) (4) months after the last dose for females and for 6 months for males.</p> <p>Included geriatric use statement (b) (4).</p>	<p>Revised recommendation to at least 3 months after the last dose based on elimination half-life.</p> <p>Revised recommendations for females to 4 months based on recommendations in Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry.</p> <p>Revised to describe the percentage of older adults in the pooled population and to state that the clinical studies included insufficient numbers of subjects to assess differences in effectiveness.</p> <p>Added subsection for renal impairment and hepatic impairment. (b) (4)</p>
Clinical Pharmacology	<p>...</p> <p>(b) (4)</p>	<p>Added a description of exposure-response relationship.</p> <p>(b) (4)</p>
Clinical Studies	(b) (4)	Removed.

	(b) (4)	
	Included not reached for median duration of response.	Added duration of response of $\geq 6$ months, because the median duration of response was not met.
Patient Counseling Information	...	Added information about REMS program.

### 13. Risk Evaluation and Mitigation Strategies (REMS)

The FDA’s Assessment:

The Division of Risk Management in the Office of Surveillance and Epidemiology reviewed this Application and concurs that additional risk evaluation mitigation strategies are required to ensure the risks of belantamab mafodotin can be adequately managed in the post-marketing setting.

A REMS with elements to assure safe use (ETASU) has been proposed because risk mitigation measures needed to prevent or reduce the risk or severity of the risk given that many patients with keratopathy are asymptomatic and labeling is unlikely sufficient to mitigate the risk given that the risk is unique to this product and oncologists likely do not have experience managing ocular toxicities.

As part of the REMS with ETASU for belantamab mafodotin, prescribers must be certified with the program and counsel patients regarding the risk for ocular toxicity and need for ophthalmic monitoring, patients must enroll in the program and comply with monitoring, and healthcare facilities must be certified and verify that patients are authorized to receive belantamab mafodotin. The REMS will also include a communication plan.

Depending on the findings from assessment of the REMS, FDA may modify the REMS or consider other regulatory actions. In the future, if the REMS assessments and/or data from other sources indicates that prescribers have gained familiarity with the ocular toxicity associated with belantamab mafodotin and are taking appropriate actions to manage and reduce the risk of ocular toxicity, FDA may determine that the REMS is no longer necessary.

### 14. Postmarketing Requirements and Commitment

The FDA’s Assessment:

The following clinical PMRs will be required under FDAAA:

- Submit the final study report and datasets from a randomized phase 3 clinical trial that

verifies and describes the clinical benefit of belantamab mafodotin in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive belantamab mafodotin compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and secondary endpoints that include overall survival and overall response rate, as well as patient-reported outcomes. This trial should include a sufficient number of older patients (ages 65-74 and  $\geq 75$ ) and patients with extramedullary disease.

- Submit an integrated pooled analysis of adverse events, outcomes, management and discussion of potential mitigation strategies for ocular toxicity, from clinical trials to further evaluate the safety of the lyophilized presentation of belantamab mafodotin in patients with relapsed or refractory multiple myeloma. Provide the datasets with the final study report.
- Conduct a study to characterize the microcyst-like corneal deposits observed in patients with relapsed or refractory multiple myeloma treated with belantamab mafodotin, via superficial keratectomy assessments. Submit an integrated final report containing data from this study, other clinical trials and other sources to further characterize the mechanisms by which belantamab mafodotin causes ocular toxicity.

The following clinical pharmacology PMRs will be required under FDAAA:

- Conduct a randomized phase 2 clinical trial to characterize the safety and efficacy of lower doses or alternative dosing regimens of single-agent belantamab mafodotin using the lyophilized presentation in patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. The study's primary objective is to assess the ocular toxicity in all treatment arms with efficacy and PK evaluations as secondary objectives. The results of this trial may inform product labeling. Submit a final report with full datasets.
- Conduct a pharmacokinetic trial to determine the appropriate dose of belantamab mafodotin in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function that may inform product labeling. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling"
- Conduct a pharmacokinetic trial to determine the appropriate dose of belantamab mafodotin in patients with severe renal impairment and end-stage renal disease (ESRD) with or without dialysis compared to patients with normal renal function that may inform product labeling. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling"
- Conduct a long-term storage stability assessment and submit the final report validating the bioanalytical measurement of cys-mcMMAF concentrations, previously submitted to this BLA, to establish the relationship between cys-mcMMAF exposure and safety events.

Support this study by updating and submitting the final report of the clinical pharmacology analysis, that was previously submitted to this BLA, including updated noncompartmental analyses, population pharmacokinetic, exposure-response analyses for efficacy and safety, concentration-QT analyses.

The following clinical PMCs will be issued:

- Submit an integrated final report and datasets from clinical trials to further characterize the efficacy of belantamab mafodotin in patients with extramedullary disease. The report should include the rates of overall response and overall survival.
- Submit an interim and a final integrated report containing data from clinical trials and other data sources such as, expanded access treatment protocols, post marketing reports and real world data, to further characterize the ocular toxicity, including keratopathy, changes in visual acuity, and other ocular symptoms, with belantamab mafodotin in older age subgroups of patients, age 65-74 years and  $\geq 75$  years, with relapsed or refractory multiple myeloma, compared to patients  $< 65$  years. The study report should also include the overall response rate and overall survival in the older age subgroups compared to patients  $< 65$  years to provide longer-term data to further characterize the benefit-risk profile in older age subgroups. The results from this study may inform product labeling.

Enhanced pharmacovigilance: For a period of 5 years from the U.S. approval date, submit all cases of changes in visual acuity to worse than 20/200, complete vision loss, corneal ulcers, and need for corneal transplant events reported with belantamab mafodotin as 15-day alert reports (as described under 21 CFR 600.80(c)(1)). Provide detailed analyses of ocular toxicity reported from clinical study and postmarketing reports in the periodic safety report, including case narratives of changes in visual acuity to worse than 20/200, complete vision loss, corneal ulcers, and corneal transplants, with the following information in table format: demographics, predisposing risk factors/comorbidities, signs, symptoms, relevant laboratory data/examination leading to diagnosis, and re-challenge/de-challenge information. The analyses should show cumulative data relative to the date of approval of belantamab mafodotin as well as relative to the prior periodic safety reports. Medical literature reviews for case reports/case series of ocular toxicity reported with belantamab mafodotin should also be provided in the periodic safety report.

## **15. Division Director (DHOT) (NME ONLY)**

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**X**

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**16. Division Director (OCP)**

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**X**

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**17. Division Director (OB)**

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**X**

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**18. Division Director (Clinical)**

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**X**

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## **19. Office Director (or designated signatory authority)**

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*This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.*

**X**

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## **20. Appendices**

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### **20.1. References**

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## **20.2. Financial Disclosure**

### The Applicant's Position:

Financial disclosure is provided for all clinical investigators involved in the studies included in this submission in Form 3455. No concerns were raised regarding the overall integrity of the data.

One investigator had disclosable financial arrangements (Table 46); this investigator was a Sub-Investigator, not a Principal Investigator. The investigator contributed >\$25,000 to the DREAMM-1 study center (b) (6). The study statisticians were consulted, and an analysis was performed, which determined no potential impact to the study.

**Table 46. Summary of Disclosable Financial Arrangements and Interest**

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
(b) (6)	(b) (6)	(b) (6)	>\$25,000	Significant payment of other sorts

**The FDA's Assessment:**

FDA notes the disclosable financial arrangement for the Sub-Investigator of the supportive DREAMM-1 study as reported above, and agrees that this issue is not anticipated to impact the integrity of the trial.

**Covered Clinical Study (Name and/or Number):\* 205678 (DREAMM-2)**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>525</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		
Significant payments of other sorts: <u>0</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in study: <u>0</u>		
Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)

\*The table above should be filled by the applicant, and confirmed/edited by the FDA.

**Covered Clinical Study (Name and/or Number):\* BMA117159 (DREAMM-1)**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
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Total number of investigators identified: <u>147</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		
Significant payments of other sorts: <u>1</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in study: <u>0</u>		
Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

\*The table above should be filled by the applicant, and confirmed/edited by the FDA.

### 20.3. Nonclinical Pharmacology/Toxicology

There are no nonclinical pharmacology/toxicology appendices.

### 20.4. OCP Appendices (Technical documents supporting OCP recommendations)

#### 20.4.1. Summary of Bioanalytical Method Validation and Performance

##### The FDA's Assessment:

##### Summary of Bioanalytical Method Validation and Performance of Belantamab Mafodotin and total mAb in Plasma

Belantamab mafodotin and total mAb were quantified in the plasma by enzyme-linked immunosorbent assays (ELISA) for Study BMA117159 and Study 205678. The method validation and performance are acceptable to support both studies. The summary of the bioanalytical method validation and performance of these assays for belantamab mafodotin and total mAb in pivotal Study 205678 are presented in Table 47 and Table 48, respectively.

**Table 47. Summary Method Performance of a Bioanalytical Method to Measure Belantamab Mafodotin in Plasma for Study 205678**

Bioanalytical method validation report name	Report number 2019N412690 Validation and Cross Validation of a Chemiluminescent Immunoassay for the Quantitation of GSK2857916 (Antibody Drug Conjugate) in Human K2EDTA Plasma		
Method description	Belantamab mafodotin was captured in human plasma using an anti-mcMMAF antibody and detected with a biotinylated anti-idiotypic minibody specific for the antibody backbone portion of belantamab mafodotin with streptavidin conjugated to a horseradish peroxidase reporter tag.		
Materials used for calibration curve & concentration	Belantamab mafodotin; 200 (anchor), 500, 750, 1000, 1750, 2500, 5000 10000 ng/mL		Acceptability Yes
Validated assay range	500 to 10,000 ng/mL		Acceptability Yes
Material used for QCs & concentration	Belantamab mafodotin; 500, 1500, 3500, 8000, 10000 ng/mL		Acceptability Yes
Minimum required dilutions (MRDs)	50-fold in assay buffer		Acceptability Yes
Source & lot of reagents (LBA)	Belantamab mafodotin, GSK, lot # 132371424 (b)(4) #112M4201) and lot # 162397940 (b)(4) #066M4208) Anti-mcMMAF mAb, GSK, hybridoma # 136414 Biotinylated recombinant mAb fragment (Fab-MH) against belantamab mafodotin, GSK, lot # AbD24594.9 HRP labelled streptavidin, ThermoFisher Scientific, lot # RJ236399 and SF252108		
Regression model & weighting	Four parameter – weighted 1/x		Acceptability Yes
<b>Validation parameters</b>	<b>Method validation summary</b>		
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7	Acceptability Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.2 to +1.4%	Acceptability Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 2.0%	Acceptability Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-7.9 to +5.0%	Acceptability Yes
	Inter-batch %CV	≤ 6.6%	Acceptability Yes
	Total error	≤ 14.5%	Acceptability Yes
Selectivity & matrix effect	The selectivity of the method in control plasma and in plasma from multiple myeloma patients was established by analyzing 10 individual donor lots of plasma from each plasma type. The precision and accuracy in 10/10 lots spiked at 500 ng/mL		Acceptability Yes

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[TRADE NAME] belantamab mafodotin

	was < 20% for both control and multiple myeloma plasma. Unspiked samples were < LLOQ.	
Interference & specificity	The ability of the method to tolerate sBCMA in human plasma was evaluated by spiking sBCMA at 25 to 1000 ng/mL into human plasma containing 1500 and 8000 ng/mL belantamab mafodotin. The precision and accuracy under the conditions tested was < 20% at sBCMA concentrations up to 250 ng/mL. The precision and accuracy of belantamab mafodotin samples containing up to 500 ng/mL sBCMA was < 20% following a 2-fold dilution. The precision and accuracy of belantamab mafodotin samples containing up to 1000 ng/mL sBCMA was < 20% following a 5-fold or 10-fold dilution. These data indicate that the method can accurately quantitate belantamab mafodotin in the presence of up to 250 ng/mL sBCMA or up to 1000 ng/mL sBCMA following 5 to 20-fold dilution. Sample dilutions and concentrations of sBCMA were reviewed prior to assessing the acceptability of the belantamab mafodotin concentrations.	Acceptability Yes
Hemolysis effect	Five lots of hemolyzed human plasma were tested blank and spiked with 500 ng/mL belantamab mafodotin. The accuracy under the conditions tested was < 20% in at least 80% of the samples. Blank hemolyzed plasma provided a response less than the LLOQ.	Acceptability Yes
Lipemic effect	Five lots of lipemic plasma were tested blank and spiked with 500 ng/mL belantamab mafodotin. The accuracy under the conditions tested was < 20%. Blank lipemic plasma provided a response less than the LLOQ.	Acceptability Yes
Dilution linearity & hook effect	Dilution linearity and hook effect were evaluated by diluting a sample containing 1,000,000 ng/mL belantamab mafodotin from 8- to 8192-fold. All replicates of the 1,000,000 ng/mL belantamab mafodotin sample diluted 8- to 64-fold were > ULOQ and samples diluted 4096- to 8192-fold were < LLOQ. The precision and accuracy of all the 128- to 2048-fold diluted samples was < 20%. Dilution linearity was considered acceptable and no hook effect was observed at or below 1,000,000 ng/mL belantamab mafodotin in human plasma.	Acceptability Yes
Bench-top/process stability	The stability of belantamab mafodotin at 1500 and 8000 ng/mL was assessed in human whole blood stored on wet ice for 2 hours or at ambient temperature for 4 hours, prior to processing to plasma. All samples were within 20% of similarly spiked samples in which the blood was processed to plasma immediately. The stability of belantamab mafodotin in human plasma stored at ambient temperature for 24 hours was assessed at 1500 and 8000 ng/mL. The precision and accuracy for the stored samples was < 20%.	Acceptability Yes
Freeze-Thaw stability	The stability of belantamab mafodotin in human plasma after 8 freeze-thaw cycles from -80°C to room temperature was	Acceptability Yes

	assessed at 1500 and 8000 ng/mL. The precision and accuracy under the conditions tested was < 20%.	
Long-term storage	The stability of belantamab mafodotin in human plasma stored at -20°C for 35 days and at -80°C for 345 days was assessed at 1500 and 8000 ng/mL. The precision and accuracy under the conditions tested was < 20%. Further long-term storage stability is ongoing.	Acceptability Yes
<b>Method performance in Study 205678</b> <b>Interim Bioanalytical Report: Determination of GSK2857916 in Human K2EDTA Plasma Samples.</b> <b>Report number 2018N390896</b>		
Assay passing rate	102/117 analytical runs met the predefined acceptance criteria. (including incurred sample reanalysis (ISR))	Acceptability Yes
Standard curve performance	Cumulative bias range: -0.6 to +1.0% Cumulative precision: ≤5.9% CV	Acceptability Yes
QC performance	Cumulative bias range: -6.4 to -0.7% Cumulative precision: ≤12.2% CV TE: not reported	Acceptability Yes
Method reproducibility	Incurred sample reanalysis was performed in 16.8% of study samples analyzed using this method and > 66.7% of samples met the pre-specified criteria	Acceptability Yes
Study sample analysis/ stability	Calibration standards were stored frozen (nominal -80°C) and used within established stability. All study samples were stored frozen at -80°C on receipt. QC samples were stored frozen at -80°C. Further long-term stability work is ongoing to cover the period of time that study samples were stored.	Acceptability Yes

**Table 48. Summary Method Performance of a Bioanalytical Method to Measure Total mAb in Plasma for Study 205678**

<b>Bioanalytical method validation report name</b>	<b>Report number 2019N396866</b> <b>Validation and Cross Validation of a Chemiluminescent Immunoassay for the Quantitation of GSK2857916 (total antibody) in human K2EDTA plasma</b>	
Method description	Total mAb was captured in human plasma using an idiotypic anti-belantamab mafodotin monoclonal minibody and detected through its Fc region using a mouse anti-human IgG (Fc specific) antibody conjugated to a horseradish peroxidase reporter tag.	
Materials used for calibration curve & concentration	Belantamab mafodotin; 200 (anchor), 500, 750, 1000, 1750, 2500, 5000 10000 ng/mL	Acceptability Yes
Validated assay range	500 to 10,000 ng/mL	Acceptability Yes
Material used for QCs & concentration	Belantamab mafodotin; 500, 1500, 3500, 8000, 10000 ng/mL	Acceptability Yes
Minimum required dilutions (MRDs)	33.3-fold in assay buffer	Acceptability Yes

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[TRADE NAME] belantamab mafodotin

Source & lot of reagents (LBA)	Belantamab mafodotin, GSK, lot # 132371424 (b) (4) #112M4201) and 162397940 (b) (4) # 066M4208) Recombinant mAb fragment (Fab-A-FH), (b) (4), lot # 10 HRP labelled mouse anti-human IgG1 (Fc), (b) (4), lot # 1708571		
Regression model & weighting	Four parameter – weighted 1/x		Acceptability Yes
<b>Validation parameters</b>	<b>Method validation summary</b>		
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7	Acceptability Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-0.8 to +1.0%	Acceptability Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 2.8%	Acceptability Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-4.4 to -3.0%	Acceptability Yes
	Inter-batch %CV	≤ 6.7%	Acceptability Yes
	Total error	≤ 11.1%	Acceptability Yes
Selectivity & matrix effect	The selectivity of the method in control plasma and in plasma from multiple myeloma patients was established by analyzing 10 individual donor lots of plasma for each plasma type. The accuracy in 10/10 control plasma and 9/10 multiple myeloma lots spiked at 500 ng/mL was < 20% for both control and multiple myeloma plasma. Unspiked samples were < LLOQ.		Acceptability Yes
Interference & specificity	The ability of the method to tolerate sBCMA in human plasma was evaluated by spiking sBCMA at 25 to 1000 ng/mL into human plasma containing 1500 and 8000 ng/mL belantamab mafodotin. The precision and accuracy under the conditions tested was < 20% at sBCMA concentrations up to 100 ng/mL. The precision and accuracy of belantamab mafodotin samples containing up to 500 ng/mL sBCMA was < 20% following dilution of 2-fold. The precision and accuracy of belantamab mafodotin samples containing up to 1000 ng/mL sBCMA was < 20% following dilution of 5- to 10-fold. These data indicate that the method can accurately quantitate total mAb in the presence of up to 100 ng/mL sBCMA, up to 500 ng/mL sBCMA following 2- fold dilution or up to 1000 ng/mL sBCMA following 5- to 10-fold dilution. Sample dilutions and concentrations of sBCMA were reviewed prior to assessing the acceptability of the total mAb concentrations.		Acceptability Yes
Hemolysis effect	Ten lots of hemolyzed human plasma were spiked with 500 ng/mL belantamab mafodotin. Hemolyzed plasma did not meet the acceptance criteria and hemolyzed samples were marked as 'Not Reportable'.		Acceptability Yes
Lipemic effect	Five lots of lipemic plasma were spiked with 500 ng/mL belantamab mafodotin. The accuracy under the conditions		Acceptability Yes

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[TRADE NAME] belantamab mafodotin

	tested was < 20%.	
Dilution linearity & hook effect	Dilution linearity and hook effect were evaluated by diluting a sample containing 1,000,000 ng/mL belantamab mafodotin from 8- to 8192-fold. All replicates of the 1,000,000 ng/mL belantamab mafodotin sample diluted 8- to 64-fold were > ULOQ and samples diluted 2048- to 8192-fold were < LLOQ. The precision and accuracy of all the 128- to 1024-fold diluted samples was < 20%. Dilution linearity was considered acceptable and no hook effect was observed at or below 1,000,000 ng/mL belantamab mafodotin in human plasma.	Acceptable? Yes
Bench-top/process stability	The stability of total mAb at 1500 and 3500 ng/mL was assessed in human whole blood stored on ice for 2 hours or at ambient temperature for 4 hours, prior to processing to plasma. All samples were within 20% of similarly spiked samples in which the blood was processed to plasma immediately. The stability of total mAb in human plasma stored at ambient temperature for 18 hours was assessed at 1500 and 8000 ng/mL. The precision and accuracy for the stored samples was < 20%.	Acceptability Yes
Freeze-Thaw stability	The stability of total mAb in human plasma after 8 freeze-thaw cycles from -80°C to room temperature was assessed at 1500 and 8000 ng/mL. The precision and accuracy under the conditions tested was < 20%.	Acceptability Yes
Long-term storage	The stability of total mAb in human plasma stored at -20°C for 309 days and at -80°C for 339 days was assessed at 1500 and 8000 ng/mL. The precision and accuracy under the conditions tested was < 20%. Further long-term storage stability is ongoing.	Acceptability Yes
<b>Method performance in Study 205678</b> <b>Interim Bioanalytical Report: Determination of GSK2857916 in Human K2EDTA Plasma Samples.</b> <b>Report number 2018N390896</b>		
Assay passing rate	93/107 analytical runs met the predefined acceptance criteria. (including incurred sample reanalysis (ISR))	Acceptability Yes
Standard curve performance	Cumulative bias range: -1.2 to +0.6% Cumulative precision: ≤5.5% CV	Acceptability Yes
QC performance	Cumulative bias range: -4.6 to -0.4% Cumulative precision: ≤11.3% CV TE: not reported	Acceptability Yes
Method reproducibility	Incurred sample reanalysis was performed in 17.1% of study samples analyzed using this method and > 66.7% of samples met the pre-specified criteria	Acceptability Yes
Study sample analysis/ stability	Calibration standards were stored frozen (nominal -80°C) and used within established stability. All study samples were stored frozen at -80°C on receipt. QC samples were stored frozen at -80°C. Further long-term stability work is ongoing to cover the period of time that study samples were stored.	Acceptability Yes

**Summary of Bioanalytical Method Validation and Performance of cys-mcMMAF in Plasma and Urine**

The cys-mcMMAF concentration data submitted in the BLA were not fully supported by long-term storage stability assessment due to the change of bioanalytical method during the late stage of the clinical development. Therefore, there is insufficient bioanalytical data of cys-mcMMAF that were validated to support PK, safety assessment (b) (4)

Adequate validation of the long-term storage stability assessment for cys-mcMMAF concentration data and an evaluation of its relationship with safety events (such as corneal events) will need to be addressed in a PMR study.

**Summary of Bioanalytical Method Validation and Performance of Free Soluble BCMA (sBCMA) and Complexed sBCMA-belantamab mafodotin**

Concentrations of sBCMA and complexed sBCMA-belantamab mafodotin in human serum were quantified using electrochemiluminescent based assays (ECL). The method validation and performance were acceptable to support both studies. The method validation and performance of the free sBCMA and complexed sBCMA-belantamab mafodotin assays for Study 205678 are summarized in Table 49 and Table 50, respectively.

**Table 49. Summary Method Performance of a Bioanalytical Method to Measure Free Soluble BCMA in Serum for Study 205678**

<b>Bioanalytical method validation report name</b>	<b>Report number 2018N393390 Validation of an Electrochemiluminescence-Based Method for the Quantification of Free BCMA in Human Serum</b>	
Method description	Free BCMA was captured in human serum using an anti-BCMA antibody and detected using a different biotinylated anti-BCMA antibody and SulfoTAG labelled streptavidin.	
Materials used for calibration curve & concentration	BCMA; 0.98 (anchor), 1.95, 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250, 500, 1000 ng/mL	Acceptability Yes
Validated assay range	1.95 to 1,000 ng/mL	Acceptability Yes
Material used for QCs & concentration	BCMA; 1.95, 6, 50, 750, 1000 ng/mL	Acceptability Yes
Minimum required dilutions (MRDs)	1:20	
Source & lot of reagents (LBA)	Glycosylated huBCMA ECD (1-53), GSK, lot # GRITS48017 and N38580-51-P1 GSK2857914, GSK, lot # 122370432 Biotinylated goat IgG anti-human BCMA pAb, (b) (4) lot # FQV0717091 SulfoTAG labelled streptavidin, (b) (4), lot # W0017855S	
Regression model & weighting	Four parameter – 1/y <sup>2</sup> weighting	Acceptability Yes
<b>Validation parameters</b>	<b>Method validation summary</b>	

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Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	Acceptability Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.0 to +2.7%	Acceptability Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.1%	Acceptability Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-3.5 to +0.3%	Acceptability Yes
	Inter-batch %CV	≤ 18.3%	Acceptability Yes
	Total error	≤ 18.6%	Acceptability Yes
Selectivity & matrix effect	The selectivity of the method in control serum and serum from multiple myeloma subjects was established by spiking BCMA at 1.95 and 750 ng/mL into 10 lots of each type of serum. The bias compared to the measured endogenous level of BCMA was ≤ 20% in 10/10 control serum lots and 9/10 multiple myeloma serum lots.		Acceptability Yes
Interference & specificity	Belantamab mafodotin at 1, 10 and 100 µg/mL significantly reduced the free BCMA concentration by up to 97.8%.		Acceptability Yes
Hemolysis effect	Free BCMA was spiked into 2% hemolyzed serum at concentrations from 0.98 to 1000 ng/mL. The bias compared to non-hemolyzed serum was ≤ 20%.		Acceptability Yes
Lipemic effect	Free BCMA was spiked into lipemic serum (containing approximately 300 to 500 mg/dL triglycerides) at concentrations from 0.98 to 1000 ng/mL. The bias under the conditions tested was ≤ 20%.		Acceptability Yes
Dilution linearity & hook effect	Dilution linearity and hook effect were evaluated by diluting a sample containing 1600 ng/mL free BCMA from 2- to 1024-fold. All replicates of the undiluted 1600 ng/mL free BCMA sample were > ULOQ and samples diluted 1024-fold were < LLOQ. The precision and accuracy of all the 2- to 512-fold diluted samples was < 20%. Dilution linearity was considered acceptable and no hook effect was observed at 1600 ng/mL free BCMA in human serum.		Acceptability Yes
Bench-top/process stability	The stability of free BCMA in human serum stored at room temperature and 4°C for 25 hours was assessed at 5.92 and 750 ng/mL. The precision and accuracy under the conditions tested was ≤ 20%.		Acceptability Yes
Freeze-Thaw stability	The stability of free BCMA in human serum after 6 freeze-thaw cycles from -70°C to room temperature was assessed at 5.92 and 750 ng/mL. The precision and accuracy under the conditions tested was ≤ 20%.		Acceptability Yes
Long-term storage	The stability of free BCMA in human serum stored at -20°C and -70°C for 31 days was assessed at 5.92 and 750 ng/mL.		Acceptability Yes

	The precision and accuracy under the conditions tested was ≤ 20%. Further long-term stability work is ongoing.	
<b>Method performance in study 205678</b> <b>The study is ongoing. Current available data are listed below, but a report is not available</b>		
Assay passing rate	63/72 analytical runs met the predefined acceptance criteria	Acceptability Yes
Standard curve performance	Cumulative bias range: -2.2 to +3.2% Cumulative precision: ≤5.9% CV	Acceptability Yes
QC performance	Cumulative bias range: -16.6 to +0.8% Cumulative precision: ≤10.7% CV TE: ≤ 27.3% CV	Acceptability Yes
Method reproducibility	Incurred sample reanalysis was not performed.	Acceptability Yes
Study sample analysis/ stability	Calibration standards were freshly prepared for each analytical run. All study samples were stored frozen at -70°C along with QC samples. Further long-term stability work is ongoing to cover the period of time that study samples were stored.	Acceptability Yes

**Table 50. Summary Method Performance of a Bioanalytical Method to Measure Complexed BCMA-belantamab Mafodotin in Serum for Study 205678**

<b>Bioanalytical method validation report name</b>	<b>Report number 2018N394332</b> <b>Validation of an Electrochemiluminescence-Based Method for the Quantification of Complexed BCMA-GSK2857916 in Human Serum</b>	
Method description	Complexed BCMA-belantamab mafodotin was captured in human serum using a biotinylated anti-BCMA antibody and detected using a SulfoTAG labelled antiauristatin MMAF antibody.	
Materials used for calibration curve & concentration	Complexed BCMA-belantamab mafodotin; 0.09 (anchor), 0.27, 0.82, 2.47, 7.41, 22.22, 66.67, 200 ng/mL	Acceptability Yes
Validated assay range	0.27 to 200 ng/mL	Acceptability Yes
Material used for QCs & concentration	Complexed BCMA-belantamab mafodotin; 0.27, 0.8, 10, 150, 200 ng/mL	Acceptability Yes
Minimum required dilutions (MRDs)	1:10	
Source & lot of reagents (LBA)	Glycosylated huBCMA ECD (1-53), GSK, lot # GRITS48017 Belantamab mafodotin, GSK, lot # 112M4200 Biotinylated anti-BCMA goat pAb, (b) (4) lot #FQV0717091 SulfoTAG labelled anti-auristatin MMAF mAb, GSK, lot # 02APR13AURTAG	
Regression model & weighting	Four parameter – 1/y <sup>2</sup> weighting	Acceptability Yes
<b>Validation parameters</b>	<b>Method validation summary</b>	
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	7 Acceptability Yes

	Cumulative accuracy (%bias) from LLOQ to ULOQ	-4.2 to +7.6%	Acceptability Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 3.4%	Acceptability Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	+1.8 to +14.6%	Acceptability Yes
	Inter-batch %CV	≤ 12.2%	Acceptability Yes
	Total error	≤ 26.4%	Acceptability Yes
Selectivity & matrix effect	The selectivity of the method in control serum and serum from multiple myeloma subjects was established by spiking complexed BCMA at 20 ng/mL into 10 lots of each type of serum. The bias compared to the measured endogenous level of complexed BCMA was ≤ 20% in 10/10 of both control and multiple myeloma serum lots.		Acceptability Yes
Interference & specificity	<p>Concentrations of belantamab mafodotin up to 20 µg/mL and free BCMA up to 200 ng/mL were not detected by the assay. To assess the ability of the method to detect complexed BCMA in the presence of belantamab mafodotin, complexed BCMA concentrations over the range of 0.09 to 200 ng/mL were spiked with belantamab mafodotin at 1, 10 and 100 µg/mL belantamab mafodotin. The presence of belantamab mafodotin interfered with the ability of the assay to detect complexed BCMA at all belantamab mafodotin concentrations tested.</p> <p>Although the results demonstrated moderate to severe interference with quantification of complexed BCMA, the interference observed is most likely because the glycosylated huBCMA does not fully complex with belantamab mafodotin and this is not anticipated to adversely impact sample analysis.</p>		Acceptability Yes
Hemolysis effect	Complexed BCMA was spiked into 2% hemolyzed serum at concentrations from 0.09 to 200 ng/mL. The bias compared to non-hemolyzed serum was ≤ 20% at complexed BCMA concentrations ≥ 2.47 ng/mL and at the assay LLOQ (0.27ng/mL). At a concentration of 0.82 ng/mL, the bias was > 20%, however, the under-recovery was attributed to incomplete complex formation between BCMA and belantamab mafodotin in the test samples and the method does not truly show interference from hemolyzed serum.		Acceptability Yes
Lipemic effect	Complexed BCMA was spiked into lipemic serum (containing approximately 300 to 500 mg/dL triglycerides) at concentrations from 0.09 to 200 ng/mL. The bias compared to non-lipemic serum was ≤ 20%.		Acceptability Yes
Dilution linearity & hook effect	Dilution linearity and prozone effect were evaluated by diluting a sample containing 300 ng/mL complexed BCMA from 3- to 2187-fold. All replicates of the undiluted 300		Acceptability Yes

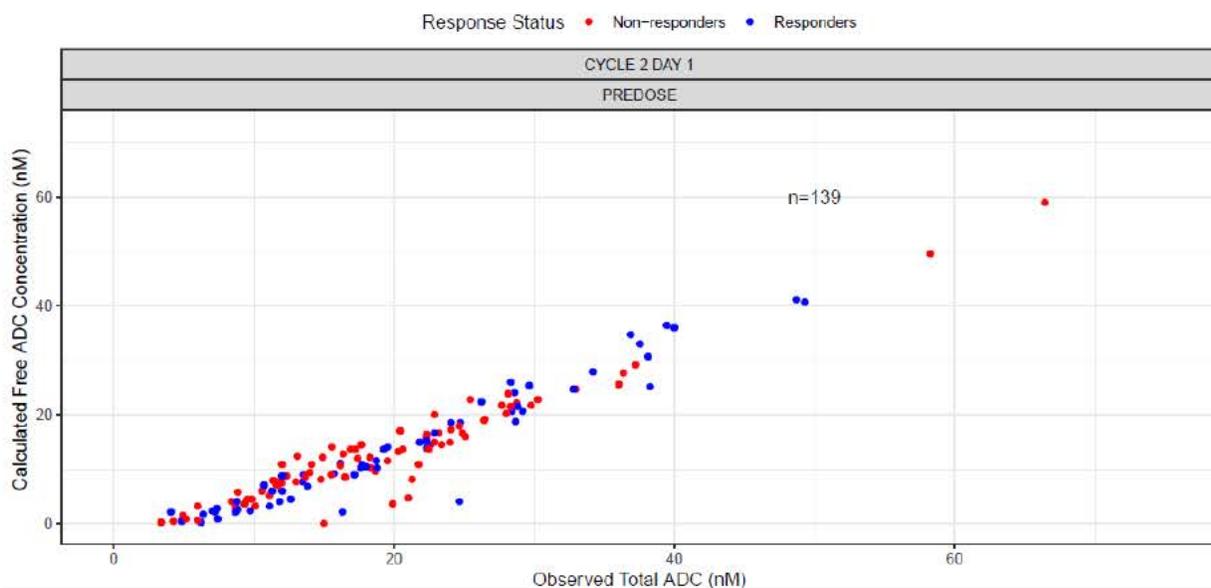
	ng/mL complexed BCMA sample were > ULOQ and samples diluted 2187-fold were < LLOQ. The precision and accuracy of all the 3- to 729-fold diluted samples was < 20%. Dilution linearity was considered acceptable and no prozone effect was observed at 300 ng/mL complexed BCMA in human serum.	
Bench-top/process stability	The stability of complexed BCMA in human serum stored at room temperature and 4°C for 24 hours was assessed at 0.8 and 150 ng/mL. The precision and accuracy under the conditions tested was ≤ 20%.	Acceptability Yes
Freeze-Thaw stability	The stability of complexed BCMA in human serum after 6 freeze-thaw cycles from -70°C to room temperature was assessed at 0.8 and 150 ng/mL. The precision and accuracy under the conditions tested was ≤ 20%.	Acceptability Yes
Long-term storage	The stability of complexed BCMA in human serum stored at -20°C and -70°C for 35 days was assessed at 0.8 and 150 ng/mL. The precision and accuracy under the conditions tested was ≤ 20%. Further long-term stability work is ongoing.	Acceptability Yes
<b>Method performance in study 205678</b>		
<b>The study is ongoing. Current available data are listed below, but a report is not available</b>		
Assay passing rate	62/82 analytical runs met the predefined acceptance criteria	Acceptability Yes
Standard curve performance	Cumulative bias range: -4.7 to +5.9% Cumulative precision: ≤6.7% CV	Acceptability Yes
QC performance	Cumulative bias range: -8.5 to -3.8% Cumulative precision: ≤11.7% CV TE: ≤ 17.1% CV	Acceptability Yes
Method reproducibility	Incurred sample reanalysis was not performed.	Acceptability Yes
Study sample analysis/ stability	Calibration standards were freshly prepared for each analytical run. All study samples were stored frozen at -70°C along with QC samples. Further long-term stability work is ongoing to cover the period of time that study samples were stored.	Acceptability Yes

Because the current enzyme-linked immunosorbent assay for belantamab mafodotin detects belantamab mafodotin (total ADC) regardless of whether it is bound to sBCMA in human plasma or not, the concentrations of complexed sBCMA-belantamab mafodotin and the percentage of complexed sBCMA-belantamab mafodotin that make up the total ADC detected in the total ADC assay were assessed. The calculated median percentage of belantamab mafodotin bound to sBCMA was low (~5%) shortly after IV infusion when belantamab mafodotin concentrations were high. There was a gradual increase in percentage bound toward the end of the first cycle, as belantamab mafodotin concentrations decreased. At the end of the first cycle, the median percentage of bound was around 34%. The applicant considers that those complexed belantamab mafodotin (measured as complexed sBCMA) still have efficacy potential based on the following rationales:

- Based on the relatively low calculated %ADC bound, it is expected that most complexes were 1:1 sBCMA. Complexes with a single sBCMA molecule bound to a belantamab mafodotin molecule still have a BCMA binding site available for binding to sBCMA to elicit efficacy.
- Complexed belantamab mafodotin has a similar potential to distribute into the bone marrow as free belantamab mafodotin because of only marginally increases the molecular weight or size.
- sBCMA-belantamab mafodotin complexes are subject to a dynamic binding equilibrium. Therefore, binding to membrane BCMA is possible for ADC-sBCMA complexes over time.

In addition, as shown in Figure 11, there is a high correlation between calculated bivalently free belantamab mafodotin concentrations and measured total belantamab mafodotin concentrations in the Cycle 2 predose samples ( $C_{tau}$ ). The free belantamab mafodotin concentrations were calculated as the difference between the measured belantamab mafodotin and complexed sBCMA concentrations in molar terms. Therefore, the exposure-response analyses conducted using total ADC is still considered clinically relevant.

**Figure 11. Correlation between Calculated Free ADC and Total ADC Concentrations at Cycle 2 Pre-dose**



Source: Applicant's response to Information Request

#### 20.4.2. Summary of Applicant's Population PK Analyses

##### The FDA's Summary of the Applicant's Analyses:

The Applicant's Population PK analyses for belantamab mafodotin and total monoclonal antibody (mAb) were conducted based on 2248 ADC and 2210 total mAb evaluable concentrations in 291 patients with RRMM from 2 trials BMA117159 and 205678. Summary

statistics of key demographics and covariates that were evaluated in the population PK analysis are shown in Table 51. The patients had a median (range) age of 65 (34, 89) years, and were primarily White (83%). There were 73 (25%), 134 (46%), 76 (26%), 7 (2%) and 1 (<1%) patients with normal renal function, mild, moderate, severe renal impairment, and ESRD respectively, according to their eGFR calculated using the Modification of Diet in Renal Disease (MDRD) formula. There were 192 (66%) patients with normal hepatic function, 24 (8%) patients with mild hepatic impairment, 2 (<1%) patients with moderate hepatic impairment, and no patient with severe hepatic impairment based on NCI-ODWG criteria. There were only 22 patients received a strong P-gp inhibitor, 1 patient received a strong OATP1B1 or OATP1B3 strong inhibitor while 1 patient received concomitant medication that contained strong inhibitor of P-gp and OATP1B1/ OATP1B3.

**Table 51. Summary of Key Demographics and Covariates for Patients Included in the Population PK Analysis**

Covariate		Subjects Included in the PPK Analysis (N=291)
		Number of subjects (%)
Age	Age<65	136 (47%)
	65≤ Age <75	116 (40%)
	Age≥75	39 (13%)
Gender	Male	156 (54%)
	Female	135 (46%)
Race	White	242 (83%)
	Black/African American	39 (13.5%)
	Asian	7 (2.5%)
	Other	3 (1%)
Presentation	Frozen Liquid	267 (92%)
	Lyophilized	24 (8%)
Renal Function	Normal (eGFR≥90 ml/min/1.73m <sup>2</sup> )	73 (25%)
	Mild Renal Impairment (60≤eGFR<90 ml/min/1.73m <sup>2</sup> )	134 (46%)
	Moderate Renal Impairment (30≤eGFR<60 ml/min/1.73m <sup>2</sup> )	76 (26%)
	Severe Renal Impairment (15≤eGFR<30 ml/min/1.73m <sup>2</sup> )	7 (2%)
	End Stage Renal Disease (eGFR<15 ml/min/1.73m <sup>2</sup> )	1 (<1%)
		<b>Median (min-max)</b>
Age (years)		65.0 (34.0 – 89.0)
Baseline body weight (kg)		74.0 (42.4 – 130)
Baseline sBCMA (ng/mL)		80.0 (1.95 – 2030) (n=279)
Baseline IgG (g/L)		8.50 (0.30 – 99.7) (n=287)
Baseline albumin (ALB) (g/L)		39.0 (19.0 – 50.0) (n=290)
Baseline eGFR/CRCL (mL/min/1.73m <sup>2</sup> )		71.6 (14.0 – 166)
Baseline alanine amino transferase (ALT) (IU/L)		16.0 (5.00 – 154) (n=289)
Baseline aspartate amino transferase (AST) (IU/L)		20.0 (8.00 – 136) (n=290)
Baseline total bilirubin (mg/dL)		0.400 (0.117 – 2.22) (n=289)

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 7.

Model development was initiated by characterizing the PK of ADC. Following establishment of the ADC base model, the covariate model was built, and a final population PK model generated for the ADC. Model development for the base total mAb population PK model and covariate analysis were performed with base ADC model.

#### **20.4.2.1. Final PK Model of ADC**

##### The FDA's Summary of the Applicant's Analyses:

A linear, two-compartment PK model with a time-varying clearance described by a sigmoidal time function was used to describe the PK of ADC. The covariate analysis identified 7 statistically significant covariates, including baseline albumin, sBCMA, IgG, body weight, doses < 1 mg/kg, and study effect on clearance (CL), baseline albumin, body weight, sex, and study effect on volume of central compartment ( $V_1$ ), and doses < 1 mg/kg on volume of peripheral compartment ( $V_2$ ). The final ADC PK model parameter estimates, along with the corresponding estimates of precision (95% CI) from Bootstrap are presented in Table 52.

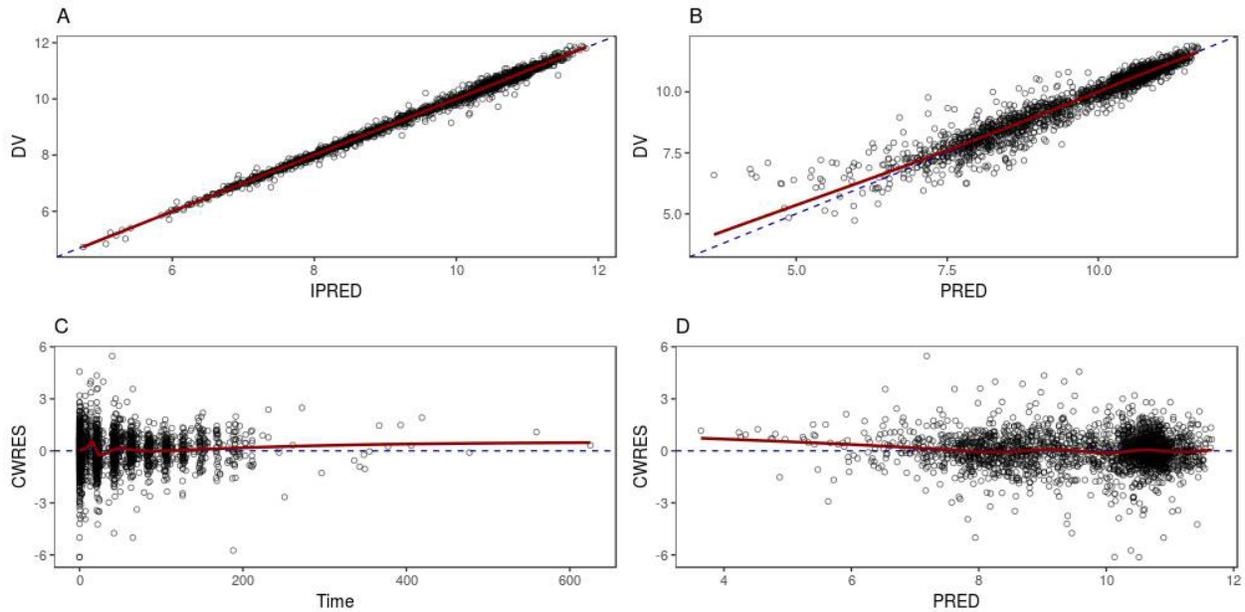
**Table 52. PK Parameter Estimates from Final ADC Population PK Model**

	BASE MODEL (run15) (-3215)	FULL MODEL (run15209) (-3863)	FINAL MODEL (run16501) (-3821)
<b>PK parameter (unit)</b>			
TVCL (L/DAY)	0.784	0.585 (no prior antiCD38)	0.748
TVV1 (L)	4.42	4.79 (no prior antiCD38)	4.47
TVQ (L/DAY)	0.760	0.711	0.753
TVV2 (L)	4.83	3.29 (no prior antiCD38)	5.38
IMAX	-0.387	-0.368	-0.378
TI50 (DAY)	51.2	52.1	52.4
GAMMA	4.29	4.92	4.65
TVCL with prior antiCD38 (L/DAY)	--	0.74	--
TVV2 with prior antiCD38 (L)	--	5.88	--
Effect of BWT on V1 ( $\theta_{V1\_BWT}$ )	--	0.512	0.484
TVV1 with prior antiCD38 (L)	--	4.29	--
Effect of BALB on CL ( $\theta_{CL\_BALB}$ )	--	-0.867	-0.832
Effect of BALB on V1 ( $\theta_{V1\_BALB}$ )	--	-0.386	-0.464
Effect of Male Sex on V1 ( $\theta_{V1\_SEX}$ )	--	1.13	1.13
Effect of BSBCMA on CL ( $\theta_{CL\_BSBCMA}$ )	--	0.119	0.124
Effect of BIGG on CL ( $\theta_{CL\_BIGG}$ )	--	0.136	0.137
Effect of BWT on CL ( $\theta_{CL\_BWT}$ )	--	0.512	0.532
Effect of BSBCMA on V1 ( $\theta_{V1\_BSBCMA}$ )	--	0.0244	--
Effect of BWT on V2 ( $\theta_{V2\_BWT}$ )	--	0.748	--
Effect of dose <1 mg/kg on V2 ( $\theta_{V2\_ADOSE<1}$ )	--	0.208	0.139
Effect of dose <1 mg/kg on CL ( $\theta_{CL\_ADOSE<1}$ )	--	0.652	0.600
Effect of DREAMM1/BMA117159 on V1	--	0.619	0.663
Effect of DREAMM1/BMA117159 on CL	--	0.668	0.576
ETA CL (%)	58.4	33.5	34.1
ETA V1 (%)	27.9	13.8	14.6
ETA Q (%)	40.3	50.8	41.8
ETA V2 (%)	82.2	43.4	55.6
ETA IMAX (%)	115	108	108
ETA TI50 (%)	35.9	33.8	34.8
RES ERR, Additive SIGMA on Log Scale	0.0212	0.0216	0.0215
<b>Pharmacokinetic parameter estimation for final model</b>			
$CL_i = \theta_{CL\_Time} \bullet (BALB/40)^{\theta_{CL\_BALB}} \bullet (BSBCMA/10)^{\theta_{CL\_BSBCMA}} \bullet (BIGG/10)^{\theta_{CL\_BIGG}} \bullet (BWT/75)^{\theta_{CL\_BWT}} \bullet \theta_{CL\_ADOSE<1}^{(ADOSE1)} \bullet \theta_{CL\_DREAMM1}^{(2-DREAMM1)} \bullet EXP(\eta_{\alpha})$			
$V1_i = \theta_{V1} \bullet (BWT/75)^{\theta_{V1\_BWT}} \bullet (BALB/40)^{\theta_{V1\_BALB}} \bullet \theta_{V1\_SEX}^{(SEX)} \bullet \theta_{V1\_DREAMM1}^{(2-DREAMM1)} \bullet EXP(\eta_{V1})$			
$Q_i = \theta_{\alpha} \bullet EXP(\eta_{\alpha})$			
$V2_i = \theta_{V2} \bullet \theta_{V2\_ADOSE<1}^{(ADOSE1)} \bullet EXP(\eta_{V2})$			
$IMAX_i = \theta_{IMAX} + (\eta_{IMAX}) \text{ and } TI50_i = \theta_{TI50} \bullet EXP(\eta_{TI50})$			
<b>Between-subject variability</b>			
Exponential Error (%CV) = $SQRT(EXP(\eta_i) - 1) \bullet 100$ and Additive Error (%CV) = $(SQRT(\eta_i) / \theta) \bullet 100$			
<b>Residual error</b>			
$Y = Ln(IPRED) + EXP(\epsilon_1)$			

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 10.

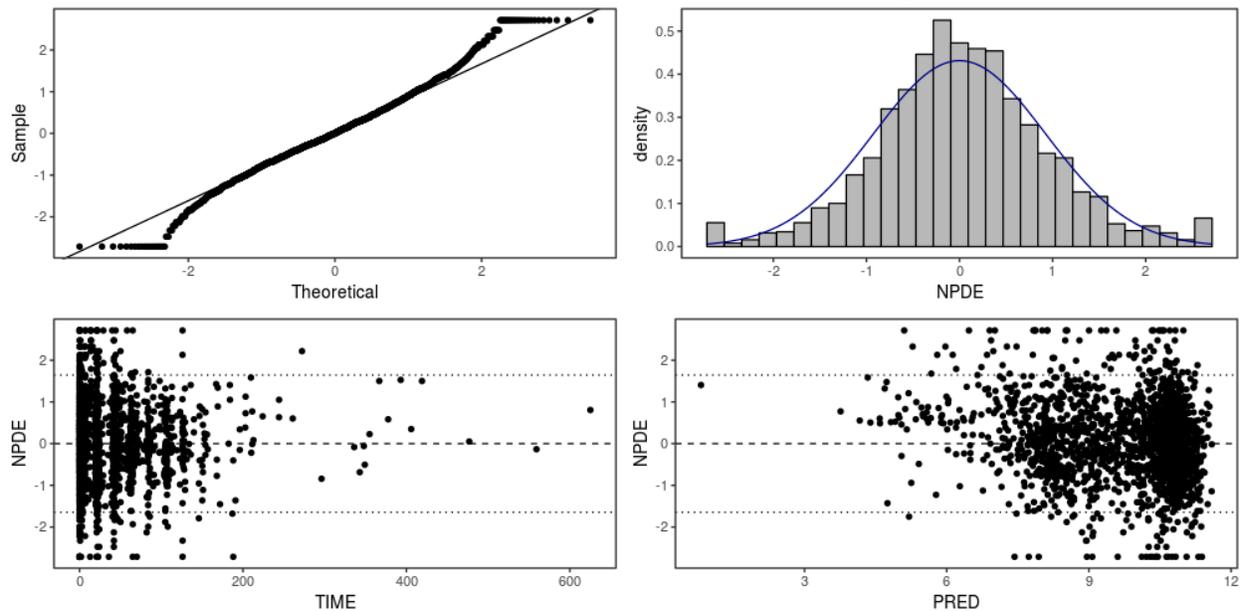
The goodness-of-fit plots, normal prediction distribution error (NPDE) plots and visual predictive check (VPC) plots for the final ADC PK model are presented in Figure 12, Figure 13, and Figure 14, respectively.

**Figure 12. Goodness of Fit Plots for Final ADC Population PK Model**



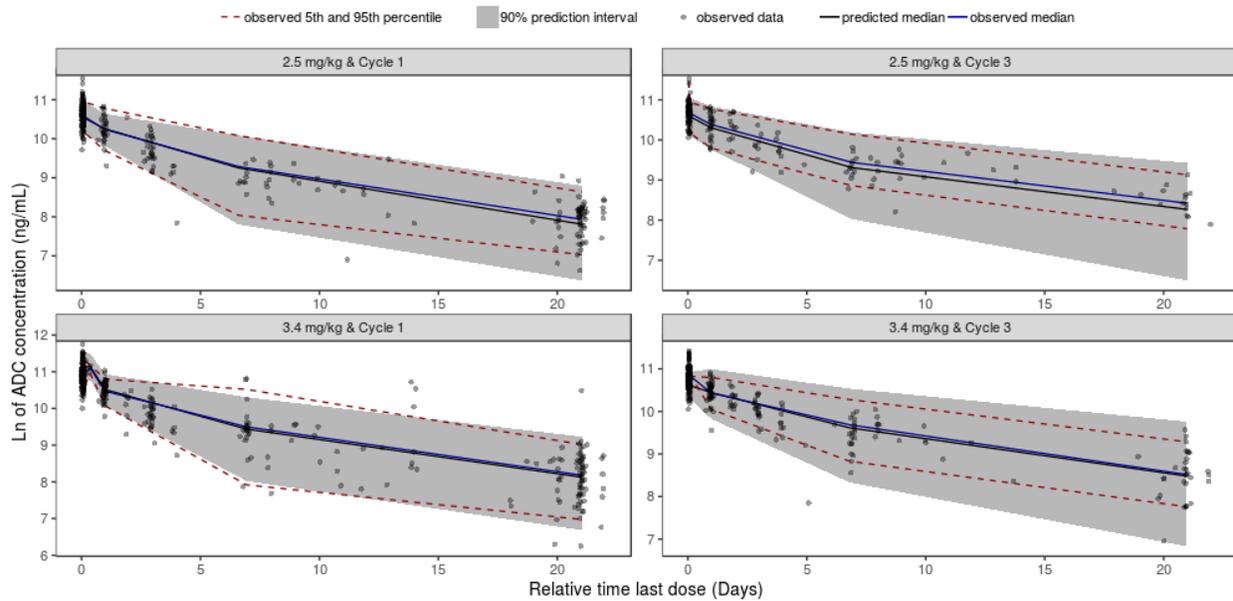
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 5.

**Figure 13. Normal Prediction Distribution Error Plot for Final ADC Population PK Model**



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 6.

**Figure 14. VPC for Final ADC Population PK Model**



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 7.

### 20.4.2.2. Final PK Model of total mAb

#### The FDA's Summary of the Applicant's Analyses:

The total mAb concentration was described as the sum of ADC and naked antibody formed via deconjugation of cys-mcMMAF using a first order rate constant. The covariate analysis identified 2 statistically significant covariates, including doses <1 mg/kg on deconjugation rate constant ( $K_{DEC}$ ) and correction factor (CORR), and study effect on CORR. The final total mAb PK model parameter estimates, along with the corresponding estimates of precision (95% CI) from Bootstrap are presented in Table 53.

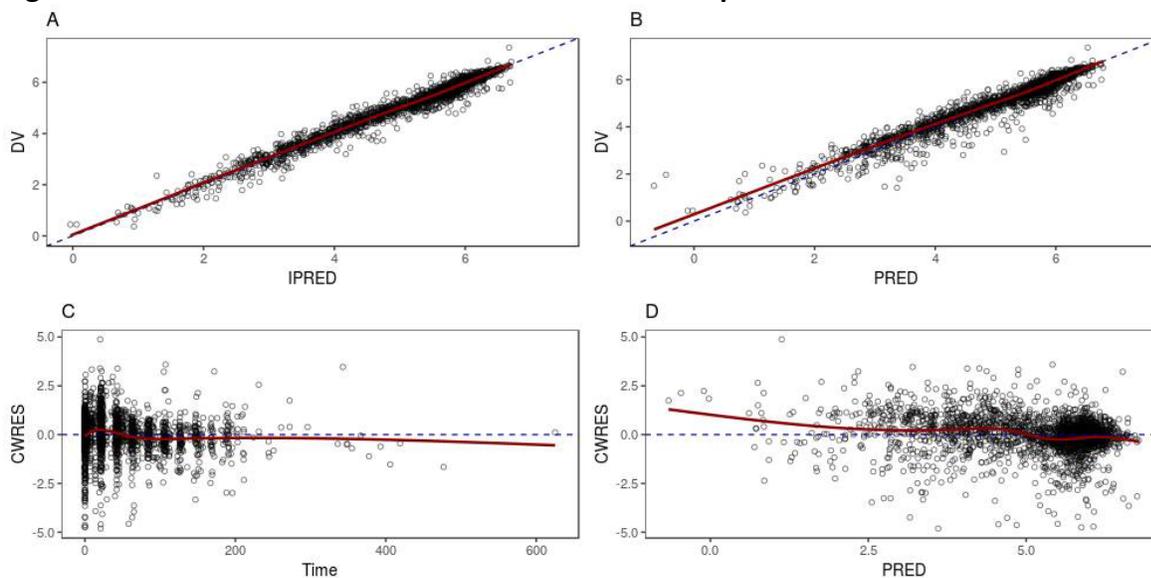
**Table 53. PK Parameter Estimates from Final Total mAb Population PK Model**

PK parameter (unit)	THETA	%RSE	Shrinkage	Bootstrap	
				Lower 95% CI	Upper 95% CI
TVKDEC (/DAY)	0.0590	2.99%	--	0.0553	0.0625
TVCORR (--)	1.14	0.872%	--	1.12	1.16
Effect of ADOSE<1mg/kg on Kdec ( $\theta_{Kdec\_ADOSE<1}$ )	0.0001 FIX	--	--	--	--
Effect of DREAMM1/BMA117159 on CORR ( $\theta_{CORR\_DREAMM1}$ )	0.848	2.72%	--	0.805	0.896
Effect of ADOSE<1mg/kg on CORR ( $\theta_{CORR\_ADOSE<1}$ )	0.846	3.66%	--	0.785	0.907
ETA(KDEC) %	38.8	18.2	18.2	30.7	46.5
ETA(CORR) %	7.58	32.9	42.4	4.77	9.63
RES ERR, Additive SIGMA on Log Scale	0.0516	6.76%	6.8%	0.0451	0.0592
<b>Pharmacokinetic parameter estimation</b> $K_{dec_i} = \theta_{Kdec} \bullet \theta_{Kdec\_ADOSE<1}^{(ADOSE1)} \bullet EXP(\eta_{CL})$ $CORR_i = \theta_{CORR} \bullet \theta_{CORR\_ADOSE<1}^{(ADOSE1)} \bullet \theta_{CORR\_DREAMM1}^{(2-DREAMM)} \bullet EXP(\eta_{CORR})$ <b>Between-subject variability</b> Exponential Error (%CV) = $SQRT(EXP(\eta_i) - 1) \bullet 100$ <b>Residual error</b> $Y = Ln[(IPRED_{ADC} + IPRED_{nakedmAb}) \bullet CORR_i] + \epsilon_1$					

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 13.

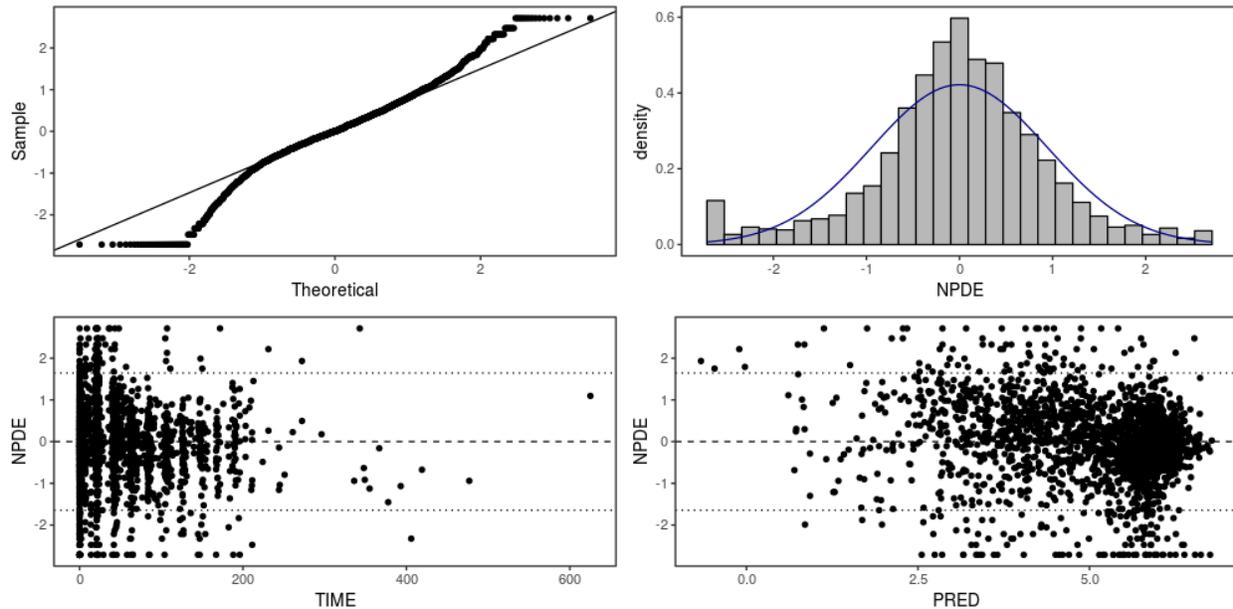
The goodness-of-fit plots, NPDE plots and VPC plots for the final total mAb PK model are presented in Figure 15, Figure 16, and Figure 17, respectively.

**Figure 15. Goodness of Fit Plots for Final Total mAb Population PK Model**



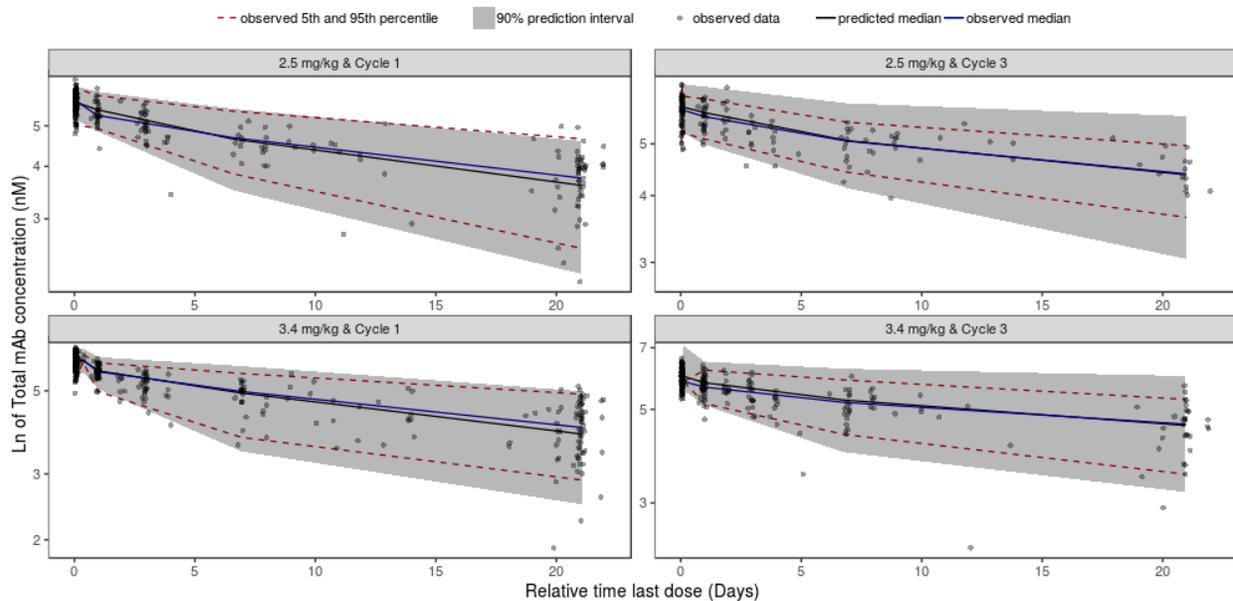
Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 9.

**Figure 16. Normal Prediction Distribution Error Plot for Final Total mAb Population PK Model**



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 10.

**Figure 17. VPC for Final Total mAb Population PK Model**



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 11.

**The FDA's Assessment:**

Although a mechanism-based target-mediated drug disposition (TMDD) PK model would be more appropriate to describe the correlations among ADC, total mAb and sBCMA plasma concentrations, the Applicant's empirical population PK models was able to reasonably describe the observed concentration-time profiles of ADC and total mAb following the administration of

belantamab mafodotin ranged from 0.03 to 3.4 mg/kg Q3W in patients with RRMM. In addition, the shrinkages values of the key PK parameters for total mAb ranged from low to moderate. The final PK models are generally acceptable to generate post-hoc exposure metrics, e.g.  $C_{max}$ ,  $C_{avg}$ , and  $C_{tau}$  of ADC following the first dose for E-R analyses of efficacy and safety measurements.

Covariate analysis revealed that body weight was significant covariate for CL and  $V_1$  of ADC, which supports the body-weight based dosing regimen. Covariate analysis also indicated that baseline sBMCA, IgG and albumin were the most significant covariates on ADC exposure.

The ADC exposures were not significantly altered by age (34 to 89 years), race (white, black, asian, others), sex, prior treatments, mild [total bilirubin  $\leq$  upper limit of normal (ULN) and AST  $>$  ULN or total bilirubin 1 to 1.5 times ULN and any AST] hepatic impairment, mild to moderate renal impairment ( $CL_{CR} \geq 30$  mL/min/1.73 m<sup>2</sup> to  $<90$  mL/min/1.73 m<sup>2</sup> as estimated by MDRD equation). Therefore, no dose adjustment is needed for the above-mentioned specific populations.

Given that PK sampling was sparse from limited patients with moderate (total bilirubin  $>$  1.5 to 3 times ULN and any AST) hepatic impairment or severe renal impairment ( $CL_{CR} \geq 15$  mL/min/1.73 m<sup>2</sup> to  $<30$  mL/min/1.73 m<sup>2</sup> as estimated by MDRD equation), the geometric means of PK metrics for ADC were estimated with large uncertainty, which may not be reliably used for the determination of dose adjustment in these specific populations. Therefore, dedicated organ impairment studies are required to assess the need of dose adjustment in patients with moderate to severe (total bilirubin  $>$  times ULN and any AST) hepatic impairment or severe renal impairment to end-stage renal disease ( $CL_{CR} < 30$  mL/min/1.73 m<sup>2</sup> as estimated by MDRD equation).

In addition, presentation of belantamab mafodotin (frozen liquid or lyophilized powder) was not found to have significant impact on the PK parameters for ADC, which may support the PK bridging between the to-be-marketed formulation (frozen liquid) and the test formulation (lyophilized powder) in clinical trials.

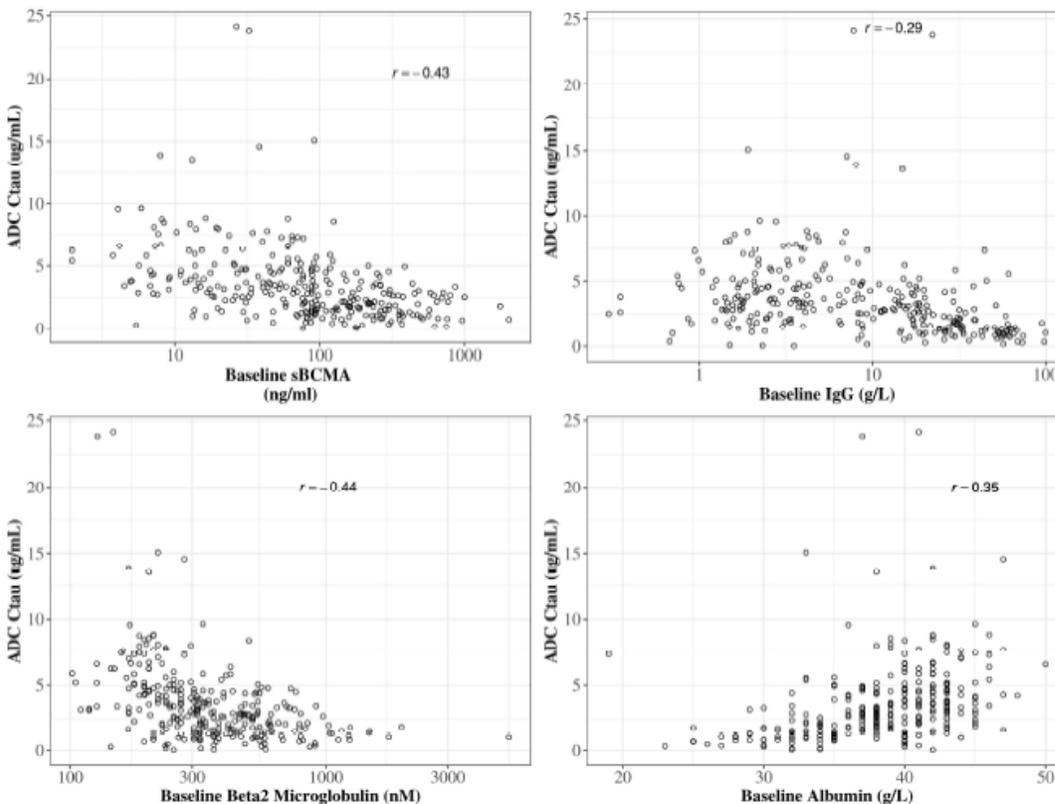
### 20.4.3. Summary of Applicant's Exposure-Response Analysis for Efficacy

#### The FDA's Summary of the Applicant's Analyses:

The Applicant conducted the E-R analyses for efficacy endpoints (i.e., probability of ORR, PFS, TTR, TTBR, and DOR) for ADC exposure measures. These analyses were conducted separately for Trial 205678 [frozen liquid presentation only (N=194) as well as full study population (N=218)] and Trial BMA117159 (N=73) due to key differences between the studies: different versions of the IMWG response criteria and response based on the IRC assessment for Trial 205678 and on the investigator assessment for Trial BMA117159. Only the analysis results based on data from two randomized frozen liquid presentation treatment arms (2.5 and 3.4 mg/kg Q3W) in Trial 205678 were summarized as follows.

In Trial 205678, there were 65 responders out of the 194 patients (33.5%) who received frozen liquid drug presentation. The Applicant’s univariate logistic regression analyses of ORR identified ADC PK metrics, baseline sBCMA,  $\beta 2$  microglobulin, IgG, and M protein were the predictors of ORR at a P value of < 0.01. However, the final multivariate logistic regression analysis only retained baseline sBCMA as the predictor of ORR at a P value of < 0.001. This is because both baseline IgG and sBCMA are inversely correlated with ADC  $C_{tau}$  (Figure 18). The results of final logistic regression model for probability of ORR are summarized in Table 54. The difference in probability of ORR by quartile of baseline sBCMA is illustrated in Figure 4.

**Figure 18. Correlation between Post hoc Exposure ADC  $C_{tau}$  by relevant covariates**



Source: Applicant’s Population PK and Exposure-Response Analyses Report, Figure 17.

**Table 54. Probability of ORR Logistic Regression Analysis Final Model Results (Trial 205678 - Frozen Liquid Presentation)**

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

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 23.

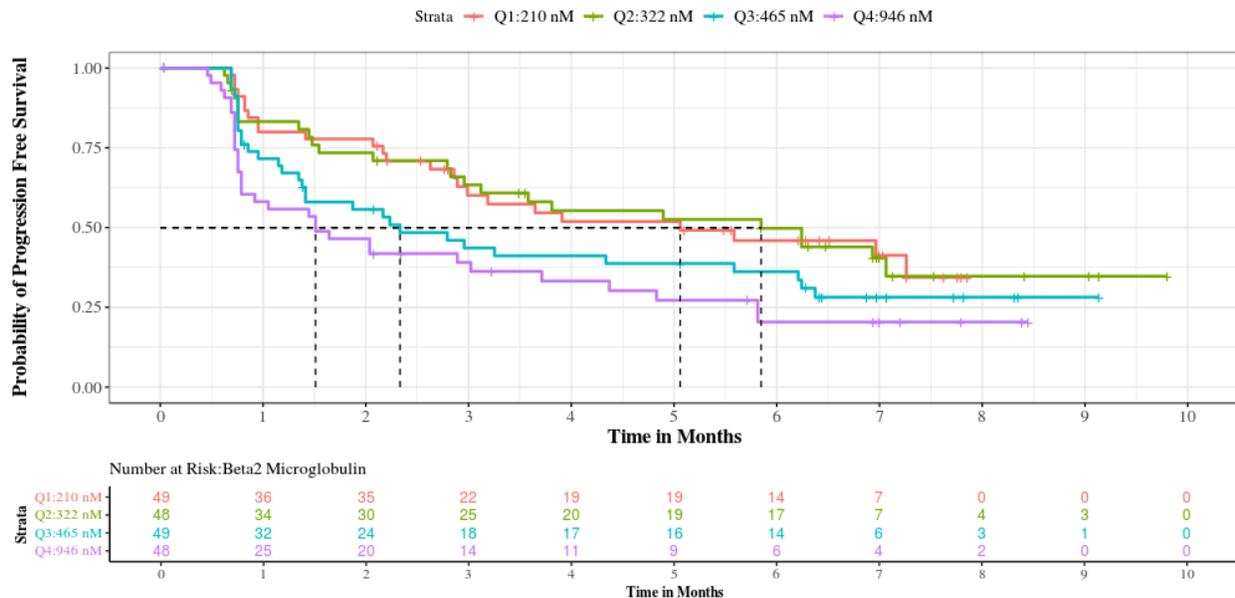
The Applicant's univariate analysis using Cox proportional hazard models resulted in baseline  $\beta 2$  microglobulin being the strongest predictor of PFS followed by baseline sBCMA, ADC  $C_{\text{tau}}$ , and ADC  $C_{\text{avg}}$  at a P value of < 0.01. However, the final multivariate logistic regression analysis excluded the ADC PK metrics as a predictor of PFS at a P value of < 0.001 due to the collinearity with baseline  $\beta 2$  microglobulin and sBCMA (Figure 18). The results of final logistic regression model for PFS are summarized in Table 55. The difference in PFS by quartile of baseline sBCMA and  $\beta 2$  microglobulin are illustrated in Figure 5 and Figure 19, respectively.

**Table 55. Cox Proportional Hazard Analysis of Progression Free Survival Final Model (Trial 205678 - Frozen Liquid Presentation)**

Covariates	Beta ( $\beta$ )	SE	95% CI	dOFV	Delta	HR (95% CI)
BB2M	0.00116	0.000240	(0.000686, 0.00163)	26.1	100	1.12 (1.07, 1.18)
BSBCMA	0.00135	0.000317	(0.000724, 0.00197)	11.9	20	1.03 (1.01, 1.04)
<b>Cox Proportional Hazard</b>						
$\text{Ln}(\lambda(t) f(X_i)/\lambda_0(t)) = \beta_{\text{BB2M}} \cdot \text{BB2M} + \beta_{\text{BSBCMA}} \cdot \text{BSBCMA}$ where $(\lambda(t) f(X_i))$ is hazard function at time t, given a predictor $X_i$ [BB2M, BSBCMA] and $\lambda_0(t)$ is hazard function at time t with no predictors						
BB2M = baseline $\beta 2$ microglobulin, BSBCMA = baseline sBCMA, SE = standard error; dOFV = drop in objective function relative null model						

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 27.

**Figure 19. Progression Free Survival Stratified by Quartile of Baseline  $\beta$ 2 Microglobulin (Trial 205678 - Frozen Liquid Presentation)**



Source: Applicant's Population PK and Exposure-Response Analyses Report, Figure 32.

#### 20.4.4. Summary of Applicant's Exposure-Response Analysis for Safety

##### The FDA's Summary of the Applicant's Analyses:

The Applicant conducted the E-R analyses for safety measurements (i.e., probabilities of corneal events, visual acuity worsening events, thrombocytopenia, neutropenia and infusion-related reactions) for ADC exposure measures. The E-R analyses for thrombocytopenia, neutropenia and infusion-related reactions were based on pooled data from Trials 205678 and BMA117159, while the E-R analyses for corneal events were conducted separately for Trial 205678 [frozen liquid presentation only (N=194) as well as full study population (N=218)] and Trial BMA117159 (N=73) due to the difference in grading of these findings between the studies. The GSK scale based on visual acuity changes and corneal changes on ophthalmic exam was used for Trial 205678 while the NCI-CTCAE version 4.0 was used for Trial BMA117159. The results of E-R analysis for corneal events based on all data from two randomized frozen liquid presentation treatment arms (2.5 and 3.4 mg/kg Q3W) and one open label lyophilized presentation treatment arm (3.4 mg/kg Q3W) in Trial 205678 were summarized as follows.

In Trial 205678, 153 (70.2%) patients had a grade 2+ and 111 (50.9%) patients had a grade 3+ corneal event (GSK scale) out of the 218 patients. The Applicant's univariate logistic regression analyses for grade 2+ or 3+ corneal event identified ADC PK metrics, baseline sBCMA, IgG, M protein,  $\beta$ 2 microglobulin, albumin and ISS stage were the predictors of corneal event at a P value of < 0.001. The final multivariate logistic regression analyses retained ADC  $C_{tau}$ , baseline sBCMA and history of dry eye as the significant predictors of grade 2+ corneal event, ADC  $C_{tau}$  and baseline sBCMA as the significant predictors of grade 3+ corneal event at a P value of <

0.001. The results of final logistic regression models for probability of grade 2+ or 3+ corneal event are summarized in Table 56 and Table 57, respectively. The difference in probability of grade 2+ or 3+ corneal event by quartile of Cycle 1 ADC C<sub>tau</sub> and baseline sBCMA are illustrated in Figure 20 and Figure 6, respectively.

**Table 56. Probability of Grade 2+ Corneal Event using GSK Scale – Logistic Regression Analysis Multivariate Results with Cycle 1 ADC C<sub>TAU</sub> (Trial 205678)**

Parameter	Estimate	SE	95% CI	dOFV	Delta	Odds Ratio (95% CI)
Intercept ( $\beta_0$ )	-1.48	0.537	(-2.57,-0.457)	NA	--	--
CTAUA	1.19	0.21	(0.812,1.64)	73.4	0.8	2.60 (1.92,3.72)
BSBCMA	-0.00446	0.00115	(-0.00691,-0.00238)	20.0	20.0	0.915 (0.871,0.953)
HISTDRYEYE	2.19	0.615	(1.07,3.5)	16.2	1.0	8.98 (2.91,33.3)
<b>Logistic Regression</b>						
$\ln(p/(1-p)) = \beta_0 + \beta_{CTAUA} \cdot CTAUA + \beta_{BSBCMA} \cdot BSBCMA + \beta_{HISTDRYEYE} \cdot HISTDRYEYE$						
BSBCMA = baseline soluble BCMA, CTAUA = ADC trough concentration; HISTDRYEYE= history of dry eye, SE = standard error; dOFV = drop in objective function relative previous model with covariate added before it.						

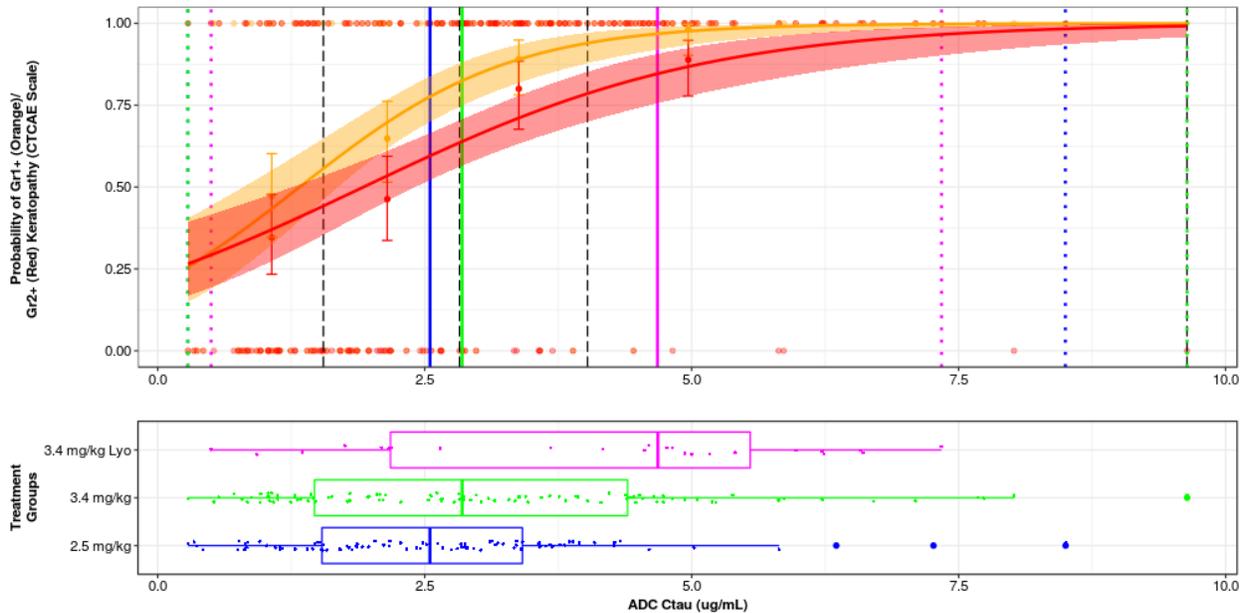
Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 11.3.1.2.2.2.

**Table 57. Probability of Grade 3+ Corneal Event using GSK Scale – Logistic Regression Analysis Multivariate Results with Cycle 1 ADC C<sub>tau</sub> (Trial 205678)**

Parameter	Estimate	SE	95% CI	dOFV	Delta	Odds Ratio (95% CI)
Intercept ( $\beta_0$ )	-0.949	0.445	(-1.84,-0.0887)	NA	--	--
CTAUA	0.606	0.125	(0.373,0.863)	60.5	0.8	1.62 (1.35,2)
BSBCMA	-0.00519	0.00134	(-0.00804,-0.00278)	22.6	20.0	0.901 (0.851,0.946)
<b>Logistic Regression</b>						
$\ln(p/(1-p)) = \beta_0 + \beta_{CTAUA} \cdot CTAUA + \beta_{BSBCMA} \cdot BSBCMA$						
BSBCMA = baseline soluble BCMA, CTAUA = ADC trough concentration; SE = standard error; dOFV = drop in objective function relative previous model with covariate added before it.						

Source: Applicant's Population PK and Exposure-Response Analyses Report, Table 11.3.1.2.1.3.

**Figure 20. Probability of Grade 2+ and Grade 3+ Corneal Event using GSK Scale by Cycle 1 ADC Ctau (Study 205678)**

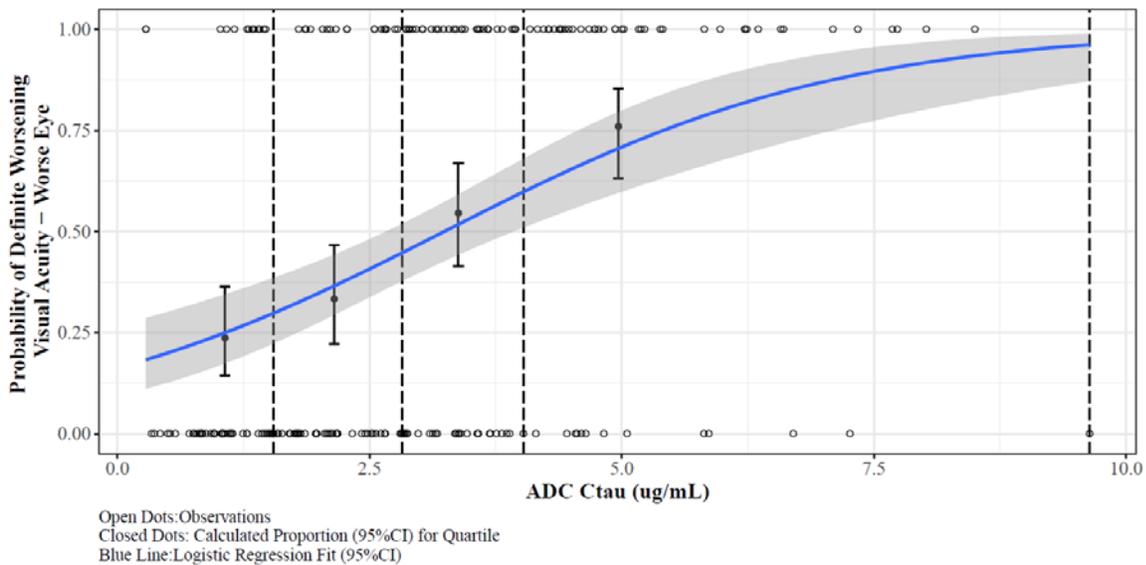


Open dots: Observations – Closed dots: Calculated proportional (95%CI) for each quartile – Lines: Logistic regression fit (95% CI)  
– Color code: Orange for grade 2+ and red for grade 3+

Source: Applicant's Responses to FDA Clinical Pharmacology Request on May 05, 2020, Figure Q.1.1.

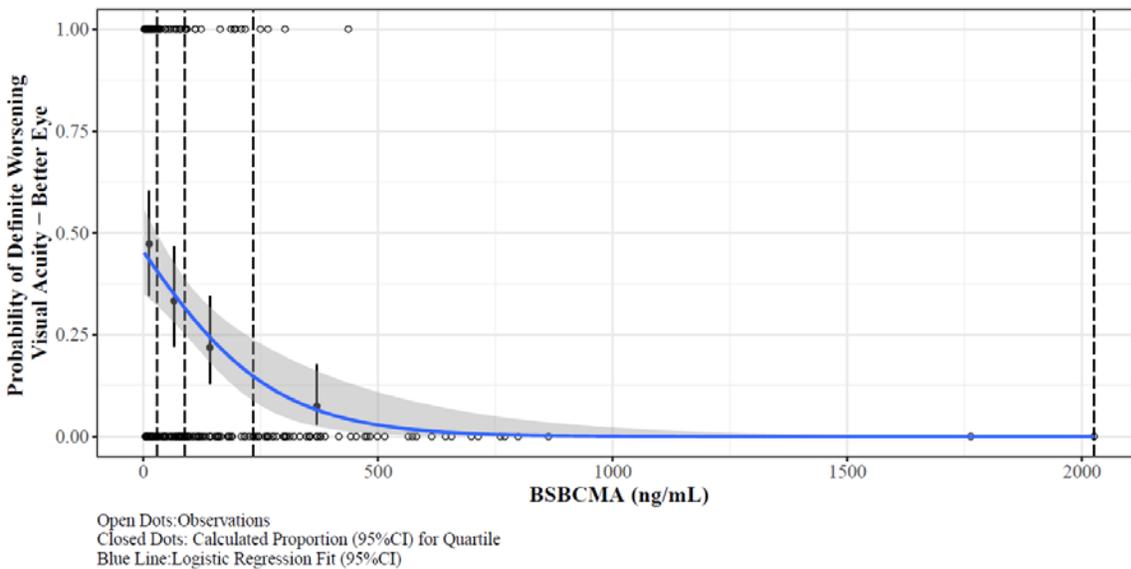
In addition, increasing belantamab mafodotin  $C_{tau}$  at Cycle 1 was associated with increasing definite worsening visual acuity in the worse eye, defined as a change from baseline in logMAR score of  $>0.3$  (Figure 21), definite worsening of visual acuity in the better seeing eye (Figure 22), unilateral worsening visual acuity 20/50 or worse (Figure 23) and bilateral worsening visual acuity 20/50 or worse (Figure 24).

**Figure 21. Probability of Definite Worsening Visual Acuity in the Worse Eye by Cycle 1 ADC C<sub>tau</sub> (Trial 205678)**



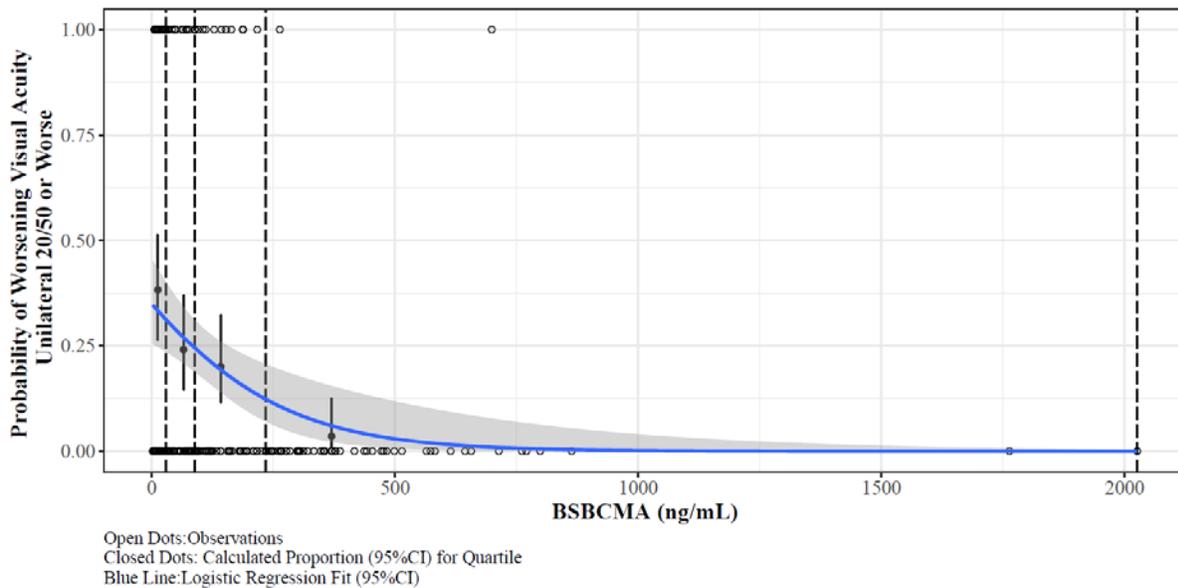
Source: Applicant's Responses to FDA Clinical Pharmacology Request on May 05, 2020, Figure Q.3.3.

**Figure 22. Probability of Definite Worsening Visual Acuity in the Better Eye by Baseline sBCMA (Trial 205678)**



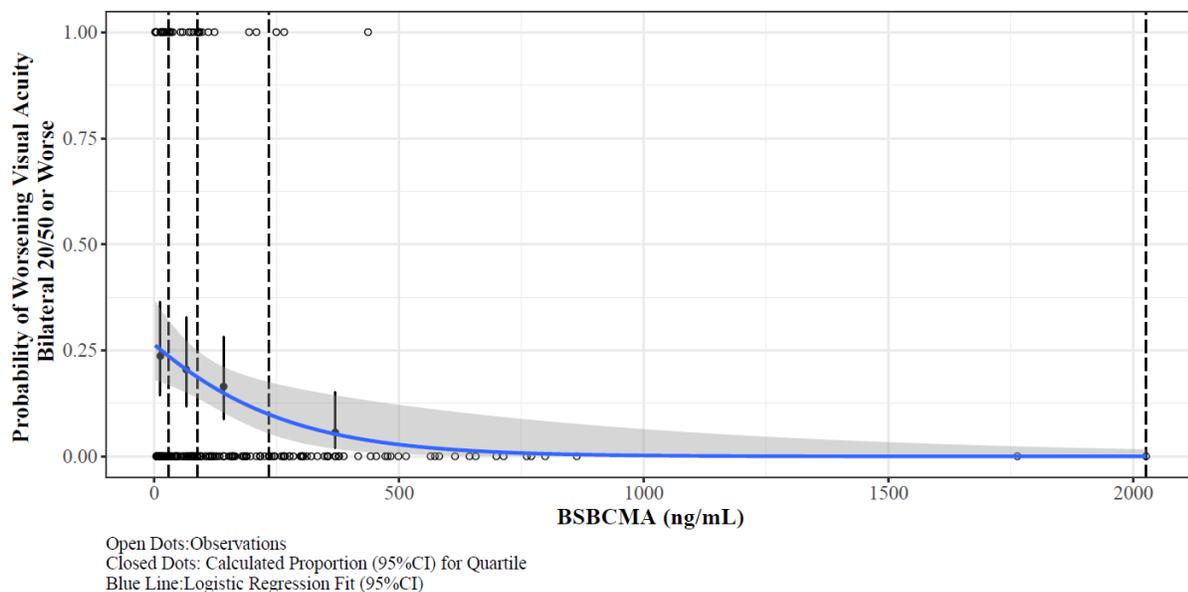
Source: Applicant's Responses to FDA Clinical Pharmacology Request on May 05, 2020, Figure Q.3.5.

**Figure 23. Probability of Unilateral Worsening Visual Acuity 20/50 or Worse by Baseline sBCMA (Trial 205678)**



Source: Applicant's Responses to FDA Clinical Pharmacology Request on May 05, 2020, Figure Q.3.20.

**Figure 24. Probability of Bilateral Worsening Visual Acuity 20/50 or Worse by Baseline sBCMA (Trial 205678)**

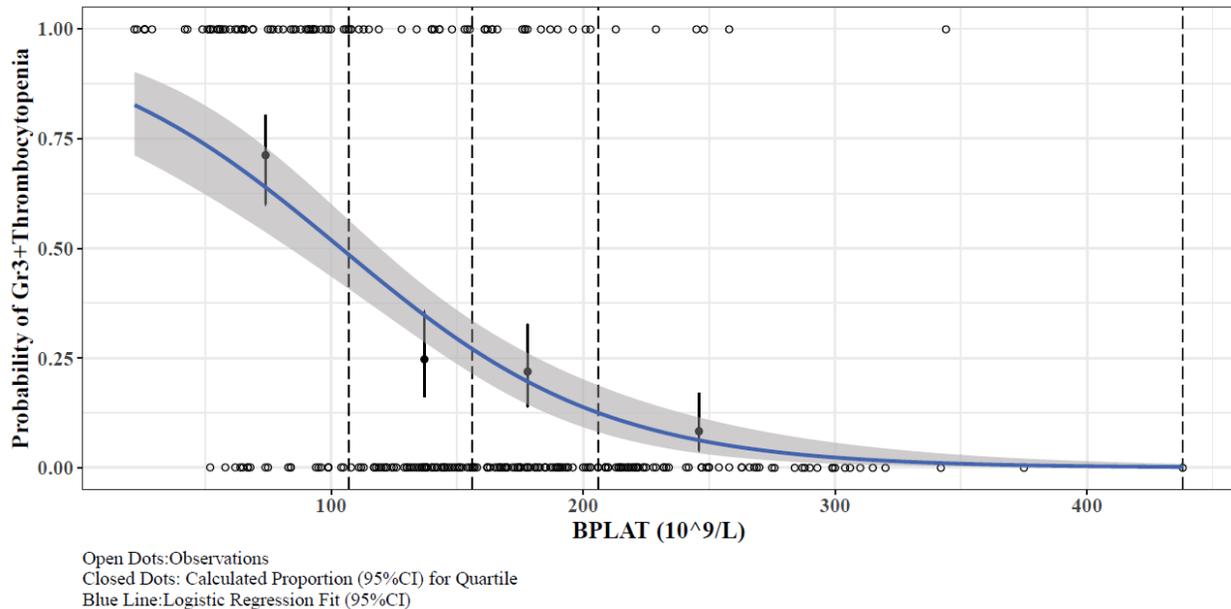


Source: Applicant's Responses to FDA Clinical Pharmacology Request on May 05, 2020, Figure Q.3.21.

After adjusted by baseline sBCMA, there was no significant relationship between belantamab mafodotin  $C_{tau}$  at Cycle 1 and definite worsening visual acuity in the better eye, unilateral worsening visual acuity 20/50 or worse or bilateral worsening visual acuity of 20/50 or worse.

Regarding the other safety measures, the Applicant’s multivariate analyses showed that the probability of grade 3+ thrombocytopenia was inversely related to baseline platelet count (Figure 25), while no covariates were found to explain the probability of grade 3+ neutropenia or infusion related reaction in cycle 1.

**Figure 25. Probability of Grade 3+ Thrombocytopenia Stratified by Quartile of Baseline Platelet Count (Trial 205678 and BMA117159)**



Source: Applicant’s Population PK and Exposure-Response Analyses Report, Figure 11.3.4.3.1.

**The FDA’s Assessment:**

The Applicant’s E-R analyses for both efficacy and safety endpoints appear acceptable. The Reviewer’s independent analyses for grade 2+ corneal event yield similar results to the Applicant’s, while the Reviewer’s analysis for grade 3+ corneal event retained ADC C<sub>tau</sub>, baseline sBCMA and history of dry eye as the significant predictors at a P value of < 0.05 (Table 58).

**Table 58. Probability of Grade 3+ Corneal Event using GSK Scale – Logistic Regression Analysis Multivariate Results with Cycle 1 ADC C<sub>TAU</sub> (Trial 205678)**

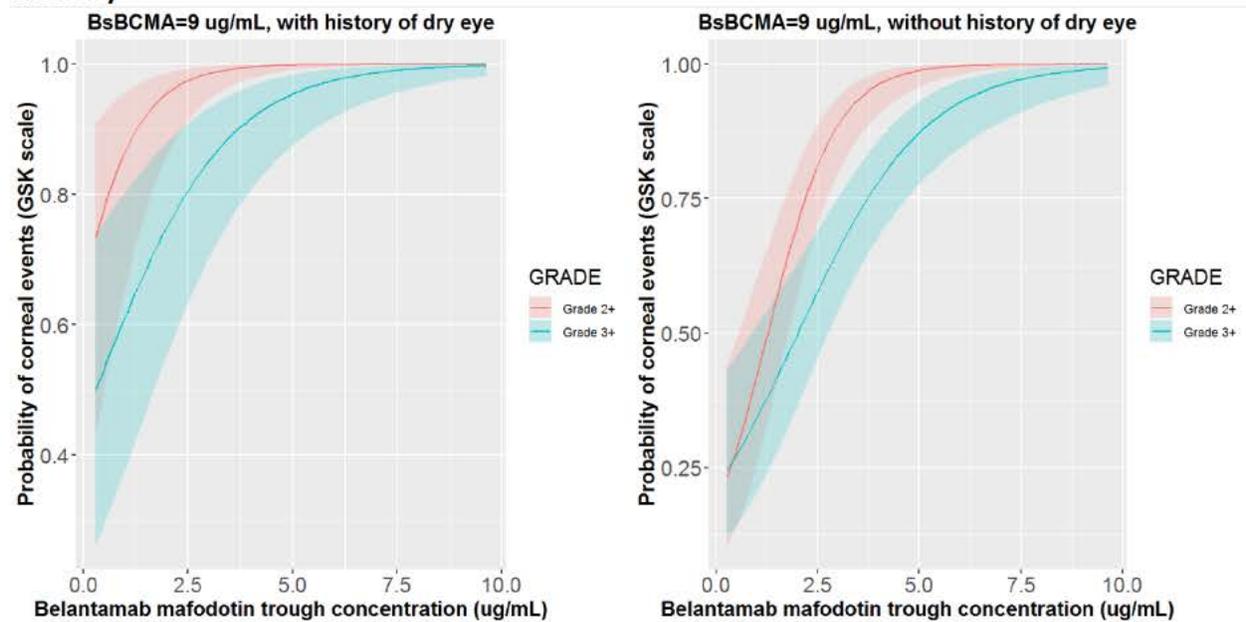
Parameter	Estimate	SE	95% CI	Z value	P value
Intercept ( $\beta_0$ )	-1.25	0.471	(-2.17, -0.325)	-2.65	$8.04 \times 10^{-3}$
CTAUA	0.64	0.129	(0.391, 0.898)	4.99	$6.19 \times 10^{-7}$
BSBCMA	-0.00534	0.00138	(-0.00804, -0.00264)	-3.88	$1.06 \times 10^{-4}$
HISTDRYEYE	1.11	0.446	(0.237, 1.99)	2.49	$1.27 \times 10^{-2}$

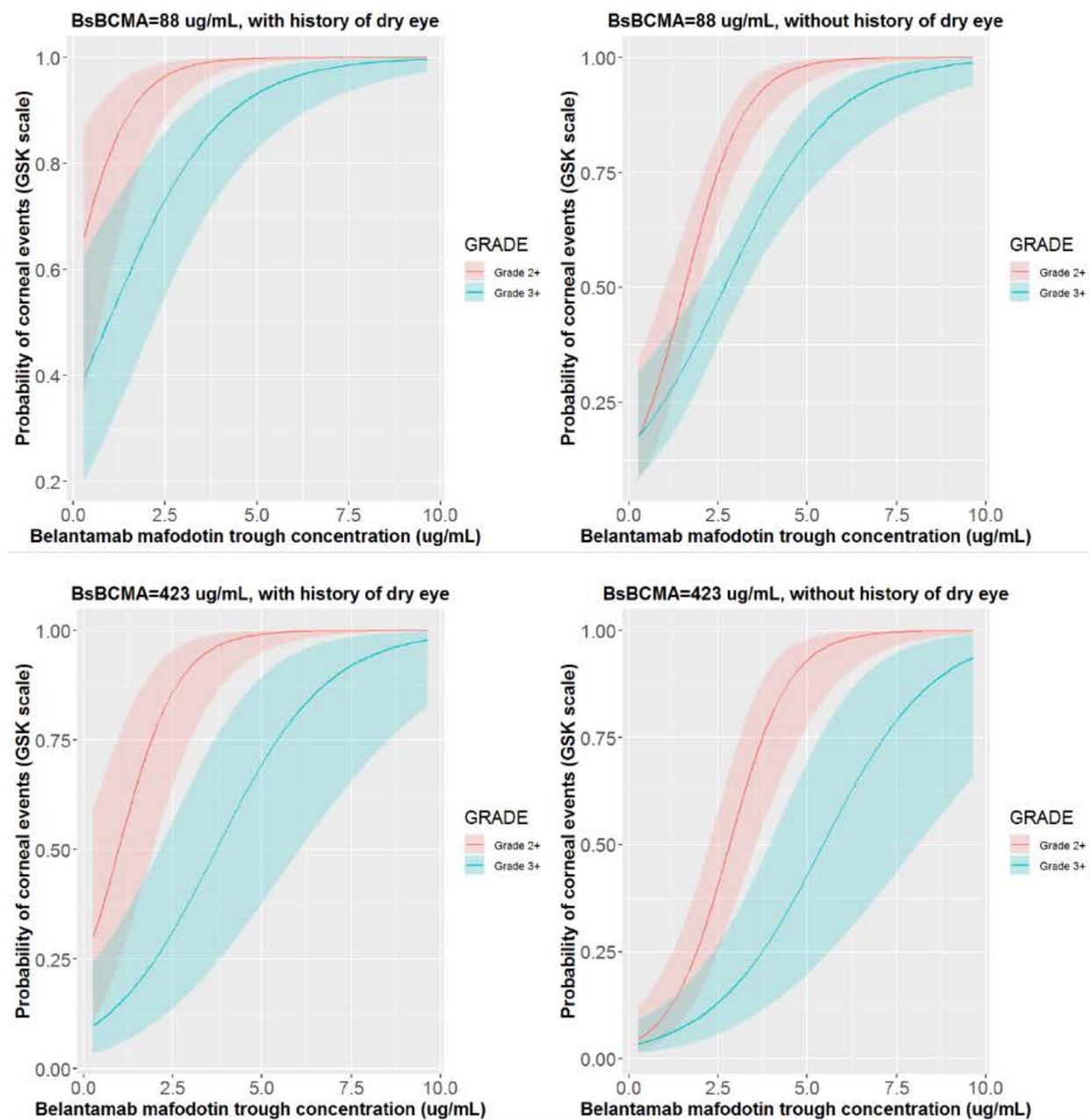
**Logistic Regression**  
 $\ln(p/(1-p)) = \beta_0 + \beta_{CTAUA} \cdot CTAUA + \beta_{BSBCMA} \cdot BSBCMA + \beta_{HISTDRYEYE} \cdot HISTDRYEYE$   
 BSBCMA = baseline soluble BCMA, CTAUA = ADC trough concentration; HISTDRYEYE= history of dry eye, SE = standard error.

Source: FDA’s analysis.

Based on reviewer's model, simulations were conducted to illustrate the E-R relationships for probability of grade 2+ or 3+ corneal event by Cycle 1 ADC  $C_{tau}$  in patients with or without history of dry eye at different baseline sBCMA, e.g., 9 ng/mL, 88 ng/mL and 423 ng/mL, representing 10%, 50% and 90% percentile of observed baseline sBCMA in Trial 205678. As shown in Figure 26, patients with history of dry eye tended to have higher probability of grade 2+ or 3+ corneal event. Further, patients with lower baseline sBCMA tended to have higher probability of grade 2+ or 3+ corneal event as compared to patients with higher baseline sBCMA.

**Figure 26. Probability of Grade 2+ and Grade 3+ Corneal Event using GSK Scale by Cycle 1 ADC  $C_{tau}$  in Patients with or without History of Dry Eye at Different Levels of Baseline sBCMA (Trial 205678)**





Source: FDA's analysis.

Therefore, additional information on belantamab mafodotin at lower doses or alternative regimens is needed to be incorporated in the E-R analyses for the determination of the optimal dosing regimen that will mitigate the risk of corneal toxicity without clinically significant impact on efficacy, especially in patients with history of dry eye and low baseline sBCMA.

## 20.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not applicable.

## 20.6. Clinical Appendices

### 20.6.1. Preferred Term Grouping

The following grouped preferred terms were utilized in the FDA safety analyses:

Any ocular symptoms: Diplopia, dry eye, eye irritation, eye pain, eye pruritus, foreign body sensation in eyes, lacrimation increased, ocular discomfort, ocular hyperemia, photophobia, vision blurred, visual acuity reduced, and visual impairment

Vision blurred: Vision blurred, diplopia, visual acuity reduced, and visual impairment

Fatigue: Fatigue and asthenia

Dry eye: Dry eye, ocular discomfort, and eye pruritus

Upper respiratory tract infection: Upper respiratory tract infection, nasopharyngitis, rhinovirus infection, and sinusitis

Cough: Cough and upper-airway cough syndrome

Pneumonia: Pneumonia, lung infection, and herpes simplex pneumonia

Sepsis: Sepsis, Staphylococcal bacteremia, and Staphylococcal sepsis

Hypertension: Hypertension and blood pressure increased

**BLA 761158 BLENREP (belantamab mafodotin-blmf)  
Multidisciplinary Review Signatures**

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Regulatory Project Manager	Wanda Nguyen, PharmD	ORO/DROOD	Sections: 3	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Wanda I. Nguyen -S	<small>Digitally signed by Wanda I. Nguyen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1.2001031724, cn=Wanda T. Nguyen -S Date: 2020.07.31 08:20:51 -0400</small>		
Nonclinical Reviewer	Natalie Simpson, PhD	OOD/DHOT	Sections: 5	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Natalie Simpson -S	<small>Digitally signed by Natalie Simpson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1.2000576562, cn=Natalie Simpson -S Date: 2020.07.29 10:52:15 -0400</small>		
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Brenda Gehrke -S	<small>Digitally signed by Brenda Gehrke -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1.0012062023 Date: 2020.07.29 12:22:36 -0400</small>		
Nonclinical Team Deputy Director (DHOT)	Haleh Saber, PhD	OOD/DHOT	Sections: 5,15	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Haleh Saber -S	<small>Digitally signed by Haleh Saber -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Haleh Saber -S, 0.9.2342.19200300.100.1.1.1300212858 Date: 2020.07.29 12:46:26 -0400</small>		
Clinical Pharmacology Reviewer	Guoxiang Shen, PhD	OCP/DCP	Sections: 6	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Guoxiang Shen -S	<small>Digitally signed by Guoxiang Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guoxiang Shen -S, 0.9.2342.19200300.100.1.1.2001813955 Date: 2020.07.29 10:54:20 -0400</small>		
Clinical Pharmacology Team Leader	Olanrewaju Okusanya, PharmD, MS	OCP/DCP	Sections: 6	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Olanrewaju Okusanya -S	<small>Digitally signed by Olanrewaju Okusanya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23.2.19200300.100.1.1-200110838, cn=Olanrewaju Okusanya -S Date: 2020.07.29 11:3:39 -0400</small>		
Pharmacometrics Reviewer	Liang Li, PhD	OCP/DPM	Sections: 6	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Liang Li -S	<small>Digitally signed by Liang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Li -S, 0.9.2342.19200300.100.1.1.2001459144 Date: 2020.07.29 11:02:57 -0400</small>		
Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 6	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Lian Ma -S	<small>Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1.2000263335 Date: 2020.07.29 11:51:18 -0400</small>		
Clinical Pharmacology Division Director (OCP)	Brian Booth, PhD	OCP/DCP	Sections: 6, 16	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Brian P. Booth -S	<small>Digitally signed by Brian P. Booth -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brian P. Booth -S, 0.9.2342.19200300.100.1.1.1300137436 Date: 2020.07.29 12:53:35 -0400</small>		

**BLA 761158 BLENREP (belantamab mafodotin-blmf)**

**Assessment Aid Signatures**

Clinical Reviewer	Andrea Baines, MD, PhD	OOD/DHMII	Sections: 1, 4, 7, 8, 9, 10, 11, 13, 14, 20	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Andrea C. Baines -S <small>Digitally signed by Andrea C. Baines -S            DN c US, o U.S. Government, ou HHS,            ou FDA, ou People,            0.9.2342.19200300.100.1.1 0010815242,            on Andrea C. Baines -S            Date 2020.07.29 11 05 37 -04'00'</small>			
Clinical Reviewer	Rachel Ershler, MD	OOD/DHMII	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 12	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Rachel E. Ershler -S <small>Digitally signed by Rachel E. Ershler -S            DN c US, o U.S. Government, ou HHS,            ou FDA, ou People,            0.9.2342.19200300.100.1.1 2000729909,            on Rachel E. Ershler -S            Date 2020.07.29 11 10 42 -04'00'</small>			
Statistical Reviewer	Qing Xu, PhD	OB/DBIX	Sections: 7, 8	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature:</b> Qing Xu -S <small>Digitally signed by Qing Xu -S            DN c US, o U.S. Government, ou HHS,            ou FDA, ou People, on Qing Xu -S,            0.9.2342.19200300.100.1.1 1300431183            Date 2020.07.29 11 17 51 -04'00'</small>			
Statistical Team Leader	Yu-Te Wu, PhD	OB/DBIX	Sections: 8	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Yute Wu -S <small>Digitally signed by Yute Wu -S            DN c US, o U.S. Government, ou HHS,            ou FDA, ou People, on Yute Wu -S,            0.9.2342.19200300.100.1.1 1300399006            Date 2020.07.29 11 47 15 -04'00'</small>			
Division Director (OB)	Thomas Gwise, PhD	OB/DBIX	Sections: 8, 17	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Thomas E. Gwise -S <small>Digitally signed by Thomas E. Gwise -S            DN c US, o U.S. Government, ou HHS,            ou FDA, ou People,            0.9.2342.19200300.100.1.1 1300369224,            on Thomas E. Gwise -S            Date 2020.08.03 11 59 17 -04'00'</small>			
Associate Director of Labeling	Stacy Shord, PharmD	OOD/DHMII	Sections: 12	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Stacy Shord -S <small>Digitally signed by Stacy Shord -S            DN c US, o U.S. Government, ou HHS,            ou FDA, ou People, on Stacy Shord -S,            0.9.2342.19200300.100.1.1 2000356537            Date 2020.07.29 13 18 59 -04'00'</small>			
Cross-Disciplinary Team Leader (CDTL)	Bindu Kanapuru, MD	OOD/DHMII	Sections: All	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Bindu Kanapuru -S <small>DN c US, o U.S. Government, ou HHS,            ou FDA, ou People, on Bindu Kanapuru -S,            0.9.2342.19200300.100.1.1 0012593628            Date 2020.07.31 08 33 55 -04'00'</small>			
Division Director (Clinical)	Nicole Gormley, MD	OOD/DHMII	Sections: All	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Nicole J. Gormley -S <small>Digitally signed by Nicole J. Gormley -S            DN c US, o U.S. Government, ou HHS,            ou FDA, ou People,            0.9.2342.19200300.100.1.1 0012754803,            on Nicole J. Gormley -S            Date 2020.07.29 12 18 07 -04'00'</small>			
Office Director or signatory	Marc Theoret, MD	OOD	Sections:	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> See appended signature page below.			

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MARC R THEORET  
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