Oncologic Drugs Advisory Committee (ODAC) Meeting

July 14, 2020

BLA# 761158

Drug Name: Belantamab Mafodotin

Applicant: GlaxoSmithKline Intellectual Property Development Ltd. England

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug belantamab mafodotin BLA 761158 to this Oncology Drugs Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

TABLE OF CONTENTS

List of Tables

List of Figures

GLOSSARY

Abbreviation	Definition
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
BCMA	B-cell maturation antigen
BCVA	Best corrected visual acuity
BLA	Biologics License Application
BTD	Breakthrough Therapy Designation
CBR	Clinical benefit rate
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
C_{tau}	Trough concentration
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaires Core 30
ETASU	Elements to assure safe use
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
HCEC	Human corneal epithelial cells
HRQoL	Health-related quality of life
IgG	Immunoglobulin G
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
IRR	Infusion-related reaction
ISS	International Staging System
IV	Intravenous
KVA	Keratopathy and Visual Acuity
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mc	Maleimidocaproyl
MEC	Microcyst-like epithelial change
MMAF	Monomethyl auristatin F
MR	Minimal response
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PR	Partial response
PRO	Patient-reported outcome
Q3W	Every 3 weeks
QoL	Quality of life
REMS	Risk Evaluation and Mitigation Strategy
RRMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
sBCMA	Soluble B-cell Maturation Antigen
SD	Stable disease
USPI	U.S. Prescribing Information
VGPR	Very good partial response
WCPB	Worst case post-baseline

1 INTRODUCTION

This briefing document presents results from the ongoing Study 205678 (DREAMM-2) as of the data cut-off of June 21, 2019 (6-month data cut-off), and updated efficacy and safety data based on the data cut-off of September 20, 2019 (9-month data cut-off). This briefing document includes the Applicant's position followed by the FDA's position as a new pilot format to reduce redundancy and improve readability.

1.1 Applicant Proposed Indication

Belantamab mafodotin is a B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate 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.

1.2 Purpose of the Meeting

The FDA's Position

The purpose of this meeting is to discuss (a) 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 (b) the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

Despite significant advances in the treatment of multiple myeloma (MM) in recent decades, it is not considered curable, and most patients will eventually relapse and are likely to develop refractory disease. Patients who become refractory to the major classes of available anti-myeloma therapies have poor outcomes. The Applicant submitted the results of the DREAMM-2 study to support its marketing application. DREAMM-2 was an open-label, multicenter study evaluating two doses of belantamab mafodotin in patients with relapsed/refractory multiple myeloma (RRMM). Patients were randomized 1:1 to receive either 2.5 mg/kg or 3.4 mg/kg of belantamab mafodotin. Patients in the DREAMM-2 trial were heavily pretreated with 50% receiving 7 or more lines of therapy including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. FDA agrees that the overall response rate (ORR) of 31% as assessed by an Independent Review Committee in DREAMM-2 with the 2.5 mg/kg belantamab mafodotin dose, with the reported duration of response, may be beneficial in this heavily pretreated population.

The key safety issue with belantamab mafodotin is ocular toxicity, including keratopathy (changes in the corneal epithelium) and changes in visual acuity assessed by ocular examinations, and symptoms of blurred vision and dry eyes.

The ocular toxicity as reported in the DREAMM-2 study with belantamab mafodotin is a unique toxicity among anti-myeloma agents.

- Ocular toxicity of 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.
- The incidence of ocular toxicities did not differ substantially between the lower 2.5 mg/kg dose and the 3.4 mg/kg dose in the DREAMM-2 study.

- 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.

The ocular toxicity with belantamab mafodotin has not been fully characterized.

- The primary mitigation strategy is dose modifications, including dose delays and dose reductions implemented based on ocular examination findings prior to each cycle of belantamab mafodotin. There are no therapeutic strategies identified to mitigate the ocular toxicity with belantamab mafodotin.
- Despite implementing dose modifications, ocular toxicities were recurrent and persistent. A high proportion of patients had keratopathy that was unresolved as of the last follow-up.
- Given the incomplete characterization of reversibility, there is uncertainty whether the dose modification strategy proposed is sufficient to mitigate the risk of ocular toxicity with belantamab mafodotin.

The concerns and uncertainties regarding the ocular toxicities raises questions about the overall benefit-risk profile of the belantamab mafodotin in the proposed patient population.

The FDA seeks input from the committee on whether the demonstrated benefit of belantamab mafodotin outweighs the risks in the proposed patient population with multiple myeloma.

1.3 Background

The Applicant's Position

Multiple myeloma, an incurable plasma cell malignancy, is the second most common hematological malignancy. Despite significant improvement in treatment outcomes with the introduction of novel therapies, most patients will relapse and become refractory to available treatments. Treatment for these patients with relapsed or refractory multiple myeloma (RRMM) is complex and there remains no consensus on a clear treatment algorithm (Mikhael, 2019). While treatment for RRMM is individualized according to patient- and disease-related factors, the same drug classes as previous lines of therapy are often reused, and with each subsequent relapse the progression-free survival is reduced. Inevitably, patients with RRMM become resistant to current standard of care options (proteasome inhibitors [PIs], immunomodulatory agents, and monoclonal antibodies [mAbs]) (Mikhael, 2020). Consequently, outcomes from studies in patients with RRMM demonstrate a particularly unfavorable prognosis with currently available treatments (median progression-free survival [PFS]: 3.4 months; and median overall survival [OS]: 6–9 months [Chari, 2019; Gandhi, 2019; Lonial, 2016; Lonial, 2020; Pick, 2018]). Specifically, in the last line of therapy for RRMM only one combination regimen of selinexor plus dexamethasone is approved which offers responses of 26.2% in patients with a median duration of response (DoR) of 4.4 months (Chari, 2019). Given the limited benefit with available therapies and the complex disease biology in the relapsed/refractory setting, therapies that target alternative disease pathways, and provide additional benefits, are required. Belantamab mafodotin is a first-in-class antibody drug

conjugate (ADC) with an afucosylated, humanized anti-B-cell maturation antigen (BCMA) mAb conjugated to a microtubule disrupting agent, monomethyl auristatin F (MMAF). Belantamab mafodotin offers a highly specific targeting mechanism for myeloma cells by binding to BCMA, thus killing myeloma cells via a multi-modal mechanism of action that induces long-term responses.

The FDA's Position

In general, FDA concurs with the Applicant's description of potential treatments for MM.

The FDA disagrees with the Applicant's statement that belantamab mafodotin offers a highly specific targeting mechanism for myeloma cells. Belantamab mafodotin will target any hematopoietic cell that expresses BCMA, including myeloma cells. Belantamab mafodotin is an antibody drug conjugate (ADC) that targets myeloma cells by binding to BCMA, thus killing myeloma cells through MMAF-induced apoptosis, as well as by tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Due to the short duration of follow-up on the study, whether or not belantamab mafodotin induces long-term responses is still under review.

1.4 Proposed Indication and Product Description

1.4.1 Proposed Indication and Dosing

GlaxoSmithKline (GSK) is seeking accelerated approval of belantamab mafodotin for the treatment of adult patients with RRMM who have received at least 4 prior therapies including an anti-CD38 antibody, a PI, and an immunomodulatory agent (triple-class refractory multiple myeloma).

The recommended dosage for belantamab mafodotin is 2.5 mg/kg administered via intravenous (IV) infusion over approximately 30 minutes, every 3 weeks (Q3W). The pivotal Phase 2 study, DREAMM-2, included a 2.5 mg/kg and 3.4 mg/kg dose of belantamab mafodotin. Additional details on dose selection are in Section 5.1. This briefing document focuses on data from the 2.5 mg/kg dose, with data from the 3.4 mg/kg dose presented when relevant.

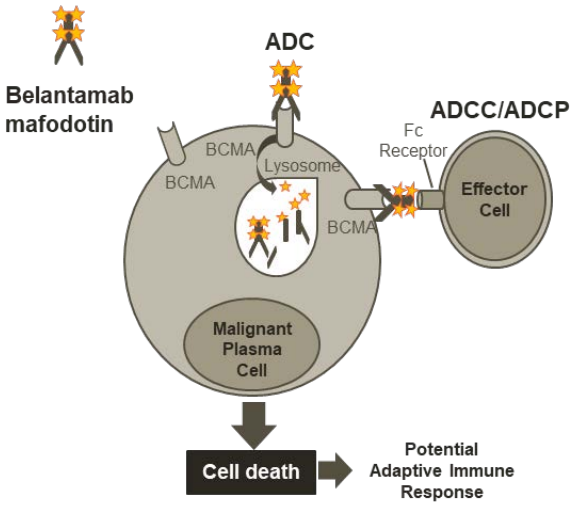
1.4.2 Belantamab Mafodotin Product Overview and Mechanism of Action

All multiple myeloma cells express BCMA, a cell-surface receptor that is a member of the tumor necrosis factor receptor family. BCMA is expressed on the surface of all normal plasma cells and late stage B cells, as well as on malignant cells in all patients with multiple myeloma. BCMA promotes the maturation and long-term survival of normal plasma cells and is also essential for proliferation and survival of malignant plasma cells in multiple myeloma. This target is specific to the lymphoid line and is not present in other organs. Thus, BCMA is an ideal therapeutic target specific to multiple myeloma cells.

Belantamab mafodotin is an ADC with an afucosylated, humanized anti-BCMA mAb conjugated to a microtubule disrupting agent, MMAF. Upon binding to BCMA, belantamab mafodotin is internalized into the myeloma cells followed by intracellular release of cys-maleimidocaproyl (mc) MMAF via proteolytic cleavage. The released cys-mcMMAF intracellularly disrupts the microtubule network, leading to cell cycle arrest, apoptosis, and release of immunogenic cell death markers that can stimulate immune cells. Belantamab mafodotin has antitumor activity in multiple myeloma cells and mediates killing of tumor cells through MMAF-induced apoptosis, as well as by immune-mediated tumor cell lysis through antibody-dependent cellular

cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) driven by effector cells which lyse target cells (Figure 1) (Tai, 2014; Montes De Oca, 2019). This multimodal MoA has the potential to lead to the induction of deep and durable clinical responses.

Figure 1: Belantamab Mafodotin Mechanism of Action



ADC=Antibody drug conjugate; ADCC/ADCP=antibody-dependent cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis
Source: Clinical Overview m2.5 Figure 2 (m2.4 NCO, Section 2.1.7)

The FDA's Position

In general, FDA concurs with the Applicant's description of nonclinical data to support the mechanism of action of belantamab mafodotin. The mechanisms described by the Applicant are commonly observed with ADCs. Toxicities secondary to the inflammatory responses observed in animals and patients are consistent with MMAF-containing ADCs.

1.4.3 Drug Product

Belantamab mafodotin was initially supplied as a frozen liquid for use in clinical trials. For commercialization, a lyophilized (freeze-dried) presentation of 100 mg/vial has been developed for which easy-to-use refrigerated storage at 2°C to 8°C is supported.

The intended commercial product has been demonstrated to be comparable to the frozen liquid presentation of belantamab mafodotin which was received by most patients in the clinical trials supporting Biologics License Application (BLA) 761158. Comparability was demonstrated by an extensive analytical package conducted in compliance with ICH Q5E (Comparability of Biotechnological/Biological Products) to support in vivo equivalence. From the patient perspective, both presentations of the drug product belantamab mafodotin are essentially identical upon dilution for IV administration. Supportive clinical experience with the intended commercial product in DREAMM-2 is summarized in the Appendix, Section 9.2.

The FDA's Position:

The FDA concurs with the Applicant's position regarding the drug product.

1.4.4 Clinical Pharmacology

Belantamab mafodotin has dose-proportional pharmacokinetics, with a time-dependent decrease in clearance. Maximum concentrations of belantamab mafodotin were observed at or

shortly after the end of infusion. There was limited accumulation (less than 2-fold) of belantamab mafodotin during subsequent cycles. Belantamab mafodotin had a systemic clearance of 0.92 L/day, a steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days after the first dose in DREAMM-2. Over 2 to 3 months after the start of treatment, clearance was reduced to 0.72 L/day with an elimination half-life of 14 days.

The FDA's Position

The FDA agrees with the general clinical pharmacology properties of belantamab mafodotin (ADC). However, due to the correction of bioanalytical method for cys-mcMMAF (payload) at a late stage of development, the number of cys-mcMMAF bioanalytical samples validated by available long-term storage stability data is not sufficient for characterizing pharmacokinetics of cys-mcMMAF or conducting any exposure-response analysis. Therefore, FDA does not concur with the Applicant's statement about exposure-response relationship for cys-mcMMAF in Section 5.1.

1.4.5 Regulatory and Development History

Belantamab mafodotin was granted Breakthrough Therapy Designation (BTD) on 15 November 2017 for the treatment of patients with multiple myeloma who have failed at least three prior lines of therapy, including an anti-CD38 mAb, and are refractory to a PI and an immunomodulatory agent. The BTD was granted based on an overall response rate (ORR) of 38% (95% confidence interval [CI]: 13.9, 68.4) and median duration of response (DoR) of 6.7 months (95% CI: 5.3, not estimable) with 3.4 mg/kg Q3W in the subgroup of designated population (in the DREAMM-1 Phase 1 study; first-in-human trial BMA 117159).

Based on the findings from DREAMM-1, the pivotal Phase 2, open-label DREAMM-2 study was designed to evaluate the efficacy and safety of belantamab mafodotin monotherapy in patients with RRMM who had 3 or more prior lines of treatment, were refractory to a PI and an immunomodulatory agent, and had failed treatment with an anti-CD38 antibody. The design of DREAMM-2, including treatment groups, endpoints, and the historical control comparator of 15% ORR, was discussed with the FDA.

The current proposed indication specifies at least 4 prior lines of therapy because 95% of patients who participated in the DREAMM-2 2.5 mg/kg cohort received at least 4 prior lines of treatment.

The totality of evidence from the pivotal DREAMM-2 study, supported by the data from DREAMM-1, forms the basis of GSK's BLA that was submitted under accelerated approval regulations. A randomized Phase 3 confirmatory study, DREAMM-3, is currently ongoing to compare belantamab mafodotin with a pomalidomide/dexamethasone combination therapy in patients with RRMM who have received 2 or more prior lines of treatment. Primary endpoint readout for DREAMM-3 study is projected for 2H 2022. Additional details on this confirmatory study are provided in Section 5.2.

The FDA's Position

The DREAMM-3 study and other potential study designs are still under FDA review.

2 EFFICACY

2.1 Description of Clinical Setting

The Applicant's Position

2.1.1 Description of the Disease Setting

2.1.1.1 Overview of Multiple Myeloma

Multiple myeloma is a hematologic cancer that forms in plasma cells. Multiple myeloma is the second most common hematologic malignancy and accounts for 1.8% of all cancers and 10% of all hematologic malignancies (Rajkumar, 2009; NCI SEER, 2019). In 2019, it was estimated that 32,110 new cases of multiple myeloma and about 12,960 multiple myeloma-related deaths would occur in the US (NCI SEER, 2019). The overall 5-year survival rate is 52% (NCI SEER, 2020).

2.1.1.2 Prognosis of Relapsed/Refractory Multiple Myeloma (RRMM)

Despite significant improvement in treatment outcomes, most patients with multiple myeloma will eventually relapse and become refractory to available treatments (Sonneveld, 2017). Most patients experience serial relapse and will be treated with most available agents at some point during their disease course. Initial treatment for multiple myeloma typically includes PIs, immunomodulators, and anti-CD38 mAbs. As previously noted, outcomes from studies in patients with RRMM who become resistant to current standard of care options indicate that these patients have a particularly unfavorable prognosis with currently available treatments (median PFS: 3.4 months; and median OS: 6–9 months) (Chari, 2019; Gandhi, 2019; Lonial, 2020; Pick, 2018).

At present, there is no clear consensus on treatment for patients with RRMM (Mikhael, 2019). Instead, treatment is individualized based on several patient-, treatment- and disease-related factors, and the same drugs are being re-used. Lines of therapy are added, and each subsequent line of therapy has the potential to increase the life span of the patient. Patients ultimately become refractory to available treatments and run out of options. In the last line of therapy for RRMM, there is only 1 approved combination regimen of selinexor plus dexamethasone available for patients (Chari, 2019); (XPOVIO™ USPI). Quality of life (QoL) for patients with RRMM deteriorates with each relapse and subsequent line of therapy (Baz, 2015), particularly due to the debilitating effects of the disease and side effects of existing therapies (see Section 2.1.1.3). Therefore, there remains a significant unmet need for new therapeutic options, particularly those with mechanisms of action that would be able to overcome resistance to currently available drugs, induce longer duration of clinical responses, offer a different safety profile, and ultimately add to patient survival time at maintained QoL.

2.1.1.3 Treatment Options for Multiple Myeloma Refractory to Anti-CD38 mAbs, Immunomodulatory Agents, and PIs

To date, 12 drugs have been approved for the treatment of patients with multiple myeloma in the US, 5 of which have one of their approved indications in patients with RRMM who have received at least 3 prior therapies.

Table 1 shows products that have received Accelerated Approval for the treatment of patients with RRMM. These products, which were investigated in patients with a median of 5–7 prior lines of therapy, showed ORRs ranging from 23–31% and DoR ranging from 4.4–7.8 months

(Richardson, 2014; Siegel, 2012; Usmani, 2016).

The most frequent Grade≥3 adverse events (AEs) reported were hematologic AEs, including neutropenia, anemia, and thrombocytopenia. Specific treatment-related AEs are also associated with these agents, including renal toxicity with pomalidomide and carfilzomib; cardiac toxicity with carfilzomib; and infusion-related reactions (IRRs) with daratumumab (Ludwig, 2018).

Table 1: Multiple Myeloma Treatments with Accelerated Approval

	Treatment	N	Median Lines of Therapy	ORR (%)	Median DoR	Overall Survival	Grade ≥3 AEs, %
Relapsed or Refractory to PI + Immuno-modulator	Pomalidomide/dex[1]	113	5	33.0%	8.3 months	16.5 months	Neutropenia (41) Anemia (22) Pneumonia (22) Thrombocytopenia (22)
	Carfilzomib[2]	257	5	23.7%	7.8 months	15.6 months	Anemia (24) Thrombocytopenia (29) Neutropenia (11) Acute renal failure (3.4)
	Daratumumab[3]	148	5	31.1%	7.6 months	20.1 months	Anemia (17.6) Thrombocytopenia (14.2) Neutropenia (10.1)
Refractory to PI, Immuno-modulator, anti-CD38	Selinexor/dex[4]	122	7	26.2%	4.4 months	8.6 months	Thrombocytopenia (58.5) Anemia (43.9) Neutropenia (21.1)

1. Richardson, 2014; 2. Siegel, 2012; 3. Usmani 2016; 4. Chari, 2019

Only the recently approved selinexor/dexamethasone regimen has been studied in patients whose disease was refractory to anti-CD38 mAbs, PIs, and immunomodulatory agents. As the only approved combination regimen in the last line of therapy for RRMM, selinexor plus dexamethasone offers an ORR of 26% with a median DoR of 4.4 months and OS of 8.6 months (Chari, 2019). Overall, 18% of the patients discontinued treatment due to an AE; the most common AEs leading to dose reduction/interruption were thrombocytopenia (43%), fatigue (16%), and neutropenia (11%). The most common Grade 3/4 AEs were thrombocytopenia (59%), anemia (44%), hyponatremia (22%), and neutropenia (21%).

Additional therapies are needed for RRMM that can extend durability of response beyond 4.4 months, extend patient survival time beyond 8.6 months, and provide alternative options for patients.

The FDA's Position

The FDA concurs with the Applicant's assessment of treatment options for patients with RRMM. There continues to be an unmet medical need in patients who have received multiple lines of therapy and are refractory to the major classes of available anti-myeloma therapies. Regarding the safety profiles of available therapies described by the Applicant above, FDA notes that ocular toxicity is not a commonly reported or serious toxicity observed with the currently approved therapies for MM.

2.2 Summary of Clinical Trials Supporting Efficacy

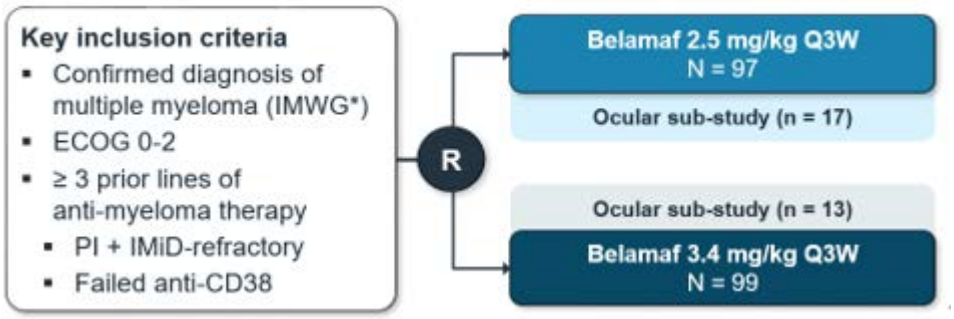
The Applicant's Position

2.2.1 Pivotal Study DREAMM-2

2.2.1.1 Study Design

DREAMM-2 is a Phase 2, open-label, randomized, two-arm, global, multicenter study conducted at 58 centers in 8 countries in patients with RRMM. Patients were randomized 1:1 to receive belantamab mafodotin 2.5 mg/kg or 3.4 mg/kg Q3W IV over approximately 30 minutes on Day 1 of each 21-day cycle, until disease progression or unacceptable toxicity, and were followed for PFS and OS (Figure 2). Patients were stratified based on number of prior lines of therapy (≤4 vs >4) and presence or absence of high-risk cytogenetic features. The study has met its primary endpoint and is still collecting long-term follow-up to further characterize the time of event endpoints (duration of response, patient survival) and safety (including resolution of corneal events).

Figure 2: DREAMM-2 Study Design



Confirmation of multiple myeloma based on International Myeloma Working Group criteria
R = randomization; Q3W = every 3 weeks; PI = proteasome inhibitor; IMiD=Immunomodulatory Agent
Source: Adapted from CSR-205678 Figure 1

The two doses of belantamab mafodotin demonstrated comparable efficacy; however, the 2.5 mg/kg dose had a more favorable safety profile (see Section 5.1). Therefore, 2.5 mg/kg is the recommended dose in the indicated population and will be the focus for the remainder of the efficacy and safety presentations. Data for the 3.4 mg/kg dose can be found in the Appendix, Section 9.3.

Since corneal events have previously been reported with other MMAF-containing antibody drug conjugates (Donaghy, 2016; Eaton, 2015) and were also observed in the preceding dose escalation study (DREAMM-1), ocular assessments were conducted for all participating patients (Appendix, Section 9.3.3). In addition, an ocular sub-study (N=17 in the 2.5 mg/kg cohort and N=13 in the 3.4 mg/kg cohort) was conducted to evaluate the effect of corticosteroid eye drops on keratopathy (corneal epithelium changes observed by ophthalmic examination) and patient-reported corneal-related symptoms.

Additionally, during the ophthalmic exam, the pre-specified Keratopathy and Visual Acuity (KVA) Scale was used to assess the following to determine appropriate dosage modifications, if any, as presented in Table 2:

- Assess the patient for corneal examination finding(s) and decline of best corrected visual acuity (BCVA).

- Determine if the decline in vision is related to examination finding(s) associated with belantamab mafodotin.
- Report the worst grade for examination finding(s) and BCVA to the treating physician.

Table 2: Dosage Modifications for Corneal Adverse Reactions

Category	Eye Examination Findings per KVA Scale	Recommended Dose Modifications
Grade 1	*Corneal examination finding(s)* Mild superficial keratopathy[a] *Change in BCVA* Decline from baseline of 1 line on Snellen score	Continue treatment at current dose.
Grade 2	*Corneal examination finding(s)* Moderate superficial keratopathy[b] *Change in BCVA* Decline from baseline of 2 or 3 lines (and Snellen score not worse than 20/200)	Withhold treatment until improvement in either corneal exam findings or BCVA and resume at current dose.
Grade 3	*Corneal examination finding(s)* Severe superficial keratopathy[c] *Change in BCVA* Decline from baseline by more than 3 lines (and Snellen score not worse than 20/200)	Withhold treatment until improvement in either corneal exam findings or BCVA to Grade 1 and resume at a reduced dose of 1.9 mg/kg.
Grade 4	*Corneal examination finding(s)* Corneal epithelial defect[d] *Change in BCVA* Snellen score worse than 20/200	Withhold until improvement in corneal exam findings and BCVA to Grade 1 and resume at a reduced dose of 1.9 mg/kg. For recurrent Grade 4 events that are unresponsive to appropriate management, consider discontinuation.

DREAMM-2 utilized a pre-specified scale, the Keratopathy and Visual Acuity scale (KVA scale) that combined examination findings (e.g., Keratopathy/MECs) with an assessment of best corrected visual acuity.

[a] Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.

[b] Moderate superficial keratopathy may be accompanied by patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

[c] Severe superficial keratopathy may be accompanied by diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

[d] Corneal epithelial defect may include corneal abrasions or ulcers. A corneal defect without stromal involvement can be managed as clinically indicated (e.g., bandage contact lens, antibiotics). Dose reductions or holds should be based on the Category, generally.

Source: 2020-05-28 draft annotated label

The FDA's Position

FDA notes that the Applicant stated 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 for some toxicities, the incidence of ocular toxicities did not differ substantially between the two dose levels (Section 3.1.1.2).

The recommended dose modifications in Table 2 above are from the draft annotated label and the dose modification guidelines used in the DREAMM-2 trial are shown in Section 9.4.1 of the Appendix.

Regarding footnote 'd' above, FDA notes that the term 'abrasions' technically means that something rubbed against the cornea to cause the injury. A more accurate statement would be corneal epithelial defect, which may include corneal defects or ulcers.

2.2.1.1.1 Key Enrollment Criteria

Patients were eligible to be included in DREAMM-2 if they met the following criteria:

- ≥18 years of age.
- an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
- Histologically or cytologically confirmed diagnosis of multiple myeloma as defined according to International Myeloma Working Group (IMWG) criteria (Rajkumar, 2015), AND:
    - Undergone autologous stem cell transplant or were considered transplant ineligible;
    - Had failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody alone or in combination, and was refractory to an immunomodulatory agent, and a proteasome inhibitor.
- Had adequate organ system function, including renal function as measured by estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, hepatic function (total bilirubin ≤1.5X ULN, ALT ≤2.5X ULN), and hematologic parameters of hemoglobin ≥8.0 g/dL , absolute neutrophil count ≥1.0 X 10^9/L and platelets ≥50 X 10^9/L.

Patients were excluded if they received prior BCMA-targeted therapies; had current corneal epithelial disease (except mild punctate keratopathy); or had any serious and/or unstable pre-existing medical condition, psychiatric disorder, or any other condition (including laboratory abnormalities) that could interfere with patients' safety, obtaining informed consent or compliance with study procedures. Patients were not excluded for other existing ophthalmologic findings or issues (e.g., cataract or visual acuity).

The FDA's Position

FDA notes that patients with mild keratopathy were not excluded from the DREAMM-2 trial. While specific estimates of the prevalence of mild keratopathy in this age group/patient population are not available, 45% of patients enrolled in DREAMM-2 had mild keratopathy evident on their baseline exam. However, FDA notes that the capture of Grade 1 events in the trial based on the KVA scale (Table 2) required a documented worsening from baseline. Therefore, a patient with mild keratopathy at baseline could have worsening of keratopathy that is a documented change from their baseline captured as a Grade 1 event.

2.2.1.1.2 Efficacy Endpoints

The primary efficacy endpoint was ORR as assessed by an Independent Review Committee (IRC), defined as the percentage of patients with a confirmed partial response (PR) or better (per IMWG criteria) (Kumar, 2016). The secondary efficacy endpoints were ORR as assessed by the investigator; clinical benefit rate (CBR), defined as percentage of patients with a minimal response (MR) or better; DoR; time to response; PFS; and OS.

2.2.1.1.3 Statistical Analyses

The trial design comparing belantamab mafodotin to historical data was discussed and agreed upon previously with FDA. In addition, no published data on efficacy outcomes in this population were 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 4th relapse (i.e., 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.

DREAMM-2 was designed as a randomized non-comparative study. Comparison with historical control ORR 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 if lower bound of two-sided 97.5% CI exceeds 15% in either cohort (i.e., no less than 24 responders for sample size of 100 in one cohort).

Results from DREAMM-2 are presented in Section 2.3.1.

The FDA's Position

The FDA generally agrees with the Applicant's description of the clinical trials used to support efficacy. 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. The applicant designed and sized the study so that the lower bound of the 97.5% CI for the ORR would exclude a historical ORR rate of 15%. FDA notes that for a single-arm study without a control arm, efficacy based on ORR rate needs to be supported by an adequate ORR magnitude and duration of response.

The secondary endpoints include CBR, DoR, time to response, PFS and OS. No hypothesis testing was performed for these endpoints. Because DREAMM-2 was not a placebo- or active-controlled study, the time-to-event endpoints are not interpretable and unlikely to constitute supportive evidence. Challenges with interpretation of time-to-event endpoints in single-arm trials 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.

2.2.2 Phase 1 Study DREAMM-1

2.2.2.1 Study Design

The supportive, first time in human DREAMM-1 study was a two-part, Phase 1 open-label, dose escalation and expansion study to investigate the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and clinical activity of single-agent belantamab mafodotin in patients with RRMM who had been pre-treated with alkylators, PI, and an immunomodulatory agent. Part 1 investigated dose levels ranging from 0.03 mg/kg to 4.6 mg/kg of belantamab mafodotin. The 3.4 mg/kg Q3W dose was selected for expansion based on safety, pharmacokinetics, and preliminary clinical activity. Part 2 was a dose expansion phase designed to further evaluate the safety and clinical activity of the recommended part 2 dose (3.4 mg/kg Q3W). For Parts 1 and 2, clinical activity was measured based on ORR as assessed by the investigator per IMWG criteria. In Part 2, a subgroup of patients had been previously treated with daratumumab, and this population was the basis of the BTD.

Results from DREAMM-1 are presented in Section 2.3.2.2.

The FDA's Position

The FDA generally agrees with the Applicant's description of the DREAMM-1 trial. 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. Only 3 patients received the 3.4 mg/kg dose in Part 1. Only 8 patients received the 2.5 mg/kg dose. Although the 3.4 mg/kg dose was originally selected as the only dose for evaluation in DREAMM-2, the protocol was amended (Amendment 1) following FDA recommendations to also evaluate the lower 2.5 mg/kg starting dose given the extent of ocular toxicity observed with the 3.4 mg/kg dose in DREAMM-1.

2.3 Efficacy Summary

The Applicant's Position

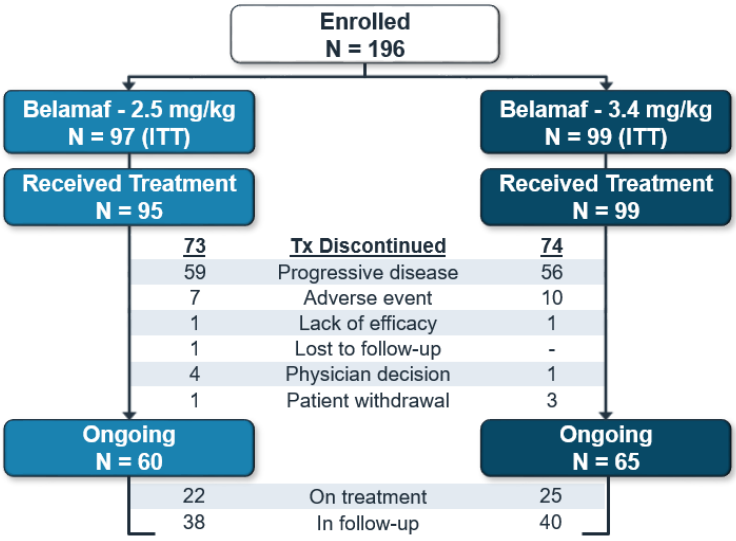
2.3.1 Pivotal Study DREAMM-2

2.3.1.1 Patient Disposition

Overall, 196 patients were enrolled, and 97 were randomized to belantamab mafodotin 2.5 mg/kg in the Intent-to-Treat population. The study was initiated on June 18, 2018, and the full enrollment of 196 patients was reached on January 3, 2019.

At the time of the primary analysis (June 21, 2019 6-month data cut-off), the majority of patients remained in the study, either with treatment ongoing (23% in the 2.5 mg/kg cohort) or in follow-up (39% in the 2.5 mg/kg cohort). Most treatment discontinuations were due to progressive disease (Figure 3).

Figure 3: DREAMM-2: Patient Disposition



ITT = intent-to-treat; TX = treatment
Source: Adapted from CSR-205678 Table 6 and Table 8 (ADSL, ADDS);
DREAMM-2, ITT Population, Cutoff date of 21JUN2019

2.3.1.1.1 Demographics and Baseline Disease Characteristics

The study population was representative of the general RRMM population, with a median age of 66 years. Patients were heavily pretreated, with a median of 7 previous lines of therapy. All

patients were refractory to immunomodulatory agents and PIs and had received a prior anti-CD38 mAb (upon analysis, all patients in the 2.5 mg/kg cohort were refractory to an anti-CD38 mAb). As expected in this advanced patient population, patients with International Staging System (ISS) stage III disease at screening (43%), extramedullary disease (23%), and high-risk cytogenetic features (27%) were well represented. Demographics and baseline characteristics for patients in the DREAMM-2 are provided in the Appendix, Section 9.3.1 in Table 26.

The FDA's Position

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

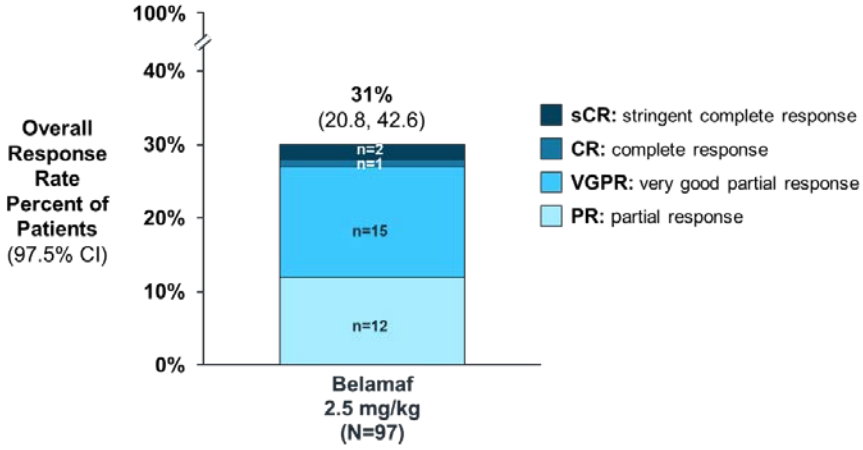
2.3.1.1.2 Efficacy Results

2.3.1.1.2.1 Primary Endpoint: IRC-Assessed Overall Response Rate (ORR)

For the primary analysis, the median follow-up was 6.3 months in 2.5 mg/kg cohort as of June 21, 2019. The ORR (PR or better as assessed by the IRC) as assessed by IRC was 31% (97.5% CI: 20.8, 42.6; Figure 4). The achieved responses were deep, with more than half of responders (60%) achieving very good partial response (VGPR) or better. Overall, the ORR as assessed by IRC was concordant with the assessment by investigators.

The median time to response was 1.4 months (95% CI: 1.0,1.6), and the median time to best response was 2.1 months (95% CI: 1.4,2.2).

Figure 4: DREAMM-2 Overall Response Rate by IRC Assessment (2.5 mg/kg Cohort)



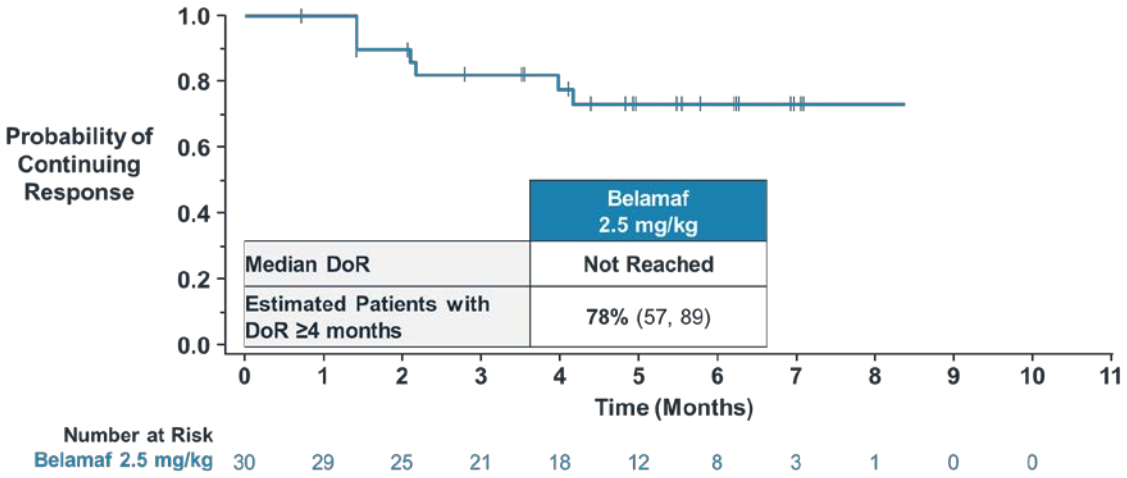
CI = confidence interval; ITT = intent-to-treat
Source: Adapted from CSR-205678 Table 17 (ADSL, ADRS); DREAMM-2, ITT Population, Cut-off date of 21JUN2019

2.3.1.1.2.2 Secondary Endpoint: Duration of Response (DoR)

At the time of data cut-off with a median follow-up of 6.3 months, the median DoR (per IRC assessment) was not reached. Further follow-up at the 9-month Update enabled better characterization of DoR (see 2.3.1.2).

Figure 5 presents the Kaplan-Meier Curve for DoR in the 2.5 mg/kg cohort.

Figure 5: DREAMM-2: Kaplan-Meier Curve of IRC-Accessed DoR (2.5 mg/kg Cohort)



Source: Adapted from CSR-205678 Table 18 and Figure 6 (ADSL, ADTTE); DREAMM-2, ITT Population, Cut-off date of 21JUN2019

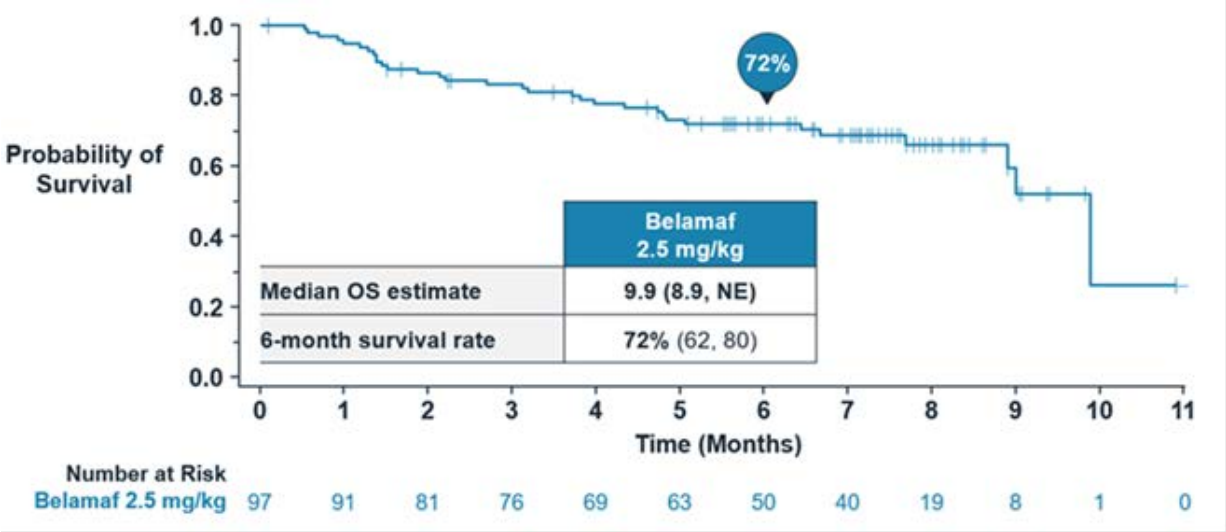
2.3.1.1.2.3 Secondary Endpoint: Progression-Free Survival (PFS)

At the time of the primary analysis, the median PFS was 2.9 months in the 2.5 mg/kg cohort. The median PFS in DREAMM-2 is aligned with the expected PFS in a heavily pre-treated RRMM patient population (Gandhi, 2019).

2.3.1.1.2.4 Secondary Endpoint: Overall Survival (OS)

The OS was not yet mature at the time of analysis. As of the data cut-off, the 6-month OS rate was 72% (95% CI: 62%, 80%) for the 2.5 mg/kg cohort (Figure 6). Like DoR, additional follow-up at the 9-month Update was needed to describe belantamab mafodotin's effect on patient survival (see 2.3.1.2).

Figure 6: DREAMM-2: Kaplan-Meier Curve of OS (2.5 mg/kg Cohort)



Source: Adapted from CSR-205678 Figure 8 (ADSL, ADTTE); DREAMM-2, ITT Population, Cutoff date of 21JUN2019

2.3.1.2 9-Month Data Update

The updated efficacy data with an additional 3 months of follow-up from DREAMM-2 are providing more clarity on durability of response and survival outcomes from belantamab mafodotin treatment and are otherwise consistent with the results of the primary analysis. The ORR remained the same (31% [97.5%CI: 20.8, 42.6]), and the median DoR has not yet been reached in the 2.5 mg/kg cohort.

To estimate the median DoR with this more mature dataset, a worst-case sensitivity analysis (assuming that all patients who were censored with follow-up ongoing would progress immediately at the next visit) was conducted, which showed the median DoR to be 9.0 months (95% CI: 4.2, 9.7), suggesting the median is at least 9 months.

As of the updated data cut-off, OS at 6 months was consistent with the primary analysis and the estimated OS rate was 72% in the 2.5 mg/kg cohort. The median OS estimate was 11.9 months in the 2.5 mg/kg cohort, although these estimates may change with a longer follow-up period.

In summary, the 9-month data Update offers a better appreciation of the durability of clinical efficacy induced by belantamab mafodotin. The estimated DoR of at least 9 months represents at least a doubling over the 4.4 month median DoR of the only approved drug combination in this population and compares favorably with the estimated median OS of 6-9 months (Gandhi, 2019). The estimated median OS of 11.9 months is approximately 3 months longer that the expected 6-9 month historical benchmark.

The FDA's Position

FDA's primary analysis and sensitivity analysis results for ORR are consistent with the results presented by the Applicant. FDA also notes that overall, the ORR as assessed by IRC was concordant with the investigator-assessed ORR. The efficacy evaluation was based on the clinical cut-off date (June 21, 2019) for the primary efficacy analysis, as pre-specified in the protocol. The 9-month data update (September 20, 2019) was mainly for the safety evaluation and additional efficacy analysis is considered exploratory.

FDA again notes that the median age of patients enrolled in DREAMM-2 was younger (65 in the 2.5 mg/kg cohort) than the median age at diagnosis of 69 years in the U.S. In addition, patients with RRMM who have received multiple lines of therapy are likely to be older than the median age at diagnosis. To understand the efficacy and safety of belantamab mafodotin in the representative older adult patient population with RRMM, FDA performed a subgroup analysis of efficacy and safety that is summarized in the Appendix (Section 9.4.5).

FDA does not agree with the Applicant's conclusions regarding OS. 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.

2.3.2 Supportive Phase 1 Study DREAMM-1

2.3.2.1 Study Population

A total of 73 patients with RRMM were enrolled into DREAMM-1 (38 in Part 1 and 35 in Part 2). As of the cut-off date of 31 August 2018, in Part 1 all patients had discontinued study treatment with 1 patient remaining in study follow-up. In Part 2, one patient continued to receive study treatment and 7 patients remained in study follow-up.

2.3.2.2 Efficacy Results

In the dose escalation part of the study (Part 1), the 3.4 mg/kg dose showed an acceptable safety profile and the highest clinical activity as all 3 patients treated at this dose responded. Therefore, the 3.4 mg/kg dose was selected as the recommended Phase 2 dose for further investigation in the dose expansion part of the study (Part 2).

The median duration of follow-up for the 35 patients in Part 2 dose expansion was 12.5 months. The ORR of the 3.4 mg/kg dose was 60% (95% CI: 42.1, 76.1), with 54% of patients achieving a VGPR or better; median DoR was 14.3 months (95% CI: 10.6, not estimable).

In the DREAMM-1 population that supported the BTD (patients with prior daratumumab and refractory to both immunomodulators and PIs [n=13]) that is similar to the population studied in DREAMM-2, the ORR was 38% (95% CI:13.9, 68.4). In addition to an ORR consistent with what was observed in DREAMM-2, the responses in this subgroup of patients were deep, with all responders achieving a VGPR or better and the median DoR was 6.7 months (95%: CI 5.3, not estimable).

The FDA's Position

The FDA generally agrees with the Applicant's assessments regarding the DREAMM-1 trial. FDA notes that only 1 out of 8 patients in the 2.5 mg/kg dose in Part 1 achieved a response (ORR 13%); responses were also observed in the lower 1.92 mg/kg (1 VGPR) and 0.96 mg/kg (1 PR) cohorts. The DREAMM-1 trial only enrolled 13 patients who were similar to the population studied in DREAMM-2. Additionally, FDA notes that although the 3.4 mg/kg dose was selected as the RP2D in DREAMM-1, there were concerns regarding the safety profile of the 3.4 mg/kg dose based on the observed ocular toxicity in the trial, which included 35 patients in total with

MM who received belantamab mafodotin at the RP2D in Part 2 (dose expansion). 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.

2.3.3 Efficacy Conclusions

In conclusion, results from the clinical development program demonstrated clinically meaningful and consistent treatment responses in patients with heavily pretreated RRMM between the DREAMM-1 and DREAMM-2 studies. At the recommended dose of 2.5 mg/kg Q3W, the ORR (PR or better as assessed by the IRC) was 31% (97.5% CI: 20.8, 42.6) in the pivotal DREAMM-2 study. Clinical responses were deep, with the majority of responders (60%) achieving a VGPR or better, and durable, with a median DoR not yet reached and estimated to be at least 9 months or longer. Median OS was estimated to be 11.9 months. Thus the durability of clinical efficacy induced by belantamab mafodotin after 9 months of follow-up compares favorably with that of other approved agents in this setting and suggest at least a doubling over the 4.4 month median DoR and an approximately 3 month extension of median OS over the of 6-9 months historical benchmark, respectively (Gandhi, 2019). Additional follow up may further solidify these findings.

The FDA's Position

The FDA generally agrees with the Applicant's assessments of efficacy in the DREAMM-2 trial. FDA notes that only 8 patients received the 2.5 mg/kg dose in the DREAMM-1 trial. FDA reiterates that the 9-month data update (September 20, 2019) was primarily for safety evaluation and the additional efficacy analysis is considered exploratory.

FDA also reiterates the challenges with interpretation of time-to-event endpoints in single-arm trials as stated in Section 2.3.1.2.

3 SAFETY

The Applicant's Position

3.1.1 Description of the Safety Profile and Adverse Events

3.1.1.1 Treatment Exposure

A total of 218 patients in DREAMM-2 and 73 patients in DREAMM-1 with RRMM have been exposed to at least one dose of belantamab mafodotin as a single agent. Of all patients exposed, 103 have been treated with the proposed dose of 2.5 mg/kg (Table 3). Clinical outcomes in the lyophilized cohort are discussed in the Appendix, Section 9.2.

Table 3: Summary of Exposure Across the Clinical Development Program

	Number of Patients Exposed to Belantamab Mafodotin[a]				
	<2.5 mg/kg	2.5 mg/kg	3.4 mg/kg	4.6 mg/kg	Total
Pivotal Study					
DREAMM-2	-	95	123[b]	-	218
Supportive Study					
DREAMM-1	21	8	38	6	73

a. Patients with RRMM exposed to at least one dose of belantamab mafodotin as of 21 June 2019 for DREAMM-2 and 31 August 2018 for DREAMM-1. b. Includes frozen liquid (N=99) and lyophilized configurations (N=24).
Source: Adapted from 2.7.4 Table 3 (ADSL)

The 2.5 mg/kg Q3W dose has been selected as the monotherapy dose for this heavily pre-treated patient population; see Section 5.1 for additional details on the selection of this dose. Since DREAMM-2 is the pivotal trial and included the majority of patients (95 out of 103) studied for the proposed indication at the 2.5 mg/kg dose, the focus of this safety discussion will be on DREAMM-2 data.

The median time on study treatment (which includes dose delays) in DREAMM-2 for the two dose cohorts is presented in Table 4. The dose intensity was closer to the intended dose in the 2.5 mg/kg cohort, likely due to fewer dose modifications.

Table 4: DREAMM-2: Belantamab Mafodotin Treatment

	Belantamab Mafodotin	
	2.5 mg/kg (N=95)	**3.4 mg/kg (N=99)**
Time on study treatment, median (range), weeks	9.1 (2–40)	12.0 (2–48)
Number of treatment cycles, median (range)	3.0 (1–11)	3.0 (1–10)
Dose intensity, median (range), mg/kg/Q3W	2.47 (0.7–2.6)	2.95 (1.0–3.7)

Source: Adapted from 2.5 Table 2 (ADSL, ADEX); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

FDA agrees with the Applicant's summary of exposure across the clinical development program and within DREAMM-2. FDA also agrees with focusing the safety discussion on the data from the pivotal DREAMM-2 trial. FDA notes that patients in both dose cohorts received a median of 3 cycles of treatment, indicating that in general, patients received very few cycles of treatment with belantamab mafodotin. Despite evaluation of the lower 2.5 mg/kg starting dose and the short median duration of study treatment, there was a high incidence of ocular toxicity.

3.1.1.2 Overall Adverse Event Profile

Overall, nearly all patients (98%) in the 2.5 mg/kg dose cohort experienced AEs, and 82% had Grade 3 or 4 AEs (Table 5). While the overall AE rates were similar across doses, the 2.5 mg/kg dose demonstrated a more favorable safety profile in comparison with the 3.4 mg/kg dose, with less need for dose reductions (29% and 41%, in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively) or interruptions/delays (54% and 62%, respectively), and fewer SAEs (40% and 47%, respectively).

Table 5: Adverse Events Overview

	Belantamab Mafodotin	
	2.5 mg/kg (N=95)	**3.4 mg/kg (N=99)**
Any AE, n (%)	**93 (98)**	**99 (100)**
AEs related to study treatment	84 (88)	94 (95)
AEs leading to permanent discontinuation of study treatment	8 (8)	10 (10)
AEs leading to dose reduction	28 (29)	41 (41)
AEs leading to dose interruption/delay	51 (54)	61 (62)
AEs related to study treatment and leading to permanent discontinuation of study treatment	6 (6)	4 (4)
Grade 3 or 4 AEs	78 (82)	81 (82)
Grade 3 or 4 AEs related to study treatment	52 (55)	62 (63)
Any SAE, n (%)	**38 (40)**	**47 (47)**
SAEs related to study treatment	10 (11)	19 (19)
Fatal SAEs	3 (3)	7 (7)
Fatal SAEs related to study treatment	1 (1)	1 (1)

Source: CSR-205678 Table 23 (ADSL, ADAE); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

FDA agrees with the Applicant's overall AE profile presented above, with the major exception that FDA does not agree with the Applicant's distinction between all AEs and AEs related to study treatment as presented in Table 5, and in Table 15 and Table 16 below. 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 that occur on a single-arm trial. FDA notes that there were no differences in the overall AE rates or rates of Grade 3 or 4 AEs between the two doses.

3.1.1.2.1 Common Adverse Events

The most commonly reported AE by preferred term in the 2.5 mg/kg cohort was keratopathy (microcyst-like epithelial changes [MECs], changes in the corneal epithelium observed on eye examination with or without symptoms; 71%). Other commonly reported AEs by preferred term were anemia (24%), nausea (24%), pyrexia (22%), thrombocytopenia (21%), and aspartate aminotransferase (AST) increased (20%) (Table 6). While this pattern was similar in the 3.4 mg/kg cohort, all these events were less frequent in the 2.5 mg/kg cohort.

Corneal events, including keratopathy (MECs), and thrombocytopenia as well as infusion-related reaction (IRR) events were identified as adverse events of special interest (AESI); further information is presented in the Appendix, Section 9.3.4.

Table 6: AEs by Preferred Term in ≥15% of Patients in Any Dose

	Belantamab Mafodotin	
Preferred Term	**2.5 mg/kg (N=95)**	**3.4 mg/kg (N=99)**
Any event, n (%) [a]	**93 (98)**	**97 (98)**
Keratopathy (MECs) [b]	67 (71)	74 (75)
Thrombocytopenia	20 (21)	44 (44)
Anemia	23 (24)	37 (37)
Nausea	23 (24)	32 (32)
Fatigue	15 (16)	26 (26)
Pyrexia	21 (22)	25 (25)
Vision blurred	17 (18)	25 (25)
AST increased	19 (20)	24 (24)
Vomiting	7 (7)	20 (20)
Cough	7 (7)	19 (19)
Epistaxis	7 (7)	19 (19)
Neutropenia	6 (6)	19 (19)
Decreased appetite	11 (12)	18 (18)
Dry eye	11 (12)	18 (18)
Upper respiratory tract infection	7 (7)	17 (17)
Hypercalcemia	13 (14)	16 (16)
Diarrhea	12 (13)	15 (15)
Platelet count decreased	15 (16)	14 (14)
Infusion related reaction	16 (17)	10 (10)

a. Number (%) of patients with AEs, sorted in descending frequency of PT in the 3.4 mg/kg cohort
b. Keratopathy (microcyst-like epithelial changes [MECs], changes in the corneal epithelium observed on eye examination with or without symptoms)

Source: Adapted from CSR-205678 Table 25 (ADSL, ADAE); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

FDA's analysis of the incidence of certain AEs differs from the Applicant's analyses presented in Table 6 due to the following issues: (1) the Applicant's analysis does not include grouping of related AE terms (e.g., fatigue and asthenia, lung infection and pneumonia), (2) the incidence of keratopathy reported in the Applicant's table is based on the AE reporting of keratopathy captured in the AE dataset rather than corneal exam findings captured in the ocular dataset, and (3) the Applicant reported incidences of laboratory abnormalities based on AE reporting

instead of shift tables based on the laboratory dataset (which may underrepresent of the incidence of laboratory abnormalities).

FDA's analysis of the AEs in ≥15% of patients in any dose which incorporates grouped preferred terms and the incidence of keratopathy based on corneal exam findings captured in the ocular dataset is in Table 7. In FDA's analysis, pneumonia is included as meeting the ≥15%, and there are higher incidences of keratopathy (3.4 mg/kg cohort only), vision blurred, IRR, fatigue, dry eye, upper respiratory infection, and cough (2.5 mg/kg cohort only) compared to the Applicant's numbers presented in Table 6. FDA notes that although the 2.5 mg/kg dose had lower rates of some AEs, the rates of keratopathy were not substantially lower with the 2.5 mg/kg dose compared to the 3.4 mg/kg dose.

Table 7: FDA Analysis of AEs in ≥15% of Patients

Adverse Event Term	**Belantamab mafodotin**	
	2.5 mg/kg (N=95) All Grades, n (%)	3.4 mg/kg (N=99) All Grades, n (%)
Any adverse event	93 (98)	99 (100)
Keratopathy†	67 (71)	76 (77)
Nausea	23 (24)	32 (32)
Pyrexia	21 (22)	25 (25)
Vision blurred*	21 (22)	30 (30)
Infusion-related reaction♦	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)

†Based on corneal exam findings
*Based on grouping of related preferred terms (see Section 9.4.4 of the Appendix for the list of grouped terms)
♦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)

FDA's analysis of hematology laboratory abnormalities worsening from baseline based on shift analysis of the laboratory dataset is in Table 8 (refer to the Appendix Section 9.4.3 for FDA analysis of chemistry laboratory abnormalities). 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 8: FDA Analysis of Hematology Laboratory Abnormalities in ≥15% of Patients

	Belantamab mafodotin	
	All Grades, n (%)*	**Grade ≥3, n (%)***

Laboratory Parameter	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
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)

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

3.1.1.2.2 Adverse Events Grade ≥3

The most frequently reported Grade ≥3 AEs in the 2.5 mg/kg cohort were keratopathy (27%), anemia (20%), thrombocytopenia (17%), and lymphocyte count decreased (13%) (Table 9). The incidences of Grade ≥3 AEs of thrombocytopenia, anemia, pneumonia, and neutropenia were higher in the 3.4 mg/kg cohort than in the 2.5 mg/kg cohort.

Table 9: AEs of Maximum Grade ≥3 in 5% of Patients in Any Dose, by Preferred Term

	Belantamab Mafodotin			
	2.5 mg/kg (N=95)		3.4 mg/kg (N=99)	
Preferred Term	Grade ≥3	Total	Grade ≥3	Total
Patients with any event, n (%) [a]	**79 (83)**	93 (98)	**82 (83)**	99 (100)
Keratopathy (MECs) [b]	26 (27)	67 (71)	21 (21)	74 (75)
Anemia	19 (20)	23 (24)	25 (25)	37 (37)
Thrombocytopenia	16 (17)	20 (21)	27 (27)	44 (44)
Lymphocyte count decreased	12 (13)	13 (14)	8 (8)	12 (12)
Hypercalcemia	7 (7)	13 (14)	3 (3)	16 (16)
Hypophosphatemia	5 (5)	7 (7)	4 (4)	7 (7)
Neutrophil count decreased	5 (5)	7 (7)	4 (4)	9 (9)
Platelet count decreased	5 (5)	15 (16)	6 (6)	14 (14)
Neutropenia	4 (4)	6 (6)	9 (9)	19 (19)
Pneumonia	4 (4)	4 (4)	11 (11)	13 (13)
Gamma-glutamyltransferase increased	3 (3)	8 (8)	8 (8)	13 (13)
Aspartate aminotransferase increased	2 (2)	19 (20)	6 (6)	24 (24)
Fatigue	2 (2)	15 (16)	5 (5)	26 (26)

a. Number (%) of patients with AEs, sorted in descending frequency of PT in the 2.5 mg/kg cohort for Grade ≥ 3 events
b. Keratopathy (microcyst-like epithelial changes [MECs], changes in the corneal epithelium observed on eye examination with or without symptoms)

Source: CSR-205678 Table 27 (ADSL, ADAE); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

FDA's analysis of the incidence of certain Grade ≥3 AEs also differs from the Applicant's analyses presented in Table 9 due to the aforementioned issues. FDA's analysis, which incorporates grouped preferred terms and the incidence of keratopathy based on corneal exam findings is shown in Table 10. FDA's analysis of Grade ≥3 hematology laboratory abnormalities is presented above in Table 8 and FDA's analysis of Grade ≥3 chemistry laboratory abnormalities is presented in the Appendix Section 9.4.3.

Table 10: FDA Analysis of Grade ≥3 AEs in ≥5% of Patients in Any Dose

Adverse Event Term	Belantamab mafodotin	
	2.5 mg/kg (N=95) n (%)	3.4 mg/kg (N=99) n (%)

	Grade ≥3	Total	Grade ≥3	Total
Any adverse event	79 (83)	93 (98)	82 (83)	99 (100)
Keratopathy†	42 (44)	67 (71)	41 (41)	76 (77)
Pneumonia*	7 (7)	9 (9)	13 (13)	18 (18)
Sepsis*	5 (5)	5 (5)	4 (4)	4 (4)
Hypertension*	2 (2)	7 (7)	6 (6)	9 (9)
Fatigue*	2 (2)	19 (20)	5 (5)	34 (34)

†Based on corneal exam findings
*Based on grouping of related preferred terms (see Section 9.4.4 of the Appendix for the list of grouped terms)
Source: FDA Analysis (ADAE and ADOCGSK datasets; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

Of note, the incidence of Grade ≥3 keratopathy based on the KVA scale as shown in Table 10 is substantially higher than the incidence of Grade ≥3 keratopathy based on the CTCAE scale as shown in Table 9 (44% vs. 27%), highlighting the limitations of the CTCAE grading scale for ocular AEs as discussed further in Section 3.1.1.2.7.2.

FDA also notes that there was no substantial difference in the rates of Grade ≥3 keratopathy between the two dose levels, and the rates of Grade ≥3 keratopathy were slightly higher in the 2.5 mg/kg cohort compared to the 3.4 mg/kg cohort (44% vs. 41%).

3.1.1.2.3 Adverse Events Leading to Dose Delay or Reduction

Overall, dose delays were less common in the 2.5 mg/kg cohort (54%) than in the 3.4 mg/kg cohort (62%) (Table 11). The most common AEs leading to dose delays (keratopathy [MECs], vision blurred, pneumonia) were similar in the two cohorts but occurred at higher rates in the 3.4 mg/kg cohort.

Table 11: AEs Leading to Dose Delays in ≥2 Patients in Any Dose

	Belantamab Mafodotin	
Preferred Term	**2.5 mg/kg (N=95)**	**3.4 mg/kg (N=99)**
Any event, n (%)	**51 (54)**	**61 (62)**
Keratopathy (MECs) [a]	45 (47)	48 (48)
Vision blurred	4 (4)	8 (8)
Pneumonia	3 (3)	4 (4)
Thrombocytopenia	0	4 (4)
Dry eye	2 (2)	3 (3)
Upper respiratory tract infection	1 (1)	3 (3)
Urine albumin/creatinine ratio increased	2 (2)	3 (3)
Anemia	0	2 (2)
Aspartate aminotransferase increased	1 (1)	2 (2)
Blepharitis	0	2 (2)
Blood creatinine increased	2 (2)	2 (2)
Blood lactate dehydrogenase increased	0	2 (2)
Lung infection	0	2 (2)
Platelet count decreased	0	2 (2)
Pyrexia	1 (1)	2 (2)

a. Keratopathy (microcyst-like epithelial changes [MECs], changes in the corneal epithelium observed on eye examination with or without symptoms)
Source: CSR-205678 Table 34 (ADSL, ADAE); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

In the 2.5 mg/kg cohort, 29% of patients had an AE leading to dose reduction (Table 12), and the most common AEs (≥3% of patients) leading to dose reduction were keratopathy (MECs, 23%) and thrombocytopenia (3%).

Table 12: AEs Leading to Dose Reduction in ≥2% of Patients in Any Dose

Preferred Term	Belantamab Mafodotin 2.5 mg/kg (N=95)	Belantamab Mafodotin 3.4 mg/kg (N=99)
Any event, n (%)	**28 (29)**	**41 (41)**
Keratopathy (MECs) [a]	22 (23)	27 (27)
Thrombocytopenia	3 (3)	11 (11)
Vision blurred	2 (2)	3 (3)
Platelet count decreased	2 (2)	2 (2)
Urine albumin/creatinine ratio increased	0	2 (2)

a. Keratopathy (microcyst-like epithelial changes [MECs], changes in the corneal epithelium observed on eye examination with or without symptoms)

Source: Adapted from CSR-205678 Table 33 (ADSL, ADAE); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

Based on the grouping of the related preferred terms of vision blurred, diplopia, visual acuity reduced, and visual impairment, FDA analysis showed that the incidence of patients requiring a dose delay due to vision blurred was 5% in the 2.5 mg/kg cohort and 9% in the 3.4 mg/kg cohort, which is higher than the incidences reported by the Applicant for the preferred term of vision blurred alone.

FDA's analyses also showed additional minor differences compared to the Applicant's analyses presented in Table 11, Table 12, Table 13, and Table 14, due to differences in grouping of preferred terms (summarized in Section 9.4.2 of the Appendix).

3.1.1.2.4 Adverse Events Leading to Discontinuation of Study Treatment

The incidence of AEs leading to discontinuation in the 2.5 mg/kg cohort was 8% (Table 13). Keratopathy led to treatment discontinuation in two patients and all other AEs leading to permanent discontinuation occurred in ≤1 patient each in the 2.5 mg/kg cohort. Discontinuation due to IRR occurred in 1 patient in the 2.5 mg/kg cohort who had multiple IRRs.

Table 13: AEs Leading to Permanent Discontinuation of Study Treatment

Preferred Term	Belantamab Mafodotin 2.5 mg/kg (N=95)	Belantamab Mafodotin 3.4 mg/kg (N=99)
Any event, n (%) [a]	**8 (8)**	**10 (10)**
Keratopathy (MECs) [b]	2 (2)	3 (3)
Cerebral hemorrhage	0	2 (2)
Pneumonia	0	2 (2)
Cardiac arrest	1 (1)	1 (1)
Acute myeloid leukemia	0	1 (1)
Hemophagocytic lymphohistiocytosis	0	1 (1)
Viral infection	0	1 (1)
Headache	1 (1)	0
Herpes simplex pneumonia	1 (1)	0
Infusion related reaction	1 (1)	0
Sepsis	1 (1)	0
Urine albumin/creatinine ratio increased	1 (1)	0

a. Number (%) of patients with AEs, sorted in descending frequency of PT in the 3.4 mg/kg cohort
b. Keratopathy (microcyst-like epithelial changes [MECs], changes in the corneal epithelium observed on eye examination with or without symptoms)

Source: CSR-205678 Table 32 (ADSL, ADAE); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

The ocular toxicities in DREAMM-2 were primarily managed with dose modifications, including dose delays/interruptions, dose reductions, and/or permanent discontinuation of study treatment. Keratopathy was the most frequent AE leading to dose modifications in DREAMM-2. The dose modifications due to keratopathy presented by the Applicant in Table 11, Table 12, and Table 13 are based on the preferred term 'keratopathy' from the AE dataset. FDA confirmed the numbers presented above by the Applicant and performed an analysis of dose modifications based on the ocular dataset, but the numbers did not differ substantially. FDA also notes that there was no difference in the rates of dose delays in the 2.5 mg/kg and 3.4 mg/kg cohorts, and only minor differences in the rates of dose reductions.

3.1.1.2.5 Serious Adverse Events

The overall incidence of SAEs reported in the 2.5 mg/kg cohort was 40% (Table 14). The incidence of SAEs was higher in the 3.4 mg/kg cohort (47%) than in the 2.5 mg/kg cohort. There were 2 cases of cerebral hemorrhage in the 3.4 mg/kg cohort, both of which were fatal (further detail in Table 16). There were no ocular SAEs.

Table 14: SAEs in ≥2 Patients in Any Dose

	Belantamab Mafodotin	
Preferred Term	**2.5 mg/kg (N=95)**	**3.4 mg/kg (N=99)**
Patients with any event, n (%) [a]	**38 (40)**	**47 (47)**
Pneumonia	4 (4)	12 (12)
Pyrexia	6 (6)	5 (5)
Febrile neutropenia	0	3 (3)
Cerebral hemorrhage	0	2 (2)
Epistaxis	1 (1)	2 (2)
Escherichia urinary tract infection	0	2 (2)
General physical health deterioration	0	2 (2)
Hyperviscosity syndrome	0	2 (2)
Influenza	0	2 (2)
Infusion related reaction	3 (3)	2 (2)
Lung infection	3 (3)	2 (2)
Osteolysis	0	2 (2)
Pathological fracture	0	2 (2)
Sepsis	2 (2)	2 (2)
Thrombocytopenia	1 (1)	2 (2)
Upper respiratory tract infection	0	2 (2)
Acute kidney injury	2 (2)	1 (1)
Pleural effusion	2 (2)	1 (1)
Hypercalcemia	4 (4)	0
Hypokalemia	2 (2)	0
Staphylococcal sepsis	2 (2)	0
Vascular device infection	2 (2)	0

a. Number (%) of patients with SAEs, sorted in descending frequency of PT in the 3.4 mg/kg cohort

Source: CSR-205678 Table 31 (ADSL, ADAE); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

3.1.1.2.6 Deaths

As of the data cut-off for the primary analysis, 33% of patients in the 2.5 mg/kg cohort and 31% of patients in the 3.4 mg/kg cohort had died, mostly due to progressive disease (Table 15). Most of these deaths occurred >30 days after the last dose of study drug and were attributed to the disease under study by the investigator (26% in the 2.5 mg/kg cohort and 23% in the 3.4 mg/kg cohort).

Table 15: Summary of Deaths

	Belantamab Mafodotin	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Deaths, n (%)	31 (33)	31 (31)
Primary Cause of Death, n (%)		
Progressive disease Under Study	25 (26)	23 (23)
SAE Possibly Related to Study Treatment	1 (1)	1 (1)
Other	2 (2)	7 (7)
Unknown [a]	3 (3)	0

a. The deaths of unknown cause include the following: information unavailable because patient had been transferred to hospice care; death certificate unavailable; and information unavailable because the patient died alone at home.

Source: Adapted from CSR-205678 Table 29 (ADSL, ADDD); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

In the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively, there were 3 and 7 patients with fatal SAEs (Table 16). Of these, 1 patient in 2.5 mg/kg cohort and 1 patient in 3.4 mg/kg cohort had a fatal SAE considered related to study drug: the patient in the 2.5 mg/kg cohort had sepsis, and the patient in the 3.4 mg/kg cohort had hemophagocytic lymphohistiocytosis.

Table 16: Patients with Fatal SAEs

Patient identifier	Time from first dose to AE leading to death (days)	Time from last dose to death (days)	Fatal SAE (Preferred term)	SAE Possibly causally related to study drug
Belantamab mafodotin: 2.5 mg/kg cohort				
1	41	20	Cardiac arrest	No
2	33	15	Sepsis	Yes
3	88	12	Pneumonia	No
Belantamab mafodotin: 3.4 mg/kg cohort				
4	66	10	Cerebral hemorrhage	No
5	12	29	Cerebral hemorrhage	No
6	55	15	Pneumonia	No
7	2 11	15	Viral infection Hemophagocytic lymphohistiocytosis	No Yes
8	114	30	Cardiac arrest	No
9	131	5	Pneumonia	No
10	201	113	Acute myeloid leukemia	No

Note: Substitute patient identifiers have been used

Source: CSR-205678 Table 30 (ADSL, ADAE) Listing 1.0520 (ADSL, ADDD); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

FDA agrees with the Applicant's summary of deaths and fatal SAEs presented above, with the exception that FDA does not agree with the Applicant's distinction between all AEs and AEs related to study treatment as discussed in Section 3.1.1.2.

3.1.1.2.7 Corneal Events

3.1.1.2.7.1 Association of Corneal Events with Belantamab Mafodotin

Changes to the corneal epithelium are a known class-effect associated with ADCs containing microtubule inhibitor payloads (e.g., auristatins and maytansinoids). The leading hypothesis regarding the mechanism of toxicity is that these events are related to the nonspecific uptake of the ADC into basal corneal epithelial cells (de Goeij , 2016; Zhao, 2018). Release of cys--mcMMAF in the cell interferes with cellular microtubulin polymerization activity that

affects cell division and migration ultimately leading to apoptosis. This clinically manifests as microcyst-like corneal surface changes (MECs or keratopathy), which may be associated with symptoms such as dry eye and blurred vision. In general, data from the literature indicate that MMAF-conjugated ADCs are associated with a consistent, anticipated set of corneal changes that can be managed with supportive care and dose modifications, and do not appear to result in permanent sequalae (e.g., corneal examination findings, symptoms or change in visual acuity).

Additional details on corneal events, including relevant information on corneal anatomy, definitions of corneal event reporting, clinical manifestations of corneal events, and measurement of visual acuity, are provided in the Appendix, Section 9.1.

The FDA's Position

The mechanism by which belantamab mafodotin causes ocular toxicity is not completely understood. FDA agrees that ocular toxicities, including keratopathy, are a known class-effect associated with ADCs containing microtubule-inhibitor payloads, such as MMAF, and generally agrees with the Applicant's assessment above. Regarding the statement that 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. If left untreated, some permanent injury could be expected.

3.1.1.2.7.2 Ocular Assessments

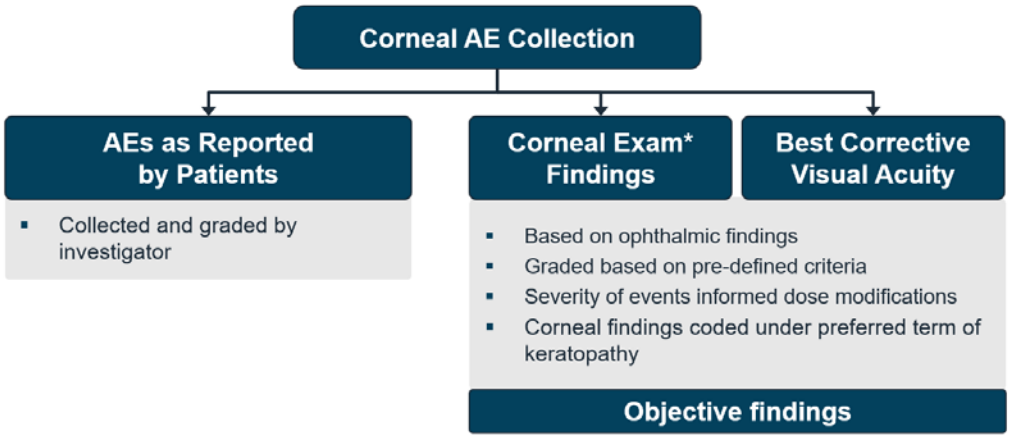
Due to the identified risk of corneal epithelial changes with belantamab mafodotin and other ADCs, a thorough evaluation of corneal events in the belantamab mafodotin clinical development program was conducted. In DREAMM-1, visual acuity was assessed, and an eye examination was performed. Corneal events (keratopathy [MECs]) observed on eye examination and patient-reported symptoms occurred in the majority of patients (n=24, 69%) in the expansion cohort of that study. Based on data from DREAMM-1 and feedback from the FDA, corneal events were thoroughly evaluated in DREAMM-2 using objective eye examination for identification of the corneal events (Keratopathy and Visual Acuity [KVA] Scale). Dose modifications were based on eye examination findings including slit lamp examination of the cornea and changes in BCVA. In addition, an ocular sub-study was implemented in DREAMM-2 to determine the utility of corticosteroid eye drops; results from that sub-study are described in Section 3.1.1.2.7.7 .

To provide a comprehensive understanding of corneal events, data were collected in two ways during the DREAMM-2 study (Figure 7):

- At baseline and every three weeks pre-dose, all patients had to undergo routine ophthalmic examination visits where objective ocular findings by slit-lamp examination and a BCVA assessment were collected. Findings were graded based on protocol-specified criteria and used to guide dose modification decisions. Results from the eye examination are presented in Section 3.1.1.2.7.3.
- Ocular AEs were also collected by the investigator and coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. Events were graded for intensity/severity using Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) grading. If the ophthalmologist recorded a corneal examination finding (e.g., moderate punctate keratopathy) on the ocular case report form (CRF), the

Investigator was instructed to report an AE of "microcyst-like epithelial keratopathy" on the AE CRF. Information on ocular AEs is provided in the Appendix, Section 9.3.2.

Figure 7: DREAMM-2: Corneal Event Collection



Note: Patients had to undergo ophthalmic exams prior to every dose.

Patient-reported outcomes (PROs) on visual functioning and QoL were also assessed. Although these instruments do not directly assess patient safety, their results are useful for interpreting the effects of corneal events on patients' QoL. The visual function PRO assessments are described in Section 3.1.1.2.7.5 and the QoL assessment is described in Section 3.1.1.2.7.6.

To assist patients and prescribing physicians with appropriate risk management related to corneal events during treatment with belantamab mafodotin, GSK has developed a Risk Evaluation and Mitigation Strategy (REMS), which is described in Section 3.1.1.2.7.8.

The FDA's Position

FDA agrees that the extensive ocular monitoring in DREAMM-2 was based on the identified risk of corneal epithelial changes with belantamab mafodotin and other ADCs, and the high incidence of keratopathy in DREAMM-1.

Regarding the grading of ocular events, 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. Specifically, patients may not notice a defect in vision in one eye if the other eye can still see, and due to a lack of pain receptors inside the eye, damage to interior eye structures may not be felt. 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. Because of the limitations of the use of CTCAE for grading of ocular events, FDA provided input on the Applicant's development of the KVA grading scale, which incorporates both corneal exam findings (e.g., keratopathy) and best corrected visual acuity (BCVA) exam findings into an overall severity grade. As stated by the Applicant, the severity score from the KVA scale (based on the severity in the worse eye) was used to guide dose modifications in DREAMM-2.

In the FDA comments, we refer to events based on the overall KVA scale (based on findings on corneal exam with or without changes in BCVA) as “keratopathy” or “corneal events”.

FDA also notes the Applicant’s use of “patient-reported symptoms” in the above section and throughout the briefing document, to describe ocular events that were captured and reported by the physician using the CTCAE grading system. FDA does not agree with the Applicant’s use of this terminology to refer to physician-captured CTCAE-graded events. Furthermore, the Applicant’s use of this terminology should not be confused with patient-reported outcomes, which represent a direct capture of patient experience.

3.1.1.2.7.3 Eye Examination for Corneal Events

An objective eye examination was conducted by an ophthalmologist to report findings of changes to the cornea (keratopathy [MECs]) and BCVA assessment. This approach was developed in agreement with recommendations by Health Authorities and external experts to better characterize belantamab mafodotin treatment related corneal events.

A pre-specified KVA Scale was designed per FDA request and used to grade corneal events and to determine appropriate dosage modifications; details regarding this scale and dosage modification procedures are provided in Table 2.

As of the data cut for the primary analysis in the 2.5 mg/kg cohort, dose delays due to corneal events occurred in 47% of patients (3.4 mg/kg cohort, 52%), and dose reductions occurred in 20% of patients (3.4 mg/kg cohort, 26%). Overall, 2% of patients discontinued treatment due to corneal events (3.4 mg/kg cohort, 5%).

Overall, 71% of patients in the 2.5 mg/kg cohort (3.4 mg/kg cohort, 77%) experienced keratopathy (MECs) as reported from the eye examination. Most keratopathy (MECs) events were diagnosed within the first 2 treatment cycles. By the end of Cycle 2, the cumulative incidence of all corneal events was 54% and 71% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. Most events were Grade 2 or Grade 3 in both cohorts, and Grade 4 events (defined as corneal ulcer) occurred at a low incidence (0 in 2.5 mg/kg cohort; 1% in 3.4 mg/kg cohort).

In the 2.5 mg/kg cohort, 62% (59/95) of patients experienced Grade 2 or above corneal exam findings (keratopathy [MECs]), with a median time to onset of the finding of 36.0 days (range: 19–143) (3.4 mg/kg cohort: 71% of patients [70/99], with median time to onset of 22.5 days [range: 9–150]). Overall in the 2.5 mg/kg cohort, 66% (39/59) of patients recovered from the first occurrence, with median time to resolution of 78 days (3.4 mg/kg cohort: 64% [45/70], with median time to resolution 80 days). Among those with Grade ≥2 findings, 39% (23/59) of patients in the 2.5 mg/kg cohort and 33% (23/70) of patients in the 3.4 mg/kg cohort had more than 1 event.

As of the last follow up for 2.5 mg/kg cohort, 41% of patient recovered. Of the 59% who had ongoing corneal events, 29% were still on treatment, 7% were in follow-up and in 24% the follow up ended due to death, withdrawal from study or lost to follow up (patient unwilling to have further ocular examination) (3.4 mg/kg cohort: 43% recovered; of the 57% not recovered; 23% on treatment; 9% in follow-up, 26% not resolved when follow up ended). The median follow-up time for those who were not resolved when follow up ended was 24 days with 93% having follow up time shorter than 80 days (3.4 mg/kg cohort: 21.5 days, with 78% having

follow up time shorter than 80 days). With increasing follow-up, the rate of resolution of corneal events increased.

The corneal epithelium, the outermost layer of the cornea, was the most affected structure. Among patients with normal corneal epithelium at baseline (51 patients in the 2.5 mg/kg cohort and 46 patients in the 3.4 mg/kg cohort), 75% in the 2.5 mg/kg cohort and 76% in the 3.4 mg/kg cohort experienced a shift from normal to abnormal in their most affected eye.

A total of 53% of patients in the 2.5 mg/kg cohort and 48% of patients in the 3.4 mg/kg cohort experienced at least one line of decrease in BCVA due to corneal finding in at least one eye (Table 17). Most events were Grade 2 or Grade 3 in both cohorts, and Grade 4 events occurred at a low incidence (2% of patients in each cohort). Grade assessment of BCVA change was based on the worse grade of the two eyes. Per ophthalmologist, it is recognized that the better seeing eye impacts the overall vision the most and therefore further assessment of BCVA change in Section 3.1.1.2.7.4 focuses on the change in the better seeing eye.

Table 17: Characteristics of Corneal Events from the Eye Examination

	Belantamab Mafodotin	
	Primary Analysis Data (21Jun19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Patients with Corneal Exam findings (MECs), n (%)	67 (71)	76 (77)
Maximum Grade for Corneal Exam findings (MECs), n/N (%)		
Grade 1	8/95 (8)	6/99 (6)
Grade 2	17/95 (18)	29/99 (29)
Grade 3	42/95 (44)	40/99 (40)
Grade 4[a]	0	1/99 (1)
Patients with BCVA Changes, n (%)	50 (53)	48 (48)
Maximum Grade for BCVA Changes, n/N (%)		
Grade 1	6/95 (6)	3/99 (3)
Grade 2	17/95 (18)	21/99 (21)
Grade 3	25/95 (26)	22/99 (22)
Grade 4	2/95 (2)	2/99 (2)

a. BCVA change Grade 2 is defined as 2-3 lines of decrease from baseline but not worse than 20/200; Grade 3 is defined as >3 lines of decrease but not worse than 20/200; Grade 4 is defined as worse than 20/200.
Source: Table 3.12773, 3.12774 (ADSL, ADOCGSK, ADOCDVA), DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

FDA agrees that the KVA grading scale utilized for grading of ocular toxicity in the DREAMM-2 trial was developed by the Applicant with input from FDA based on the limitations of the CTCAE scale as discussed above in Section 3.1.1.2.7.2. In addition to its importance for grading the severity of corneal events, the severity score from KVA scale was used to guide dose modifications for management of these events. The recommended dose modifications presented in Table 2 have some differences from the guidelines in the DREAMM-2 protocol (see Section 9.4.1 in the Appendix) and are still under discussion.

FDA agrees with the data presented by the Applicant for dose modifications due to corneal events. Nearly half (47%) of the patients in the 2.5 mg/kg cohort required at least one dose interruption due to keratopathy. In the 2.5 mg/kg cohort, one patient permanently discontinued study treatment due to Grade 2 keratopathy after 1 cycle of treatment and one patient discontinued due to Grade 3 keratopathy after 3 cycles of treatment. In the 3.4 mg/kg cohort, three patients discontinued due to Grade 3 keratopathy and two patients discontinued

due to Grade 2 keratopathy. Even though the DREAMM-2 protocol only recommended discontinuation for Grade 4 keratopathy (Appendix Section 9.4.1), some patients discontinued treatment due to Grade 2 or 3 keratopathy. As stated in Section 3.1.1.2.4, FDA also notes that there were no differences in the rates of dose delays due to keratopathy between the 2.5 mg/kg and 3.4 mg/kg doses of belantamab mafodotin and only minor differences for rates of dose reduction between the two doses.

FDA agrees that 71% of patients in the 2.5 mg/kg cohort and 77% of patients in the 3.4 mg/kg cohort had at least one event of keratopathy based on corneal exam findings, and the majority of events were Grade 2 or 3, with only one Grade 4 event occurring in the 3.4 mg/kg cohort. Of note, the incidence of keratopathy by grade differs substantially for Grade 2 and 3 events based on the KVA scale as compared to the CTCAE scale (Table 18).

Table 18: FDA Analysis of Grading of Keratopathy by KVA vs. CTCAE Grading Scales

	Belantamab mafodotin 2.5 mg/kg (N = 95)	
Grade	KVA Grading Scale*	CTCAE Grading Scale†
1	8 (8)	12 (13)
2	17 (18)	29 (31)
3	42 (44)	26 (27)
4	0	0

* Based on corneal exam finding portion of the KVA scale only
† Based on grouping of preferred terms of keratopathy, keratitis, and corneal epithelium defect
Source: FDA Analysis (ADAE and ADOCGSK datasets; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

FDA confirmed the median time to onset for patients with Grade ≥2 (moderate) keratopathy and the numbers for the incidence of patients Grade ≥2 keratopathy with more than 1 event presented by the Applicant; however, we do not agree with excluding patients with Grade 1 events from this analysis, as capture Grade 1 keratopathy events required documented worsening from baseline. For example, a patient with mild keratopathy at baseline could have worsening that is a documented change from their baseline exam, that is captured as a Grade 1 event (Table 2). The median time to onset for Grade ≥2 keratopathy was prior to the start of Cycle 3 in both cohorts, indicating that keratopathy develops early in the course of treatment with belantamab mafodotin. It is notable that nearly 40% of patients with Grade ≥2 keratopathy had recurrent events in the 2.5 mg/kg cohort and recurrent events were more frequent with the 2.5 mg/kg dose compared to the 3.4 mg/kg dose (33%).

FDA does not agree with the Applicant's decision to present the recovery rate and median time to resolution for the first occurrence. FDA believes the recovery rate based on the last occurrence and the median time to resolution based on all occurrences that resolved are more clinically relevant since a substantial proportion of patients had more than 1 event (39% of patients in the 2.5 mg/kg cohort and 33% of patients in the 3.4 mg/kg cohort, among patients with Grade ≥2 events). FDA agrees with the Applicant's presentation of rates for the last event, but notes that this only includes patients with Grade ≥2 events since recovery was defined as improvement to Grade ≤1. The recovery rate for the last event was 41% in the 2.5 mg/kg cohort and 43% in the 3.4 mg/kg cohort, indicating that Grade ≥2 keratopathy did not resolve in a substantial proportion of patients. Despite dose modifications, patients experienced persistent keratopathy which lasted nearly 2 months in half of the patients. The median time to resolution for all occurrences that resolved was 62 days (range 11-193) in the 2.5 mg/kg cohort and 60 days (range 12-253) in the 3.4 mg/kg cohort.

Based on data from the 9-month safety update compared to the 6-month data cut-off, the percentage of patients with resolution increased from 41% to 48% in the 2.5 mg/kg cohort and 43% to 46% in the 3.4 mg/kg cohort. However, more than 50% of the patients in the proposed 2.5 mg/kg cohort had unresolved keratopathy, even with the longer 9-month follow-up. As of the 9-month data cut-off, FDA also notes that information on resolution for 24% (14/59) of the patients with a Grade ≥2 keratopathy event in the 2.5 mg/kg cohort is not available, as these patients either died or were lost to follow-up with persistent keratopathy as of the last assessment. Given the incomplete data regarding the reversibility of ocular toxicity, there is uncertainty at this time whether the dose modification strategy proposed by the Applicant is sufficient to mitigate the risk of ocular toxicity with belantamab mafodotin.

FDA agrees with the Applicant's data presented regarding the incidence of ≥1 line decrease in BCVA due to corneal findings. More than half the patients experienced a decline in visual acuity (≥1-line decrease) during treatment with belantamab mafodotin and quarter of the patients had a BCVA worse than 20/40 or more than 3 lines of decreased vision from known baseline. FDA concurs with the Applicant's analysis presented in Table 17.

To better understand the ocular symptoms that patients with keratopathy may experience, FDA performed an analysis of the incidence of ocular symptoms among patients with keratopathy (based on the KVA scale) in the 2.5 mg/kg cohort (N=67) and 3.4 mg/kg cohort (N=76). The incidence of ocular symptoms in all patients (with or without keratopathy) is shown in Table 19.

Table 19: FDA Analysis of Ocular Symptoms in DREAMM-2 (All Patients)

Adverse Event Term	**Belantamab mafodotin**	
	2.5 mg/kg (N=95) All Grades, n (%)	3.4 mg/kg (N=99) All Grades, n (%)
Keratopathy†	67 (71)	76 (77)
Any ocular symptoms*	30 (32)	43 (43)
Vision blurred*	21 (22)	30 (30)
Dry eye*	13 (14)	23 (23)
Photophobia	3 (3)	5 (5)
Eye pain	1 (1)	3 (3)

†Based on KVA scale (corneal findings on exam)
*Based on grouping of related preferred terms (see Section 9.4.4 of the Appendix for the list of grouped terms)
Source: FDA Analysis (ADAE dataset; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

Using a broad grouping of AE terms representing symptoms that may occur in patients with keratopathy, the overall incidence of any ocular symptoms was 32% in the 2.5 mg/kg cohort and 43% in the 3.4 mg/kg cohort. Only occurred in 1 patient in each cohort had any of these symptoms in the absence of keratopathy.

The incidence of ocular symptoms among patients with keratopathy is shown in Table 20.

Table 20: FDA Analysis of Ocular Symptoms in DREAMM-2 (Patients with Keratopathy)

Adverse Event Term	Belantamab mafodotin	
	Patients with keratopathy	
	2.5 mg/kg (N=67) All Grades, n (%)	3.4 mg/kg (N=76) All Grades, n (%)
Any ocular symptoms*	29 (43)	42 (55)
Vision blurred*	21 (31)	29 (38)
Dry eye*	12 (18)	18 (24)
Photophobia	3 (4)	5 (7)
Eye pain	1 (1)	3 (4)

*Based on grouping of related preferred terms (see Section 9.4.4 of the Appendix for the list of grouped terms)
Source: FDA Analysis (ADAE dataset; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

Among patients with keratopathy, the incidence of any ocular symptoms was 43% in the 2.5 mg/kg cohort and 55% in the 3.4 mg/kg cohort. It is notable that less than half of the patients in the 2.5 mg/kg cohort with keratopathy experienced any of these ocular symptoms during the course of their treatment, indicating that patients may not exhibit symptoms despite findings on ophthalmic exam.

3.1.1.2.7.4 Visual Acuity Assessment

The Snellen visual acuity chart was used for assessment of visual acuity in DREAMM-2; details on the chart and the interpretation of its measurements are provided in Section 9.1.5.

As of the primary analysis data cut in the 2.5 mg/kg cohort, 17% (16/95) of patients experienced a BCVA of 20/50 or worse in their better-seeing eye at least once during or after the treatment period (3.4 mg/kg cohort, 17%). Among those, 13 patients had a baseline BCVA of 20/25 or better (3.4 mg/kg cohort, 13 patients) and 3 patients had a baseline BCVA of 20/30–20/40 in the better seeing eye (3.4 mg/kg cohort, 4 patients).

As of the last follow up in the 2.5 mg/kg cohort, 94% of patients recovered (BCVA better than 20/50 or better; 3.4 mg/kg cohort, 82%) (Table 21). The median time to resolution of first occurrence was 22 days in both cohorts. Therefore, most patients recovered after one assessment interval (conducted every 21 days). One patient in the 2.5 mg/kg cohort and 2 patients in the 3.4 mg/kg cohort experienced a worsening of BCVA to 20/200 in their better seeing eye. In the one patient with this event in the 2.5 mg/kg cohort, their baseline BCVA was worse than 20/400 in the other eye.

Table 21: Clinically Meaningful Changes in BCVA in the Better Seeing Eye

	Bilateral BCVA of 20/50 or Worse		Bilateral BCVA of 20/200 or Worse	
	2.5 mg/kg (n=95) [a]	3.4 mg/kg (n=99) [a]	2.5 mg/kg (n=95) [b]	3.4 mg/kg (n=99) [b]
n (%)	16 (17)	17 (17)	1 (1)	2 (2)
Median time to onset (range), days	64.5 (20–190)	63.0 (42–259)	21.0 (21–21)	56.5 (49–64)
Median time to resolution for the first occurrence (range), days	22.0 (7–64)	22 (8–127)	22.0 (22–22)	18.5 (15–22)
Resolved as of last assessment, n	15	14	1	2

BCVA, best-corrected visual acuity. Data represent BCVA changes in the patients better seeing eye.

[a] Better than 20/50 at baseline in the better seeing eye and 20/50 or worse post baseline in the better seeing eye. Recovery is defined as better than 20/50 in the better seeing eye.
[b] Better than 20/200 at baseline in the better seeing eye and 20/200 or worse post baseline in the better seeing eye. Recovery is defined as better than 20/200 in the better seeing eye.
Source: Table 3.50051, 3.50071 (ADSL, ADOCCHAR), DREAMM-2, Safety Population, Cut-off date of 21JUN2019

The FDA's Position

FDA agrees with the data presented by the Applicant from the visual acuity assessments in DREAMM-2. FDA notes that in both dose cohorts, 17% of patients had a treatment-emergent decline in BCVA to 20/50 or worse (a level at which patients may not be legally able to drive, depending on the state) in the better seeing eye. In addition, one patient in the 2.5 mg/kg cohort (with baseline BCVA in one eye that was worse than 20/400) and 2 patients in the 3.4 mg/kg cohort had a decline in BCVA to 20/200 (a level considered legally blind in the U.S.) in the better seeing eye. Based on these results, keratopathy had a significant impact on patients' vision, including severe vision loss in some patients.

3.1.1.2.7.5 Visual Function PROs

The impact of belantamab mafodotin on visual symptoms and vision-related functioning was assessed in DREAMM-2 using 2 visual function questionnaires, the Ocular Surface Disease Index (OSDI) and the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25). Neither of the ocular PROs have been validated to evaluate ocular toxicity, especially in oncologic disease where a therapy may confer an overall survival or partial response benefit; therefore, results assessing meaningful change should be interpreted with caution. This section focuses on the recommended dose 2.5 mg/kg cohort.

NEI-VFQ-25: Item-Level Analysis

The NEI-VFQ-25 consists of items covering multiple general vision and vision-related functional domains including assessments of daily living, such as driving and reading. Evaluation of the NEI-VFQ-25 shows similar trends to the OSDI across domains covering general vision, near activities and driving difficulties, with an initial deterioration, stabilization of symptoms and some resolution from worst case post-baseline (WCPB) to end of trial.

GSK sought to better understand and better define the impact of ocular-related AEs on specific activities of daily living by conducting an item-level analysis of the NEI-VFQ-25 driving and reading questions. The primary analysis is presented for the item-level analysis.

Changes and shifts in responses from baseline to WCPB were assessed to understand the worst score that a patient provided at any point in DREAMM-2. An additional analysis was conducted to understand the time to onset, resolution rate, and time to resolution of giving up a particular activity due to an impact on visual function.

For the 2.5 mg/kg cohort at baseline, 70 of 95 patients (74%) reported having no difficulty or a little difficulty driving during the daytime in familiar places; 19 of 95 patients (20%) were not driving at baseline and 6 of 95 (6%) had missing values.

Among the 70 patients who at baseline reported having no difficulty or a little difficulty driving during daytime in familiar places, 15 patients (21%) reported giving up driving due to eyesight at some time during the study (Table 22). For these 15 patients that gave up driving, the median time to onset was 63 days, with 7 patients (47%) having returned to driving from the

first occurrence prior to end of treatment exposure and median time for going back to driving of 64 days based on available PRO assessments.

Table 22: DREAMM-2 NEI-VFQ-25 - Shift in Response from Baseline for Difficulty Driving During Daytime (Among Patients with No Difficulty at All or A Little Difficulty at Baseline)

		Continue to Drive While on Treatment				Stopped Driving At Worst Score		Missing, Post-Baseline
2.5 mg/kg (N=70)	Baseline n (%)	No Difficulty n (%)	A Little Difficulty n (%)	Moderate Difficulty n (%)	Extreme Difficulty n (%)	Gave Up Driving Due to Eyesight n (%)	Gave Up Driving Due to Other Reason n (%)	Missing n (%)
Shift in response from No Difficulty At All or A Little Difficulty	70 (100%)	28 (40%)	11 (16%)	7 (10%)	0	15 (21%)	3 (4%)	6 (9%)

Source: Table 8.50040 (ADSL, ADHEO), DREAMM-2, Safety Population, Cut-off date of 21JUN2019

A similar analysis was done for reading. At baseline, 83 of 95 (87%) patients reported that they had no difficulty or a little difficulty reading ordinary print in newspapers (Table 23). Five of 95 (5%) patients had moderate difficulty, 1 of 95 (1%) had extreme difficulty, 3 of 95 (3%) were not reading, and 3 of 95 (3%) had missing values at baseline.

Among the 83 patients reading with no or a little difficulty at baseline, 7 patients (8%) reported that they stopped reading due to their eyesight at some time during the study. Eight patients stopped reading ordinary print due to eyesight, including 1 patient with moderate difficulty reading at baseline. The median time to onset of reading difficulty was 76 days. For the first occurrence, 4 patients who stopped reading (50%) started reading again prior to end of treatment exposure and 2 patients (25%) resolved post end of treatment exposure. PRO data are not available to assess whether all patients started reading again.

Table 23: DREAMM-2 NEI-VFQ-25 - Shift in Response from Baseline for Difficulty Reading (Among Patients with No Difficulty At All or A Little Difficulty at Baseline)

		Continue to Read While on Treatment				Stopped Reading At Worst Score		Missing, Post-Baseline
2.5 mg/kg (N=83)	Baseline n (%)	No Difficulty n (%)	A Little Difficulty n (%)	Moderate Difficulty n (%)	Extreme Difficulty n (%)	Stopped Doing this Because of Eyesight n (%)	Stopped doing this for other reasons or not interested in doing this n (%)	Missing n (%)
Shift in response from No Difficulty At All or A Little Difficulty	83 (100%)	19 (23%)	18 (22%)	21 (25.3%)	10 (12%)	7 (8%)	0	8 (10%)

Source: Table 8.50020 (ADSL, ADHEO), DREAMM-2, Safety Population, Cut-off date of 21JUN2019

For those that had resolution of reading difficulty, the median time to resolution was 22 days based on available PRO assessments.

OSDI

The OSDI instrument measures vision-related function. The 12 items included assessment of ocular symptoms, visual-related functioning, and environmental triggers. Scores can vary from 0 to 100, with higher scores indicating a worse status.

On average, worst case post-baseline (WCPB) for OSDI vision-related functioning domain was an increase (deterioration) of 31.7 points. Patients typically improved by the end of treatment visit from WCPB, suggesting some resolution of symptoms.

The FDA's Position

FDA notes that the Applicant collected patient-reported visual symptoms using PRO-CTCAE, NEI-VFQ and OSDI. There is considerable overlap between the NEI-VFQ and OSDI, and FDA focused on the NEI-VFQ and PRO-CTCAE results for analysis.

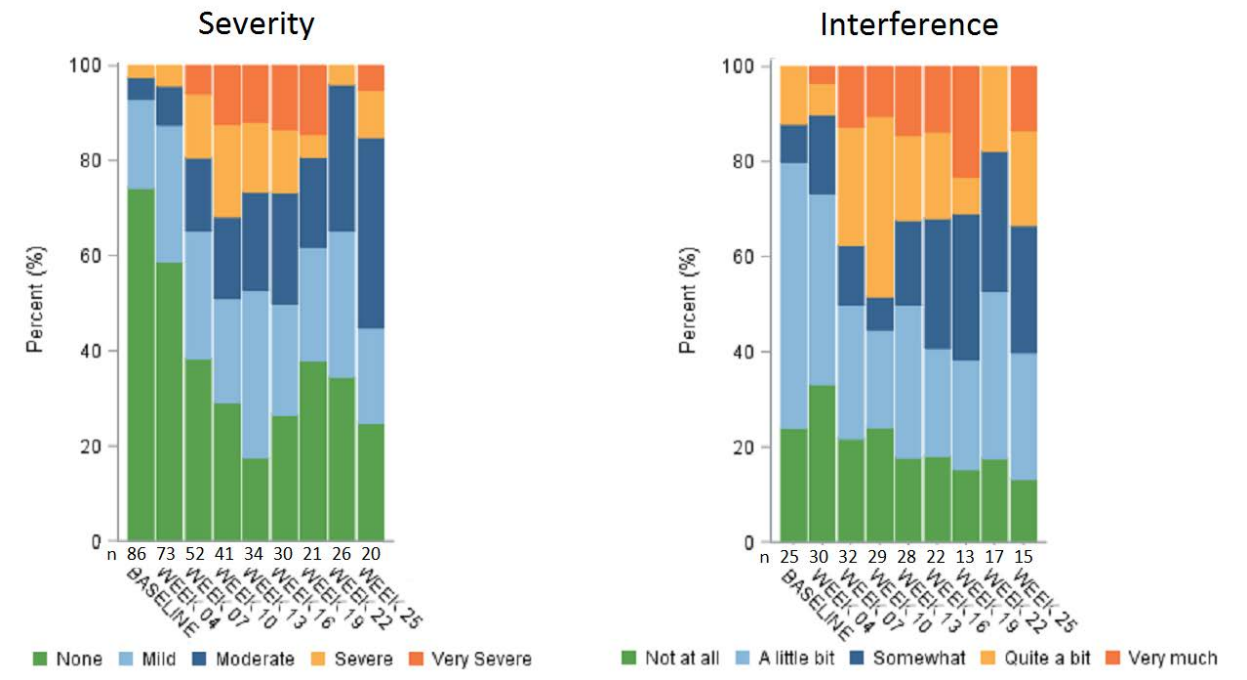
Regarding the FDA assessment of visual PRO results from DREAMM-2, FDA notes that the completion rate for the NEI-VFQ ranged between 69% and 89% of expected patients at any on-treatment assessment timepoint in the 2.5 mg/kg cohort. Attrition due to disease progression, death, treatment discontinuation due to AE in addition to suboptimal completion from expected PRO assessments were limitations to the interpretability of the PRO results. For example, at week 10 only 40 patients out of the 95 patients in the safety population completed the NEI-VFQ.

Despite these limitations, the FDA notes that of patients who completed the NEI-VFQ (who had little to no baseline symptoms), 21% gave up driving and 20% had extreme difficulty or gave up reading due to visual toxicity. This represents a meaningful impact on patients' lives.

The Applicant also assessed patient-reported blurry vision using the PRO-CTCAE blurry vision severity and interference items. Patients were asked "In the last 7 days, what was the severity of your blurry vision at its worst?" (None/Mild/Moderate/Severe/Very Severe). If patients responded that they had mild or worse blurry vision, they were asked a follow up question of "In the last 7 days, how much did blurry vision interfere with your usual or daily activities?" (Not at all/A little bit/Somewhat/Quite a bit/Very much).

The figure below shows the proportion of patients at each timepoint by severity and interference. After week 4, the majority of patients who responded at each timepoint reported some degree of blurred vision, and at week 13 over 80% of respondents reported at least mild blurred vision.

Figure 8: PRO-CTCAE Blurry Vision Results – 2.5 mg/kg Cohort



Source: FDA Analysis

According to the DREAMM-2 clinical study report, of the patients who responded to PRO-CTCAE blurry vision severity item (n=83), 27 patients (33%) reported severe or very severe blurry vision at any on-treatment timepoint. Of the patients who responded to the PRO-CTCAE blurry vision interference item (n=58), 26 patients (45%) reported “quite a bit” or “very much” interference due to blurry vision at any on-treatment timepoint.

In summary, analysis of the visual patient-reported outcomes is limited by small sample size, high attrition, and sub-optimal completion in eligible patients. Despite these limitations, based on the NEI-VFQ and the PRO-CTCAE results, a substantial proportion of patients report severe visual symptoms which resulted in significant interference in activities of daily living.

3.1.1.2.7.6 Health-Related Quality of Life (HRQoL)

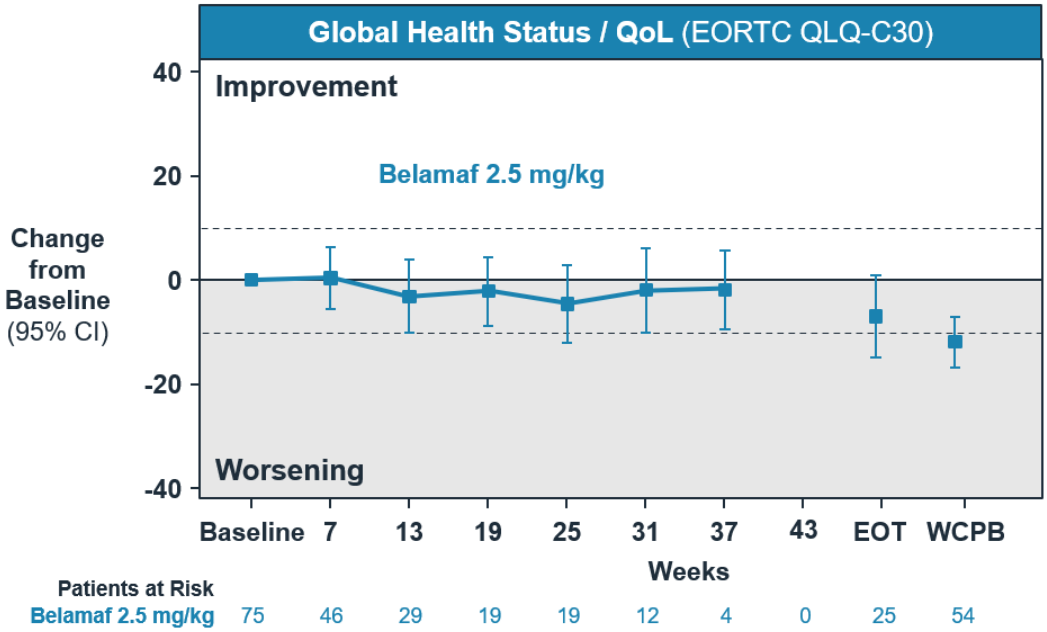
Patients with MM, including those with relapsed/refractory disease, often report significant impairment in health-related quality of life (HRQoL) due to disease-related symptoms such as fatigue, pain, and reduced physical function. Few treatment options available for patients have evaluated the impact of treatment on HR-QoL. Among studies that have evaluated HRQoL, improvement in quality of life (QoL) is not often observed (Weisel, 2020; Ludwig, 2019; Moreau, 2019; Richardson, 2018). Maintenance and stability of QoL with acceptable tolerability and efficacy, is an important finding, particularly in the triple-class refractory patient population (Martino, 2019).

In DREAMM-2, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module (EORTC QLQ-C30) was used. It is a 30-item questionnaire containing both single- and multi-item measures of disease-state symptoms (e.g., fatigue) (

Aaronson, 1993). When HRQoL is evaluated, the EORTC QLQ-C30 is among the most commonly employed PRO measures used for this purpose in patients with RRMM (Sonneveld, 2013).

For patients remaining on treatment in the 2.5-mg/kg cohort, the EORTC-QLQ-C30 Global Health Status/QoL score remained stable over time, indicating a stability in QoL (Figure 9).

Figure 9: DREAMM-2: Plot of Mean Change from Baseline for EORTC QLQ-C30 Global Health Status/QoL Domain – 2.5 mg/kg Cohort



EOT: End of Treatment; QoL: quality of life; WCPB: Worse Case Post-Baseline
Source: CSR-205678 Figure 29 (ADSL, ADHEO); DREAMM-2, Safety Population, Cut-off date of 21JUN2019

GSK conducted descriptive analysis to stratify patients by changes in vision to evaluate if global health or functioning are impacted with increasing severity of change in vision acuity. The EORTC-QLQ-C30 Global Health Status/QoL scores were stratified by changes in visual acuity, PRO-CTCAE blurred vision severity, Corneal Exam Finding, Overall KVA Scale Grade. Analysis were also completed to assess Global Health Status/QoL among patients with blurred vision and dry eye events.

The results demonstrated that scores appear similar across the severity levels (Grades), trends or patterns cannot be observed with these assessments, and standard deviations overlap considerably, suggesting limitations due to sample size or general stability across the grades. In general, EORTC-QLQ-C30 Global Health Status/QoL remained stable over time or improved among patients remaining on treatment with blurred vision and dry eye events.

It is also important to consider that GSK is conducting a trial-embedded interview sub-study in DREAMM-2. An interim analysis including 58 patients interviewed at Cycle 4 has been completed. At the end of each interview, patients were asked to comment on their degree of satisfaction with the study treatment by rating it on a scale from 0 (not satisfied) to 10 (extremely satisfied). Of those interviewed at Cycle 4, patients reported an average score of 8.2 and median score of 9.

The FDA's Position

Regarding the Health-Related Quality of Life 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 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 AE were not satisfied with their treatment and were not likely captured at Cycle 4.

3.1.1.2.7.7 DREAMM-2 Ocular Sub-study

In the ocular sub-study in DREAMM-2, 30 patients (n=17 in 2.5 mg/kg cohort and n=13 in 3.4 mg/kg cohort) were randomized to receive topical corticosteroids in only one eye for the first four cycles of study treatment (additional details on the sub-study design are provided in Section 2.2.1.1). The results of this sub-study suggested that corticosteroid eye drops were not beneficial in a prophylactic setting.

The FDA's Position

FDA agrees that based on the results of this limited study with small sample size, there is no data to suggest that topical steroids can mitigate the observed risks of ocular toxicity. Given the limitations, it is unclear if this lack of benefit is due to a true lack of effect. Additionally, the Applicant has not systematically evaluated other therapeutic strategies to mitigate risk of ocular toxicity with belantamab mafodotin. The only currently identified mitigation strategy is appropriate monitoring for ocular toxicity and implementation of dose modifications. Although the DREAMM-2 protocol included recommendations for use of lubricant eye drops, patients still developed keratopathy and symptoms of dry eye.

3.1.1.2.7.8 Ocular Risk Evaluation and Mitigation Strategy (REMS)

GSK has developed a REMS to provide education to all physicians prescribing belantamab mafodotin and their patients regarding the risk of corneal adverse reactions. In addition, elements to assure safe use (ETASU) are planned to help provide a positive impact on the benefit: risk ratio in patients receiving belantamab mafodotin in the post-marketing setting.

The ETASU is designed to ensure that the proposed monitoring and dose modifications are implemented in patients being treated with belantamab mafodotin.

The FDA's Position

FDA agrees with the Applicant that a REMS would be necessary to ensure that the benefits of belantamab mafodotin outweigh the risks of ocular toxicity. In order to mitigate the risk of ocular toxicity, the proposed REMS should include education and certification of prescribers

and health care settings, ensure patients are counseled about the risks, and support patient monitoring and dose modifications to minimize the ocular toxicity.

3.1.1.2.7.9 9-Month Data Update

As of the data cut-off for the 9-Month Update, the overall proportion of patients who experienced AEs and SAEs was consistent with the primary analysis. There were 4 additional patients in the 2.5-mg/kg cohort and 2 additional patients in the 3.4-mg/kg cohort who had an AE that led to dose reduction in the updated data compared with the primary analysis. There was no change in the number of patients in the 2.5-mg/kg cohort who experienced a fatal SAE; there were 2 additional patients in the 3.4-mg/kg cohort who had a fatal SAE, including one report of cerebral hemorrhage which was assessed as related to belantamab mafodotin by the reporting investigator.

For corneal events observed on eye examination (keratopathy [MECs]) as of the 9-Month Update, 48% and 46% in the 2.5-mg/kg and 3.4-mg/kg cohort, respectively, recovered from Grade≥2 event. The remaining patients in the 2.5-mg/kg and 3.4-mg/kg cohorts were still on treatment (22% and 17%, respectively), under follow up (5% and 7%, respectively) or were not resolved when follow-up ended (25% and 30%, respectively).

As of the data cut-off for the 9-Month Update, the incidence and recovery rate of decline in BCVA to 20/50 or worse in their better-seeing eye remained the same for 2.5-mg/kg cohort: the one patient with this event who did not recover was lost to follow up. In the 3.4 mg/kg cohort, 19% experienced a decline in BCVA to 20/50 or worse in their better-seeing eye; 95% recovered as of the last follow-up. There was no change in the incidence or recovery of worsening in BCVA to 20/200 or worse in their better seeing eye.

Regarding PRO assessments at the 9-Month Update, NEI VFQ-25 and OSDI results were consistent with the primary analysis. The EORTC QLQ-C30 Global Health Status/QoL scores demonstrated stability overall that persisted throughout the additional follow-up period in the 2.5-mg/kg cohort and showed some improvement from baseline during the additional follow-up period in the 3.4-mg/kg cohort.

The FDA's Position

FDA agrees with the data presented above from the 9-month update. FDA notes there was a Grade 4 keratopathy event of bilateral corneal ulcers reported in 1 patient in the 2.5 mg/kg dose cohort at the 9-month update that was not presented above. As stated in Section 3.1.1.2.7.3, significant proportion of patients with Grade ≥2 keratopathy had unresolved events. FDA also notes that two additional patients permanently discontinued study treatment due to AEs of blurred vision as of the 9-month update and less than 50% of patients with Grade ≥2 keratopathy had resolution at 9 months of follow up. FDA does not agree that any definitive conclusions can be drawn regarding the stability of PRO scores based on the available data and limitations as described in Section 3.1.1.2.7.5.

3.1.2 Safety Conclusions

Belantamab mafodotin has an acceptable safety profile, mainly characterized by thrombocytopenia, anemia, and corneal events. Corneal events represent a novel type of AE for

physicians who treat patients with multiple myeloma, and have therefore been systematically evaluated, and require education regarding their management.

Corneal events are expected with MMAF-containing ADCs. The incidence of keratopathy (MECs) observed on eye examination was 72% in the 2.5 mg/kg cohort. However, few patients permanently discontinued treatment due to corneal events and there have been no reports of corneal event SAEs and no reports of permanent complete vision loss to date. Management of these events can be achieved in most patients with dose modifications (dose delays and dose reductions). At the primary analysis, resolution of corneal events during the study occurred in 41% of patients. With an additional 3-months of follow-up, the rate of resolution of corneal events also increased (to 48%). Although patients may experience a decrease in vision and symptoms (blurred vision and dry eye), which may lead to giving up activities such as driving, they remain independent while attending to daily activities and overall report a high level of treatment satisfaction based on PRO data.

In contrast to AEs commonly observed during treatment with selected PIs and immunomodulatory agents, few patients reported cardiotoxicity, renal events, peripheral neuropathy, gastrointestinal and neutropenic AEs with belantamab mafodotin. While IRRs following belantamab mafodotin treatment are common, they are less frequent than with other agents, such as daratumumab, and do not require routine pre-medications.

The updated safety data with an additional 3 months of follow-up from DREAMM-2 are consistent with the 6-month results (primary analysis) and supportive of the original conclusion: belantamab mafodotin has an acceptable safety profile in a heavily pre-treated, RRMM population.

In summary, the safety profile of belantamab mafodotin administered at a 2.5 mg/kg dose is comprised of conventional AEs for anti-myeloma treatments, such as thrombocytopenia and anemia, which were familiar to physicians. Novel AEs such as corneal events require education for their management. Corneal events such as keratopathy (MECs) were common and mainly managed with dose modifications. Regular eye exams are required to ensure keratopathy (MECs) is recognized, and managed. Despite ocular symptoms, patients who remained on treatment continued to experience stability in disease-related symptoms and QoL as compared to an expected decline due to myeloma progression and reported a high level of treatment satisfaction. Overall, the novelty of corneal events requires education and careful management but represents an AE that can be managed while the patient remains on belantamab mafodotin.

The FDA's Position

The key safety issue with belantamab mafodotin is ocular toxicity, including keratopathy and changes in visual acuity assessed by ocular examinations, and adverse events of blurred vision and dry eyes.

Keratopathy was the most common AE in DREAMM-2, occurring in 71% of patients in the 2.5 mg/kg cohort and 77% of patients in the 3.4 mg/kg cohort. Severe (Grade 3-4) keratopathy occurred in 44% of patients in the 2.5 mg/kg cohort and 41% of patients in the 3.4 mg/kg cohort. The rates and severity of keratopathy did not differ substantially between the two dose cohorts. Keratopathy occurred early, with a median time to onset for the first occurrence of keratopathy of 36 days (range 19-143) in the 2.5 mg/kg cohort and 22.5 (range 9-150) days in

the 3.4 mg/kg cohort. The median time to resolution for keratopathy events that resolved was 62 days (range 11-193) in the 2.5 mg/kg cohort and 60 days (range 12-253) in the 3.4 mg/kg cohort.

Treatment with belantamab mafodotin was also associated with decreases in visual acuity, including severe vision loss. The median time to onset for the first occurrence of visual acuity changes was 63.5 days (range 20-213) in the 2.5 mg/kg cohort and 46 days (20-259) in the 3.4 mg/kg cohort. In both dose cohorts, 17% of patients experienced a treatment-emergent decline in BCVA to 20/50 or worse (a level at which patients may not be legally able to drive, depending on the state) in the better seeing eye. In addition, one patient in the 2.5 mg/kg cohort (with baseline BCVA in one eye that was worse than 20/400) and 2 patients in the 3.4 mg/kg cohort had a decline in BCVA to 20/200 (a level meeting the definition for legal blindness in the U.S.) in the better seeing eye.

Among the ocular symptoms that occurred in patients, the most frequent AEs were vision blurred and dry eye (see Sections 9.3.3.2 and 9.3.3.3 of the Appendix). Among patients with keratopathy, AEs of blurred vision and dry eye only occurred in 31% and 18% of patients, respectively, in the 2.5 mg/kg cohort. Furthermore, only 43% of patients with keratopathy in the 2.5 mg/kg cohort experienced any AEs corresponding to ocular symptoms that may be seen in association with keratopathy.

The absence of other ocular symptoms in more than half of patients raises concern that in the absence of close monitoring with frequent ophthalmic exams, keratopathy could go undetected; and in the absence of appropriate management, including dose modifications, patients could develop serious sequelae, including corneal ulcers and severe vision loss.

Dose modifications, including dose delays/interruptions, dose reductions, and/or permanent discontinuation of study treatment, were the primary strategy used to manage ocular toxicities in DREAMM-2, and the ocular sub-study failed to show any impact on the incidence of ocular toxicity with the use of topical corticosteroids. Keratopathy was the most frequent AE leading to dose modifications in DREAMM-2. In the 2.5 mg/kg cohort, 47% of patients had at least one dose interruption due to keratopathy and 23% of patients had a dose reduction due to keratopathy. There was no difference in the rates of dose delays in the 2.5 mg/kg and 3.4 mg/kg cohorts and only minor differences in the rates of dose reductions.

Although few patients permanently discontinued belantamab mafodotin due to keratopathy (2 patients in the 2.5 mg/kg cohort and 5 patients in the 3.4 mg/kg cohort), discontinuations occurred in patients with Grade 2 or Grade 3 keratopathy, and overall, few patients (23%) enrolled in the 2.5 mg/kg cohort were still receiving treatment at the time of the primary analysis (median of 3 cycles of treatment). Despite evaluation of the lower 2.5 mg/kg starting dose and the short median duration of study treatment, the incidence of ocular toxicity was high and required dose modifications.

Although the ocular toxicity associated with belantamab mafodotin appears to be reversible in some patients, 59% of the patients in the 2.5 mg/kg cohort who had at least one Grade ≥2 keratopathy event (N=59) did not have resolution of keratopathy as of the last assessment based on the 6-month data cut-off. This did not improve substantially with extended follow-up (52% of patients did not have resolution as of the last assessment based on the 9-month data cut-off). Because follow-up had ended for 24% (14/59) of the patients without resolution as of

the last assessment based on the 6-month data cut-off date, information regarding reversibility of keratopathy is not available for these patients. Given the incomplete data regarding the reversibility of ocular toxicity, there is uncertainty at this time whether the dose modification strategy proposed by the Applicant is sufficient to mitigate the risk of ocular toxicity with belantamab mafodotin.

FDA does not agree with the Applicant's statements that despite ocular symptoms, patients had stability in disease-related symptoms and reported a high level of treatment satisfaction based on the available data and given that the PRO assessments were not designed to assess treatment satisfaction. For further discussion of the limitations with the PRO analysis, refer to the FDA comments in Section 3.1.1.2.7.5.

FDA notes that the toxicity profile of belantamab mafodotin is unique compared to the currently approved therapies for MM and ocular toxicity is the key safety issue. However, FDA notes that gastrointestinal toxicities and cytopenias also occurred in a significant percentage of patients in DREAMM-2. In the 2.5 mg/kg cohort, 24% of patients had nausea, 62% had thrombocytopenia, 32% had anemia, and 28% of patients had neutropenia.

4 CLINICAL OUTCOME ASSESSMENT ANALYSES

The Applicant's Position

Please refer to Sections 3.1.1.2.7.5 and 3.1.1.2.7.6 for discussion of DREAMM-2 patient reported outcomes.

The FDA's Position

Refer to the FDA assessments of visual PROs and health-related quality of life in Sections 3.1.1.2.7.5 and 3.1.1.2.7.6 above.

5 OTHER SIGNIFICANT ISSUES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

5.1 Dose Justification

The Applicant's Position

Based on the comparable efficacy with a more favorable safety profile, the 2.5 mg/kg Q3W dose has been selected as the monotherapy dose for the heavily pre-treated population of patients with RRMM. The Q3W schedule was selected prior to DREAMM-1 based on the predicted half-life in humans (approximately 12 days) and clinical experience with other ADCs at the time.

Relevant key efficacy and safety results for the two cohorts in DREAMM-2 that support the selection of the 2.5 mg/kg Q3W dose were as follows:

- The efficacy results were similar for the two dose levels. For the primary analysis, the ORR was 31% (97.5% CI: 20.8, 42.6) in the 2.5-mg/kg cohort and 34% (97.5% CI: 23.9, 46.0) in the 3.4-mg/kg cohort; the responses were deep (18% and 20% achieving VGPR or better i.e. 60% achieved VGPR or better).

- The safety data showed better tolerability in the 2.5-mg/kg cohort than in the 3.4-mg/kg cohort:
    - The overall incidence of SAEs was 40% in the 2.5-mg/kg cohort and 47% in the 3.4-mg/kg cohort;
    - Thrombocytopenia (based on pooled preferred terms of thrombocytopenia and platelet count decreased) were reported in 35% of patients in the 2.5-mg/kg cohort and 59% of patients in the 3.4-mg/kg cohort;
    - Neutropenia (based on pooled preferred terms of neutropenia, neutrophil count decreased, and febrile neutropenia) was reported in 14% of patients in the 2.5-mg/kg cohort and 27% of patients in the 3.4-mg/kg cohort;
    - AEs leading to dose delays occurred in 54% of patients in the 2.5-mg/kg cohort and 62% of patients in the 3.4-mg/kg cohort; and
    - AEs leading to dose reductions occurred in 29% of patients in the 2.5-mg/kg cohort and 41% of patients in the 3.4-mg/kg cohort.

Exposure-response analyses determined that both efficacy and safety endpoints were associated with disease factors and patient characteristics. The probability of response and PFS were not associated with exposure after disease factors and patient characteristics were included in these models. Exposure-safety relationships showed increased probability of corneal events with higher plasma belantamab mafodotin exposure and increased probability of thrombocytopenia with higher plasma cys-mcMMAF exposure, when accounting for baseline patient and disease characteristics such as baseline platelet count. The integrated exposure-response analysis 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.

The clinical efficacy results and exposure-efficacy relationships showed similar benefit at the two dose levels in DREAMM-2. The clinical safety results, including more AEs leading to dose modifications in the 3.4-mg/kg cohort, 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 proposed dosing regimen for single-agent belantamab mafodotin in patients with RRMM is 2.5 mg/kg Q3W as an IV infusion over approximately 30 minutes until disease progression or unacceptable toxicity.

The FDA's Position

FDA does not concur with the Applicant's statement of, "increased probability of thrombocytopenia with higher plasma cys-mcMMAF exposure," due to the bioanalytical issue related to cys-mcMMAF measurement (see FDA's position in Section 1.2.4).

The proposed dosing regimen of 2.5 mg/kg Q3W for belantamab mafodotin shows a similar efficacy profile (Section 9.3.2) and lower rates of some AEs compared to the 3.4 mg/kg Q3W belantamab mafodotin dose (Section 3.1.1). However, given the high rates of corneal AEs 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 determine the optimal dose that will mitigate the risk of corneal toxicity without a clinically significant impact on efficacy.

The FDA's E-R analysis for efficacy and safety are included in Appendix 9.4.5

5.2 Post-Market Plan: Confirmatory Study

The Applicant's Position

A confirmatory study (DREAMM-3) has been designed to evaluate the efficacy and safety of belantamab mafodotin compared with pomalidomide/dexamethasone combination treatment. DREAMM-3 is a Phase 3, randomized controlled trial that will enroll 320 patients with RRMM previously treated with ≥2 prior therapies that included both lenalidomide and a PI and who progressed on or within 60 days of last therapy; prior daratumumab treatment is not mandated. Enrolled patients will be randomized at 2:1 ratio to single-agent belantamab mafodotin (2.5 mg/kg Q3W) or pomalidomide/dexamethasone. The 2:1 randomization will increase the safety experience with belantamab mafodotin against this well-characterized and established standard of care. The randomization will be stratified by: prior anti-CD38 therapy (Y/N); ISS stage (I/II vs III); and number of prior lines of therapy (<3 vs >3).

The primary endpoint of DREAMM-3 is PFS; the key secondary endpoint is OS. The study will have one interim PFS analysis for futility only, a final PFS analysis, and a later OS analysis. The final PFS analysis, if positive, will serve as a basis for marketing application submissions. The study is currently open for enrollment in multiple countries, and patients screening is ongoing. Detailed ocular assessments and associated risk management strategies are also being conducted for patients enrolled in the study.

DREAMM-3 will be conducted in 19 countries in North America, European Union, South America, and North East Asia. The study is ongoing and is projected to complete the targeted enrollment of 320 patients by 4Q 2021 and the primary analysis (PFS) is expected in the second half of 2022.

The FDA's Position

The DREAMM-3 study and other potential study designs are still under FDA review.

6 POINTS FOR THE ADVISORY COMMITTEE TO CONSIDER

The Applicant's Position

6.1 Benefit-Risk Discussion

Patients with RRMM who have had disease progression following treatment with ≥4 prior therapies have a substantial unmet medical need for new treatment options with multimodal MoAs that can provide durable responses with an acceptable safety profile. With its specific targeting mechanism for BCMA, its multimodal and novel mechanism of action, single agent belantamab mafodotin fills this need and offers an opportunity to overcome resistance to current treatment options and provide long-lasting responses to about one- third of patients with heavily pretreated disease. In the pivotal Phase 2 study, belantamab mafodotin 2.5 mg/kg Q3W demonstrated clinically meaningful responses, with a durability of at least 9 months or more. Deep responses (VGPR or better) were achieved in 60% of responders, with some patients experiencing complete remission despite being heavily pretreated. The median DoR

was not reached at the time of primary analysis data cut off with a median follow-up of 6.3 months. Both the estimated median DoR of at least 9 months and the estimated median OS of 11.9 months compare favorably with that of other approved agents in this setting and suggest at least a doubling over the 4.4 month median DoR of the only approved drug combination in this population (Chari, 2019), and an ~3 month extension of median OS over the 6–9 months historical benchmark (Gandhi, 2019; Pick, 2018).The updated efficacy data based on 3 additional months of follow-up (September 20, 2019 data cut-off) are consistent with the results of the primary analysis. Additional follow-up may further confirm the durability of response.

The recommendation for belantamab mafodotin single-agent therapy with the 2.5-mg/kg Q3W dose given as an IV infusion over approximately 30 minutes is supported by the similar clinical efficacy and exposure-efficacy observed compared with the 3.4-mg/kg dose, but with better tolerability.

To date, one death was possibly related to belantamab mafodotin 2.5 mg/kg (sepsis) in DREAMM-2, and few patients discontinued treatment due to AEs. No new safety signals have been identified with additional follow-up. The most common AEs excluding keratopathy (MECs), were thrombocytopenia and anemia. These hematologic AEs are frequently reported with approved RRMM treatments, common in patients with heavily pretreated disease, and are routinely monitored for and actively managed in this patient population (Ludwig H, , 2019). Keratopathy [MECs], with or without symptoms, observed with belantamab mafodotin treatment are a novel aspect of this myeloma therapy and are a clinically important component of the overall risk of treatment. Evidence suggests these events are time-limited (median duration of first moderate or severe keratopathy [MECs] event: 85 days [range: 8–270]) and can be managed with dose modifications without the need for patients to discontinue treatment (3% discontinued due to any corneal event). Patients may experience a decrease in visual acuity and ocular symptoms (blurred vision and dry eye), which may lead patients to give up certain activities of daily living, such as driving or reading. However, these symptoms tend to improve on therapy and are reversible. As of the data cut-off, permanent complete vision loss has not been reported. Health-related quality of life and cancer-related symptoms remain stable over time despite the high incidence of corneal events, suggesting that these events do not impact the patient's overall quality of life. The current recommendations for the management of corneal events includes regular follow-up with an eye care professional (ophthalmic examinations prior to each dose), dose modification, and frequent use of preservative-free lubricant eye drops.

In conclusion, belantamab mafodotin offers an important treatment option to address a high unmet medical need. The deep responses achieved in approximately one-third of patients treated with belantamab mafodotin, with a DoR longer than the expected OS in this patient population, provides an unprecedented benefit over currently approved agent in this heavily pre-treated relapsed refractory multiple myeloma patient. This benefit is balanced with its safety profile comprised of corneal and hematologic events, which require careful management but largely resolve over time, and allow patients to maintain their QoL while they avoid clinical deterioration due to myeloma progression. Thus, belantamab mafodotin offers a positive benefit-risk profile when given as a single agent at the 2.5 mg/kg dose level to heavily pretreated patients with RRMM and offers extended durability of clinical efficacy over existing

therapies, thus representing a differentiated treatment option to address a high unmet medical need.

For patients to achieve the potential benefit of belantamab mafodotin treatment while ensuring their safety, GSK is proposing a comprehensive REMS, including a Communication Plan and ETASU. This includes ophthalmic examinations (including slit lamp examination and BCVA assessments) prior to each cycle, and promptly for worsening symptoms, which ensures that patients are examined prior to each dose. GSK believes the proposed measures will ensure the positive benefit-risk of belantamab mafodotin in this RRMM patient setting.

The FDA's Position

Despite significant therapeutic advances, MM remains incurable, and there is an unmet medical need for additional therapeutic options for patients who relapse and become refractory to available therapies. Belantamab mafodotin is a first-in-class anti-BCMA ADC with a novel mechanism of action compared to the currently approved therapies for MM. FDA agrees that the demonstrated ORR of 31% in the patients who received the 2.5 mg/kg dose of belantamab mafodotin in the DREAMM-2 trial may be beneficial in this heavily pre-treated population of patients with RRMM.

However, the ocular toxicity associated with treatment with belantamab mafodotin is a major safety concern. The mechanism is not completely understood, and this is a novel toxicity that is not typically seen with other anti-myeloma therapies. The incidence and severity of keratopathy observed in DREAMM-2 was high and associated with clinically relevant decreases in visual acuity, including severe vision loss in some patients, and significant interference with patients' activities of daily living and impacts on driving and reading. Dose modifications, including dose interruption, dose reduction, and discontinuation of study treatment, are the primary mitigation strategy for the ocular toxicity observed with belantamab mafodotin. The ocular sub-study evaluating the use of prophylactic steroid eye drops failed to show any mitigating effects on the incidence or severity of keratopathy. Despite evaluation of the lower 2.5 mg/kg starting dose of belantamab mafodotin, close monitoring with comprehensive ophthalmic exams at baseline and prior to each dose, and implementation of dose modifications, many patients had recurrent and/or unresolved events. Because many patients had significant keratopathy on ophthalmic exam in the absence of other ocular symptoms, there is also a concern that keratopathy could go undetected in the absence of close monitoring, potentially leading to serious sequelae, including the development of corneal ulcers. Although the observed changes in the corneal epithelium appear to be reversible in some patients, there is inadequate characterization of the reversibility and severity given that a significant proportion of patients had keratopathy that was not resolved as of the last assessment, including some patients for whom follow-up had ended.

Overall, considering the frequency and severity of ocular toxicity associated with belantamab mafodotin, the lack of clear mitigation strategies, and incomplete data regarding reversibility and severity, there is uncertainty whether the proposed dose modification strategy is sufficient to mitigate the risks. Although the efficacy results from DREAMM-2 suggest a benefit with belantamab mafodotin in the proposed population of patients with RRMM, it is not clear whether the benefit outweighs the risks of ocular toxicity.

7 DRAFT TOPIC FOR ADVISORY COMMITTEE DISCUSSION

Does the demonstrated benefit of belantamab mafodotin outweigh the risks in the proposed patient population with multiple myeloma?

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9 APPENDICES

9.1 Appendix 1: Corneal Events Background Information

9.1.1 Introduction

The ADC belantamab mafodotin is a first-in-class antibody-drug conjugate with an afucosylated, humanized anti-BCMA monoclonal antibody conjugated to the microtubule disrupting agent, MMAF. Afucosylated monoclonal antibodies are engineered such that the oligosaccharides in the Fc region of the antibody lack fucose sugar units, thereby enhancing ADCC.

ADCs containing auristatin and maytansinoid (such as DM1 and DM4) derivatives are known to cause ocular toxicity in the form of corneal changes; these AEs are therefore considered a class effect. Commonly reported ocular toxicities include blurred vision, keratitis, dry eye and microcyst-like corneal epithelial changes (Eaton, 2015; Donaghy, 2016). ADCs with monomethyl auristatin E show ocular toxicity similar to ADCs with MMAF. For example, the recently FDA-approved enfortumab vedotin-ejfv showed a 46% rate of ocular disorders in 310 treated patients. These events included keratitis, dry eye symptoms, and blurred vision (PADCEV USPI, 2019)

The ocular AEs and findings on ophthalmic exam observed with all auristatin- and maytansinoid-containing agents were almost always reversible with sufficient follow-up, or sometimes without, treatment discontinuation.

9.1.2 Potential Mechanism of Corneal Events

Ocular changes associated with belantamab mafodotin were observed in rats and rabbits, but not in monkeys, and were described as minor histological changes. Increased mitosis was observed, consisting of several basal cells that appeared in anaphase and/or bilateral single cell necrosis of corneal epithelial cells. These histological findings are consistent with the posited mechanism of corneal epithelial cell death in MMAF-treated patients and occur in the absence of any clinical findings, as observed in patients treated with belantamab mafodotin. In biodistribution studies in rats, belantamab mafodotin was detected at much higher levels in the liver and kidneys than in the eye. Belantamab mafodotin signal in the eye was associated with the connective tissue and muscle rather than the cornea. Biodistribution was not affected by the conjugated payload. Following IV administration of belantamab mafodotin to rabbits, ADC, total mAb, and cys-mcMMAF were detected qualitatively in tear fluid.

BCMA is not expressed in human eye; therefore, the uptake of belantamab mafodotin observed in primary human corneal epithelial cells (HCEC) is nonspecific. Reduced uptake of belantamab mafodotin is observed in the presence of EIPA [5-(N-Ethyl-N-isopropyl) amiloride], suggesting a role for macropinocytosis. Intracellular co-localization of labelled belantamab mafodotin within lysozymes of HCEC has been demonstrated and cytoplasmic levels of cys-mcMMAF have been measured following catabolism of the antibody. Belantamab mafodotin causes cytotoxicity of HCECs via apoptosis following microtubule depolymerization, consistent with the MMAF mechanism of cell death and with data in a recent publication (Zhao, 2018). Although animal and/or in vitro models have been informative for exploring the mechanism of corneal toxicity, both have significant limitations; therefore, the most relevant experience comes from humans.

The FDA's Position

In general, the FDA concurs with the Applicant's description of potential mechanisms of corneal events. Based on the FDA review of ocular findings in rats and rabbits, the severity of the findings (e.g., increased mitosis and single cell necrosis of corneal epithelial cells) were minimal to mild . FDA notes the Applicant's statement that belantamab mafodotin was detected at much higher levels in the liver and kidneys than in the eyes in rats. This observation depended on the assay; by immunoassay, concentrations were higher in the eyes than liver. Of note, while concentrations of the ADC in the organs are important in inducing toxicities, sensitivity of organs are equally important. Ocular toxicities may reflect high sensitivity of the eyes to low ocular concentrations of the payload or the ADC. Additionally, based on systemic inflammatory responses seen in the animals, we cannot ignore ocular toxicities secondary to the general pro-inflammatory response seen with this payload and ADC.

FDA notes that while there are other approved ADCs containing monomethyl auristatin E (MMAE) that are associated with ocular toxicity, such as enfortumab vedotin, there are no currently approved MMAF-containing ADCs. In addition, based on data from the literature, incidences of ocular toxicity may be higher in association maytansinoid- and MMAF-containing ADCs (Eaton, 2015). FDA agrees that the incidence of ocular toxicity associated with enfortumab vedotin was 46% in the EV-201 trial; however, given the challenges of making cross-trial comparisons, including issues such as differences in patient populations, underlying risk factors, and frequency and methods of assessment, it is difficult to make any comparisons to the occurrence of ocular toxicity with belantamab mafodotin in DREAMM-2.

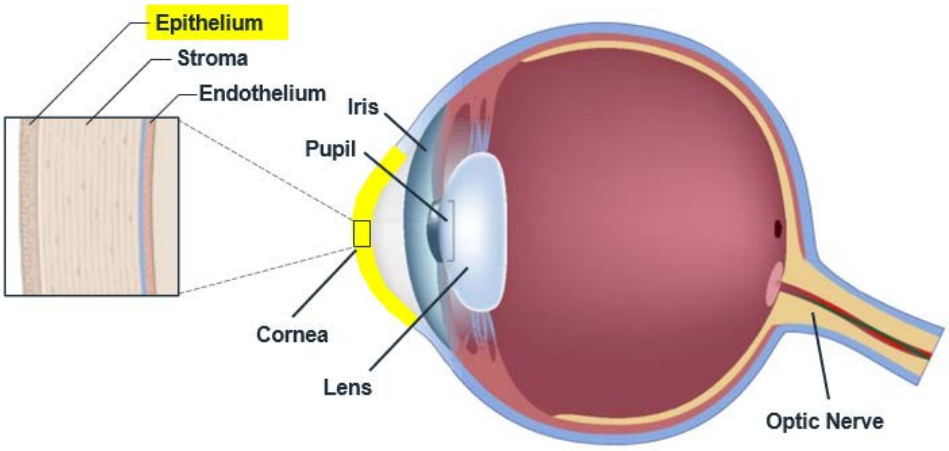
9.1.3 Corneal Events Background

9.1.3.1 Corneal Anatomy

The corneal epithelium is the protective lining of the cornea, is richly innervated, and helps stabilize the tear film. Epithelial irregularities or changes can lead to ocular symptoms. Furthermore, as the tear film-air interface is the first refracting surface of the eye, an irregular or damaged epithelium can affect visual function. The following symptoms are commonly occurring symptoms associated with epithelial irregularities or changes: foreign body sensation, irritation, feeling that the eye is dry, eye pain, blurred vision.

The corneal toxicity seen with belantamab mafodotin primarily affects the epithelium. As the most superficial layer lining the surface of the eye, the corneal epithelium regenerates continuously and is about five to six layers thick. It takes roughly two weeks for a newly-formed basal epithelial cell migrate to the ultimate anterior location before naturally being sloughing off. Although the corneal epithelial turnover is relatively short, because belantamab mafodotin has a half-life in plasma of about two weeks, it can take considerably longer for complete resolution of the corneal changes.

Figure 10: Corneal Anatomy



9.1.3.2 Definitions of Corneal Adverse Event Reporting

Corneal AEs seen with belantamab mafodotin are coded through MedDRA and are designated as a keratopathy. A keratopathy is a disease or disorder of the eye's cornea.

Belantamab mafodotin can lead to keratopathy (MECs). Superficial and punctate epitheliopathy (findings commonly seen with dry eye) are not frequently noted on exam.

9.1.4 Clinical Corneal Events in Patients Treated with Belantamab Mafodotin

9.1.4.1 Symptomatology

As would be expected based on the age of the patient population, many patients had ophthalmic conditions at the time of enrollment in DREAMM-2.

Not all patients treated with belantamab mafodotin develop ocular symptoms, despite the relatively high rate of corneal exam findings observed with belantamab mafodotin therapy. Approximately 23% of patients can expect to report blurred vision at some point while being treated, while approximately 14% of patients will describe symptoms associated with the clinical condition called dry eye syndrome (burning sensation, itchy eyes, dryness sensation, photophobia, blurred visions etc.). In DREAMM-2, based on the CTCAE grading scale, almost all events were mild to moderate, with only 1% and 4% of patients developing severe dry eye and blurred vision symptoms, respectively.

Patients may have some eye examination visits where measured visual acuity is decreased from baseline, but patients are not always symptomatic or not always acutely aware of the change. Often, decreases in visual acuity are within the variability of the test or not considered a clinically meaningful change. Patients may notice decreased ability to read and may choose to decrease or even stop driving for some period of time while on therapy.

Patients will use preservative-free lubricant eye drop about four times per day, and their eye care provider may make other recommendations to reduce symptoms. Sometimes, a change in glasses may help (Eby et al, 2017).

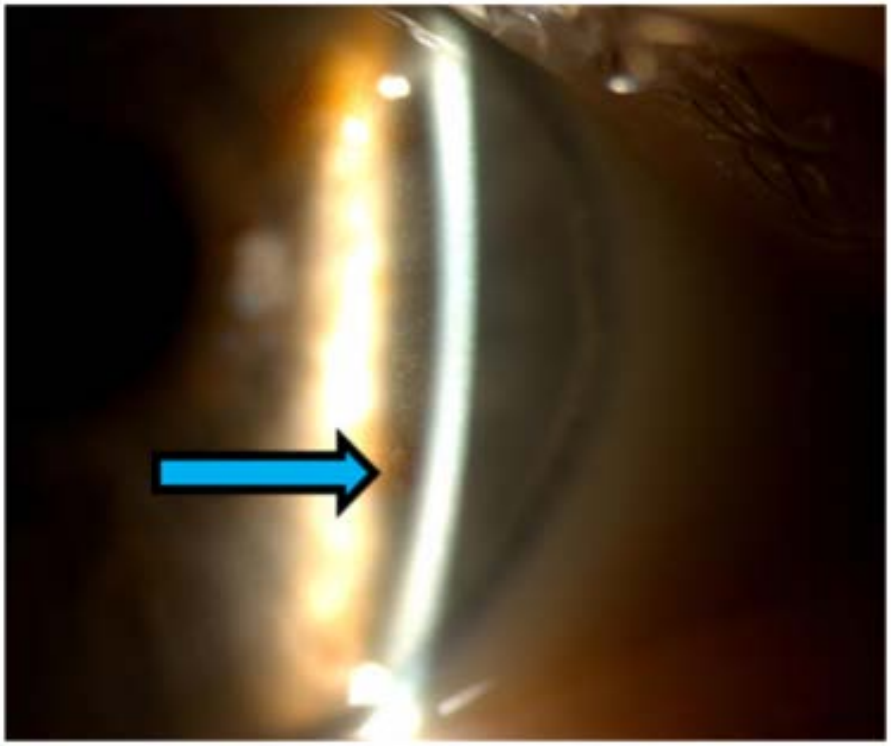
Patients are educated to contact their eye doctor urgently in the event that changes in vision or symptoms take place between scheduled visits.

9.1.4.2 Clinical Findings on Examination

The most common and expected finding seen on detailed examination of the cornea is a microcyst-like epithelial keratopathy, a finding well described in association with ADC therapy (Figure 11).

This finding is noted in about two-thirds of patients. Other epithelial findings commonly seen in dry eye syndrome can become manifest including, a punctate or superficial epithelial keratopathy (which often requires fluorescein staining of the cornea to best visualize).

Figure 11: Slit Lamp Microscopic Image of Microcyst-Like Epithelial Changes

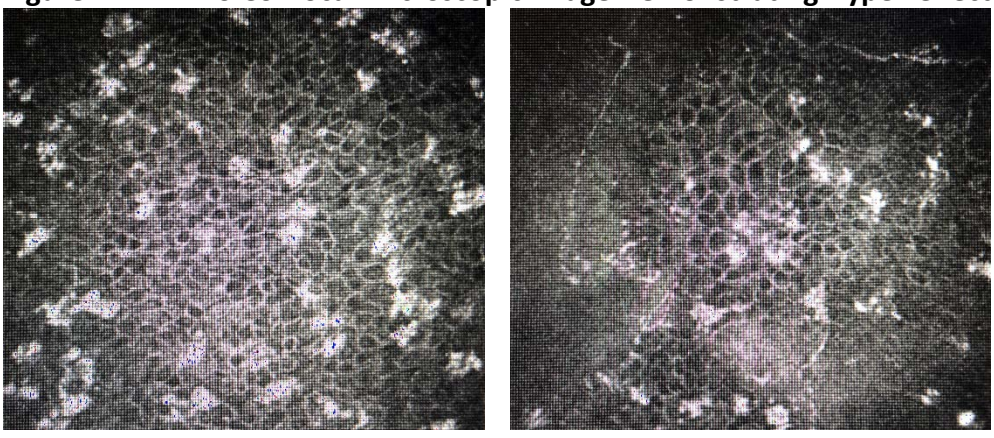


Above: Slit lamp microscopic image demonstrating microcyst-like epithelial changes (see arrowhead). The lesions are small, located within the corneal epithelium, and are seen here in the corneal periphery and mid-periphery.

9.1.4.3 Clinical Findings with Specialized Imaging

Specialized imaging modalities, such as in vivo confocal microscopic imaging, can reveal that the MECs observed on clinical exam are associated with hyperreflective opacities (Figure 12).

Figure 12: In Vivo Confocal Microscopic Image Demonstrating Hyperreflective Opacities



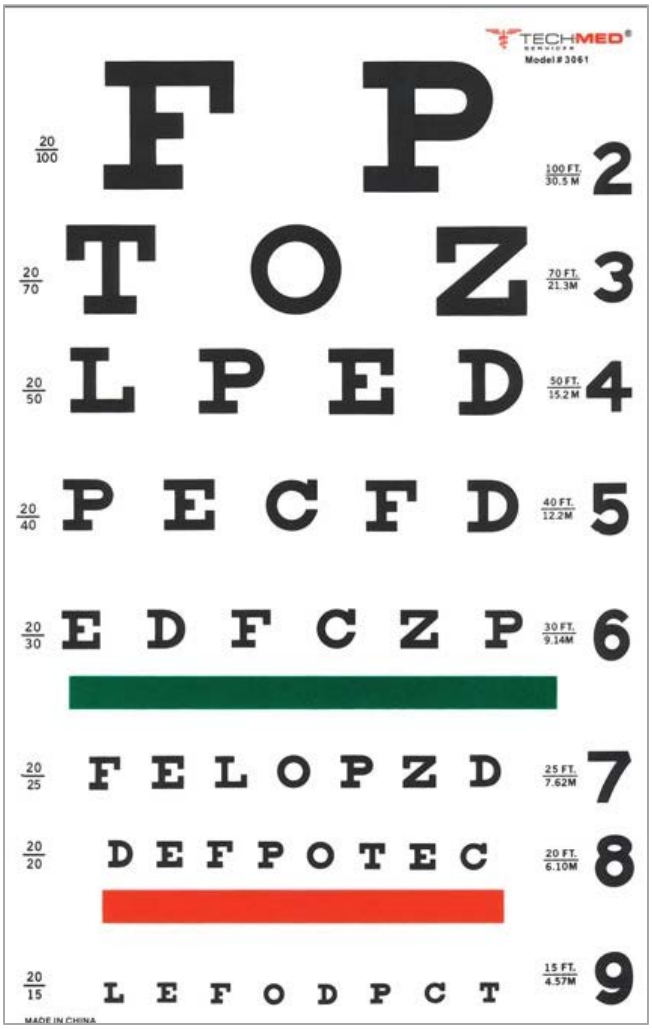
Above: In vivo confocal microscopic image demonstrating hyperreflective opacities within the corneal epithelium. These opacities were noted to be most prominent in the wing cells (left image) and basal cells (right image) and were seen less in the outer most superficial layer of epithelium. Hyperreflective opacities were not visualized within the corneal stroma (central cornea) or endothelium (back lining of the cornea).

9.1.5 Measuring and Interpreting Visual Acuity

Visual acuity testing is performed using the best possible glasses. This is called best-corrected visual acuity (BCVA) and is used so that test results can be accurately compared across visits.

Snellen charts (Figure 13) are the clinical standard for BCVA testing. These charts rely on high contrast letters measured at a set distance, typically 20 feet away, from the patient. The smallest visible line of letters read accurately determines the acuity level for the tested eye on a given day; this is called distance vision. However, distance vision is used to represent the best vision overall as simply changing the power of the glasses should make the near vision the same or better than distance vision under normal circumstances.

Figure 13: Snellen Visual Acuity Chart



"Normal" vision is considered 20/20, and worsening vision has a higher number in the denominator (e.g., 20/40).

Normal vision is not a requirement for enrollment in oncology studies or for starting clinical oncologic therapy and patients may initiate belantamab mafodotin treatment with various levels of baseline BCVA. Thus, in addition to BCVA testing at each eye examination, measuring the change in BCVA from baseline, is also important when evaluating BCVA data.

When interpreting Snellen BCVA for an individual, the performance of the better-seeing eye can be primarily considered because that is the patient's overall vision. Worsening in the better-seeing eye is referred to as bilateral worsening for reporting purposes, as opposed to the vision of one of two eyes which is called unilateral worsening herein. Visual quality of life is driven by the better seeing eye.

There are several important approaches to interpreting the meaning of a certain Snellen BCVA value or change in Snellen BCVA.

The International Classification of Diseases 11 classifications of visual function by Snellen acuity are shown in Table 24.

Table 24: Classification of Visual Function by Snellen Acuity

BCVA value	Impairment level	Notes
Normal to 20/40	Minimal to no impairment	20/40 or better is the cut-off for an unrestricted driver's license in most states in the US.
Worse than 20/40 to 20/60	Mild	
Worse than 20/60 to 20/200	Moderate	20/200 is considered legally blind in the USA.
Worse than 20/200 to 20/400	Severe	
Worse than 20/400	Blindness	

For context, 20/40 vision in the better seeing eye is the cut-off for an unrestricted driver's license in most states, and thus, 20/50 (one line worse) implies the patient would require a restricted license limiting driving to daytime only. A patient with 20/200 vision in the better-seeing eye qualify for Social Security disability based on visual function. It has been reported by several authors that even mild visual impairment may impact overall quality of life and also an individual's ability to optimally perform activities of daily living. However, this information does not factor in the therapeutic survival benefit of patients receiving a clinical oncologic therapy that is also secondarily affecting visual acuity (Stevenson et al, 2004; O'Conor et al, 2018; Cumberland et al, 2016).

Another important way to interpret visual function is by calculating the change in BCVA from the BCVA recorded at baseline. It is acceptable in clinical situations (especially when patients start with good vision) to consider a three-line change in Snellen acuity to be a significant change. For example, if a patient went from Snellen 20/20 to Snellen 20/50, that would be three lines of change, and clinically meaningful.

These methods are important to understand when evaluating visual acuity results.

The FDA's Position

FDA does not agree with the Applicant's statement that Snellen charts (Figure 13) are the clinical standard for BCVA. Snellen charts represent one method for BCVA testing. Regarding the statement under Figure 13 that, "Normal" vision is considered 20/20, it should be noted that with correction (glasses), half of all individuals can see better than 20/20. FDA also notes that worsening of vision in the better-seeing eye is strongly correlated with vision using both eyes (bilateral vision) and is sometimes referred to as bilateral worsening. FDA notes that patients with worsening to 20/50 may not legally be able to drive, depending on the state. The Applicant's statement that "it is acceptable in clinical situations (especially when patients start

with good vision) to consider a three-line change in Snellen acuity to be a significant change," is not always correct. A doubling of the visual angle is clinically meaningful (20/20 to 20/40). The Snellen chart does not have equal spacing between lines. On the Snellen chart, a doubling of the visual angle, can vary between 1 line (20/100 to 20/200), 2 lines (20/50 to 20/100, or 3 lines (20/20 to 20/40). The example provided has an error, "a patient went from Snellen 20/20 to Snellen 20/50" is actually a four-line change.

The FDA agrees that not all patients with keratopathy had associated symptoms of blurred vision or dry eye. Patients on the trial were closely monitored with ophthalmologic examinations at baseline and prior to each dose. In the absence of close monitoring there is a concern that keratopathy could go undetected, potentially leading to serious sequelae, including the development of corneal ulcers.

9.1.6 Recovery

The corneal events association with belantamab mafodotin are frequent and due to a drug-related toxicity affecting the corneal basal epithelial cell. As of the data cut-off for the 9-Month Update, there is no evidence that the underlying limbal stem cells, which serve as the precursor for basal epithelial cells are permanently damaged.

Signs of recovery of corneal events are also seen with belantamab mafodotin treatment. First, patients improve (events become less severe) with dose delays. Improvement is required for re-dosing, and all patients in DREAMM-2 were able to re-initiate treatment, except one patient who discontinued due to keratopathy (MECs) and an additional two patients who discontinued due to blurred vision. Second, an analysis of the extent of epitheliopathy shows improvement in many cases over time, even while patients remain on therapy. As expected, in a clinical trial study evaluating terminally ill patients approaching end-of-life care, there is limited follow-up once patients discontinue study treatment. As of the last follow-up, 50% of patients with blurred vision and 69% of patients with symptoms of dry eye had recovered. Of the 19 patients (among 95 total in the 2.5-mg/kg cohort) who showed a unilateral worsening of BCVA as defined by a Snellen acuity of 20/50 or worse, 89% had recovered at the last assessment with a median time to resolution of 22 days (range: 8–57). For 5 patients with unilateral-worsening who had one eye decline to 20/200 or worse, 4 had recovered by the last assessment, with a median time to resolution of 22.5 days (range: 21–54). Sixteen patients showed bilateral decline of vision to 20/50 or worse in the better-seeing eye and 15/16 (94%) recovered at the last assessment with a median time to resolution of 22 days (range: 7–64). The one patient with a bilateral decline showed a BCVA reduction to 20/200 or worse in the better-seeing eye that patient recovered in 22 days.

Visual quality of life data also shows improvements over time following the worst-case post-baseline PRO assessments. For example, 16/70 patient (23%) gave up driving due to visual function at some point during the study, but 7 of those 16 (44%) returned to driving prior to the end of treatment. Similarly, 9/83 patients stopped reading a newspaper because of vision changes, but 5 of these 9 returned to this activity while on therapy, and an additional 2 returned to this activity after stopping therapy. Thus, the study results show that 78% of patients who stopped reading were able to return to this activity.

A review of ADC-related corneal toxicity literature is highly supportive of the conclusion that the corneal epitheliopathy seen in patients treated with belantamab mafodotin is reversible

(Corbelli et al, 2019; Younes et al, 2012; Tannir et al, 2014; de Goeij et al, 2016; Thompson et al, 2015).

The FDA's Position

Regarding the Applicant's reference to the impact of belantamab mafodotin on the corneal basal epithelial cells, FDA notes that there is no evidence that the observed dysfunction of underlying limbal stem cells, which serve as the precursor for basal epithelial cells, is due to permanent damage of the underlying stem cells.

FDA agrees with the data presented above regarding the proportion of patients with resolution of symptoms of blurred vision and dry eye. FDA also agrees with the data presented regarding the proportion of patients with resolution as of the last assessment for patients with unilateral or bilateral worsening of BCVA to 20/50 or worse and 20/200 or worse and the corresponding median time to resolution for each group. Although the majority of patients had events that were resolved as of the last assessment, one patient with unilateral decline to 20/200 or worse and one patient with bilateral decline to 20/50 or worse had not recovered as of the last assessment. FDA notes that despite follow up of 9 months not all patients had complete resolution of symptoms.

FDA reiterates the limitations of the collected visual PRO data, as described in Section 3 above. The small sample size, suboptimal completion rate, and high attrition provides an incomplete picture of resolution of patient-reported visual symptoms. Although some patients were able to return to driving and reading, the Applicant's analysis does not provide information on whether patients were able to resume these important activities of daily living without residual difficulty. Therefore, FDA does not completely agree with the Applicant's statement regarding improvements over time based on visual quality of life data. FDA also disagrees with the Applicants conclusion that "literature is highly supportive of the conclusion that the corneal epitheliopathy seen in patients treated with belantamab mafodotin is reversible". The referenced literature to support this conclusion included data from early phase trials and included small numbers of patients. Additionally, given the challenges of making cross-trial comparisons it is difficult to make any comparisons to the occurrence of ocular toxicity with belantamab mafodotin in DREAMM-2.

9.1.7 Management

Although keratopathy (MECs) was frequent in patients treated with single agent belantamab mafodotin, effective approaches have been put in place to maximize patient comfort and vision. Preservative-free lubricant eye drop administration is recommended at least four times daily in each eye for all patients throughout treatment. The eye care provider may recommend symptomatic care as indicated, and punctal plugs, autologous serum, bandage contact lenses, and warm eye compresses have been used in this setting. Patient education and access to an eye care professional is integral to the belantamab mafodotin program. Clinical monitoring is an important component of care, as well. Dosing decisions will be made based on the eye examination and BCVA findings and communication with the patient and treating oncologist will be streamlined. Through this approach permanent changes in vision or damage to the cornea have been avoided to date.

The FDA's Position

Although autologous serum has been used, it has never been demonstrated to be effective in controlled trials and it is not an approved therapy. FDA disagrees with the Applicant's statement that permanent changes in vision or damage to the cornea have been avoided to date. FDA notes that there is incomplete information on resolution or severity for some patients who had persistent keratopathy when follow up ended (Section 3.1.1.2.7.9). Otherwise FDA concurs with the Applicant's discussion of management.

9.1.8 Summary

Corneal events are the most frequently reported AEs associated with belantamab mafodotin in clinical studies. The events are consistent with those reported in the literature for other MMAF-conjugated ADCs. Although the incidence of corneal events was high in DREAMM-2, there have been no reports of permanent loss of vision and few patients have permanently discontinued treatment due to corneal events.

At this time, GSK believes dose modification (reduction and/or delays) is the most important mitigation strategy for belantamab mafodotin-associated corneal events. Concomitant use of preservative-free lubricant eye drops may also ease symptoms and be beneficial.

GSK has developed detailed risk mitigation plans for marketed use of belantamab mafodotin, including guidance in the prescribing information and educational materials for prescribers, eye care professionals, and patients. Development of a consultation network is proposed to ensure optimal coordination of care between oncologists and eye care providers.

GSK believes belantamab mafodotin represents an important treatment advance for heavily pre-treated RRMM patients and that despite a high frequency of corneal AEs, the benefit-risk remains positive.

The FDA's Position

FDA does not agree with the Applicant's assertions above. As stated in Section 3.1.1.2.7.3, keratopathy was unresolved in half of the patients in the 2.5 mg/kg dose with 9-months of follow-up. Information on resolution for 25% of the patients with persistent keratopathy at the last assessment in the 2.5 mg/kg cohort will not be available, as these patients either died or were lost to follow-up. Given the incomplete data on resolution, there is uncertainty regarding reversibility of ocular toxicity in all patients and the extent of severity of ocular toxicity with belantamab mafodotin. At this time there remains residual uncertainty whether the dose modification strategy proposed by the Applicant is sufficient to mitigate the risk of ocular toxicity with belantamab mafodotin.

9.1.9 References for Corneal Events Background Information

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9.2 Appendix 2: Clinical Experience with the Lyophilized Product

DREAMM-2 study included a small, independent cohort to generate clinical experience with the intended commercial drug product to support the analytical package. In accordance with ICH Q5E (Comparability of Biotechnological/Biological Products), an extensive analytical comparability study was conducted to support the in vivo equivalence of the lyophilized (commercial) and frozen liquid (used in the main part of DREAMM-2) presentations.

The frozen liquid presentation and proposed commercial product provide, upon dilution, the same solution for IV administration.

Conduct of the lyophilized cohort and the main study was identical, except enrollment commenced for the lyophilized cohort in November 2019 (approximately 5 months after the main study); all patients on the lyophilized cohort received the higher dose evaluated in the main study (3.4 mg/kg Q3W), based on the efficacy and safety data available at the time the

study was designed. Direct comparisons cannot be made due to the non-randomized nature of enrollment into the lyophilized cohort and the relatively small number of patients compared with the frozen liquid cohort.

Overall, demographic and baseline disease characteristics were similar; however, patients in the lyophilized cohort had received a median of 5 prior lines of treatment (compared with 6 for the frozen liquid cohort), fewer patients had high-risk cytogenetics (20% lyophilized vs 32% frozen liquid) and patients had notably lower median baseline soluble BCMA (sBCMA; 50 ng/ml vs 89.0 ng/ml) and immunoglobulin G (IgG; 3.83 vs 12.6) compared to the frozen liquid cohort.

The efficacy analyses summarized below for the lyophilized cohort were based on 25 patients following the intent-to-treat principal, and safety analyses on 24 patients who were actually treated with the lyophilized presentation.

Efficacy: At the time of the primary analysis, 10 patients (40%) were ongoing on study treatment and 14 patients (58%) discontinued, of whom 4 patients (16%) died (cause: disease under study). With 3 months of additional follow-up, 4 additional patients in the lyophilized cohort had discontinued study treatment; 3 due to progressive disease and 1 due to an AE. Overall, 17% of patients in the 3.4-mg/kg lyophilized cohort died compared with 31% in the 3.4-mg/kg frozen liquid cohort.

The ORR by IRC assessment was numerically higher in the lyophilized cohort compared with the frozen liquid cohort (48% vs 34%) (Table 25). At the 90-day safety update, the median DoR was reached in the frozen liquid cohort (6.2 months, 95% CI: 4.8, not reached) but not in the lyophilized cohort, most likely due to the shorter duration of follow-up on the lyophilized cohort.

Table 25: Best Response at Primary Analysis and 9-Month Follow-Up for the Frozen Liquid and Lyophilized Cohorts

	Number (%) of Patients			
	Belantamab Mafodotin			
	Primary Analysis (21Jun19)		Updated Data (20Sep19)	
	3.4 mg/kg Frozen (N=99)	3.4 mg/kg Lyophilized (N=25)	3.4 mg/kg Frozen (N=99)	3.4 mg/kg Lyophilized (N=25)
Best Response				
Stringent Complete Response (sCR)	3 (3)	0	1 (1)	0
Confirmed response (CR)	0	0	3 (3)	1 (4)
Very Good Partial Response (VGPR)	17 (17)	6 (24)	19 (19)	5 (20)
Partial response (PR)	14 (14)	6 (24)	12 (12)	7 (28)
Minimal response (MR)	5 (5)	1 (4)	5 (5)	1 (4)
Stable disease (SD)	23 (23)	5 (20)	22 (22)	4 (16)
Progressive disease (PD)	26 (26)	6 (24)	29 (29)	6 (24)
Not evaluable	11 (11)	1 (4)	8 (8)	1 (4)
Overall Response Rate				
sCR+CR+VGPR+PR	34 (34)	12 (48)	35 (35)	13 (52)
97.5% CI	(23.9, 46.0)	(25.5, 71.1)	(24.8, 47.0)	(28.9, 74.5)

IRC: Independent Review Committee
Source: 90 Day Safety Update Table 68 (ADSL, ADRS); DREAMM-2, Full Analysis Population, 90 DSU.

The FDA's Position

Given the small sample size (N=25) in the lyophilized cohort and the observed differences in baseline disease characteristics compared to the frozen liquid cohort, any statement regarding the comparison of efficacy endpoints between cohorts is misleading. The numerical difference can be attributed to the underlying heterogeneity and does not measure the clinical effect.

The DoR data in the lyophilized cohort is based on 12 patients in the risk set. 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.

FDA also notes that the 9-month data update was mainly for safety evaluation and additional efficacy analysis of this data is considered exploratory.

Safety: The AE profile for the two cohorts was generally similar, with no new safety signals identified. However, the incidence of SAEs was numerically higher in the lyophilized cohort compared with the frozen liquid cohort (63% vs 47%), but there was no clustering of specific SAEs occurring in ≥2 patients and the profile for Grade ≥3 AEs was comparable. In the lyophilized cohort, there appeared to be a higher incidence of corneal events (92% vs 77%, respectively) and a lower incidence of thrombocytopenic events (42% vs 59%, respectively).

Overall, AEs leading to dose modifications were consistent in the two cohorts. Keratopathy (MECs; 67% in the lyophilized cohort vs 49% in the frozen liquid cohort) and vision blurred (21% vs 9%, respectively) were the most common AEs leading to dose delays in both cohorts. The higher rate of corneal AEs in the lyophilized cohort was associated with differences in key individual patient characteristics between the two cohorts. Pharmacokinetic assessments have shown that, with lower baseline IgG or sBCMA levels or higher baseline albumin levels, belantamab mafodotin clearance is slower, resulting in higher overall belantamab mafodotin exposure. Higher belantamab mafodotin trough concentration (C_{tau}) is associated with higher probability of keratopathy/corneal events. Thus, lower baseline sBCMA and lower baseline IgG in the patients in the lyophilized cohort increased belantamab mafodotin C_{tau} and the probability of keratopathy/corneal events in this cohort.

The incidence of IRRs was comparable between the two cohorts (13% in the lyophilized cohort and 16% in the frozen liquid cohort) and no Grade ≥3 events occurred in the lyophilized cohort.

Summary

Comparability of the lyophilized and frozen liquid presentations used in DREAMM-2 has been demonstrated by an extensive analytical package conducted in compliance with ICH Q5E (Comparability of Biotechnological/Biological Products).

The frozen liquid and lyophilized presentation (proposed commercial product) provide, upon dilution, the same solution for IV administration.

The clinical experience with the lyophilized product supports analytical comparability. The trend toward higher corneal event rates in the lyophilized cohort is associated with differences in key individual patient characteristics between the two cohorts that result in higher median belantamab mafodotin exposure. Higher belantamab mafodotin C_{tau} was associated with a higher probability of corneal events. Presentation was not a significant factor in the population pharmacokinetic and exposure-response analyses for belantamab mafodotin. Therefore, GSK considers the trend toward differences in certain clinical outcomes observed in the lyophilized

cohort is not attributable to presentation but instead reflects differences in patient characteristics.

The FDA's Position

FDA does not agree with the Applicant's statement that differences in certain clinical outcomes observed in the lyophilized cohort are not attributable to the difference in presentation. Due to the small number of patients in the lyophilized cohort, definitive conclusions cannot be drawn. FDA also notes the trend toward higher incidences of keratopathy in the lyophilized cohort, but for the reasons noted above, does not agree that a definitive conclusion can be drawn as to whether this is related to individual patient characteristics that may have influenced belantamab mafodotin exposure between the two cohorts. Given the small number of patients who received the lyophilized presentation of belantamab mafodotin at the 3.4 mg/kg dose and the fact that that there is no data with the lyophilized presentation of belantamab mafodotin at the 2.5 mg/kg dose (the planned dose and formulation proposed for commercialization), there is some residual uncertainty regarding the safety of the lyophilized presentation given the increased incidence of keratopathy observed within the lyophilized cohort.

9.3 Appendix 3: Supplemental Data from DREAMM-2

9.3.1 DREAMM-2 Patient Demographics, Baseline Disease, and Clinical Characteristics

Table 26: DREAMM-2 Patient Demographics, Baseline Disease, and Clinical Characteristics

	Belantamab Mafodotin 2.5-mg/kg Q3W cohort (N=97)	Belantamab Mafodotin 3.4-mg/kg Q3W cohort (N=99)	Total population (N=196)
Age, median (range), years	65 (39–85)	67 (34–84)	66 (34–85)
18 to <65 years	45 (46)	36 (36)	81 (41)
65 to <75 years	39 (40)	46 (46)	85 (43)
³75 years	13 (13)	17 (17)	30 (15)
Sex, n (%)			
Female	46 (47)	43 (43)	89 (45)
Male	51 (53)	56 (57)	107 (55)
Race, n (%)			
White/Caucasian/European Heritage	72 (74)	83 (84)	155 (79)
Black or African American	16 (16)	11 (11)	27 (14)
Renal impairment per eGFR, n (%)[a]			
Normal (³90 mL/min/1.73m²)	19 (20)	17 (17)	36 (18)
Mild (³60 to <90 mL/min/1.73m²)	48 (49)	52 (52)	100 (51)
Moderate (³30 to <60 mL/min/1.73m²)	24 (25)	22 (22)	46 (23)
Severe (³15 to <30 mL/min/1.73m²)	2 (2)	5 (5)	7 (7)
ISS Stage at screening, n (%)			
Stage I	21 (22)	18 (18)	39 (20)
Stage II	33 (34)	51 (52)	84 (43)
Stage III	42 (43)	30 (30)	72 (37)
Unknown	1 (1)[b]	0	1 (<1)
High-risk cytogenetics[c], n (%)	26 (27)	32 (32)	58 (30)
17p13del	16 (16)	22 (22)	38 (19)
t(4;14)	11 (11)	11 (11)	22 (11)
t(14;16)	7 (7)	2 (2)	9 (5)
Myeloma immunoglobulin, n (%)			
IgG	65 (67)	73 (74)	138 (70)
Non-IgG and missing	32 (33)	26 (26)	58 (30)
Extramedullary disease, n (%)	22 (23)	18 (18)	40 (20)

	Belantamab Mafodotin 2.5-mg/kg Q3W cohort (N=97)	Belantamab Mafodotin 3.4-mg/kg Q3W cohort (N=99)	Total population (N=196)
Number of prior lines of therapy completed at screening[d]			
Median (range)	7 (3–21)	6 (3–21)	6 (3–21)
£4 lines, n (%)	16 (16)	17 (17)	33 (17)
>4 lines, n (%)	81 (84)	82 (83)	163 (83)
Prior therapies received, n (%)			
Steroids	97 (100)	99 (100)	196 (100)
Immunomodulator	97 (100)	99 (100)	196 (100)
Proteasome Inhibitor	97 (100)	99 (100)	196 (100)
Monoclonal Antibody	97 (100)	98 (99)[a]	195 (>99)
Chemotherapy	92 (95)	95 (96)	187 (95)
Stem Cell Transplant	73 (75)	86 (87)	159 (81)
Other	34 (35)	33 (33)[a]	67 (34)
HDAC Inhibitor	11 (11)	9 (9)	20 (10)
Refractory to prior therapies[e], n (%)			
Proteasome Inhibitor	95 (98)[b]	99 (100)	194 (99)
Immunomodulator	95 (98)[b]	98 (99)[b]	193 (98)
Monoclonal Antibody	97 (100)	92 (93)	189 (96)
Steroids	94 (97)	91 (92)	185 (94)
Chemotherapy	66 (68)	70 (71)	136 (69)
Other	29 (30)	28 (28)[a]	57 (29)
Stem Cell Transplant	11 (11)	13 (13)	24 (12)
HDAC Inhibitor	11 (11)	8 (8)	19 (10)
Immunomodulator and Proteasome Inhibitor	93 (96)[b]	98 (99)[b]	191 (97)

Data are n (%) unless otherwise specified. Full analysis set (all randomized patients, regardless of treatment administration).

a. Renal impairment data are missing for 4 patients in the 2.5-mg/kg cohort and 3 patients in the 3.4-mg/kg cohort.
b. Patient confirmed to have ISS Stage I disease.
c. High-risk cytogenetics defined as: t(4;14), t(14;16), or 17p13del.
d. The number of prior lines of therapy was derived as the number of prior anti-cancer regimens received by a patient. Combination therapy containing multiple components was counted as one regimen
e. Due to data entry errors, 4 patients in the 2.5-mg/kg cohort and 1 patient in the 3.4-mg/kg cohort were incorrectly categorized as not refractory to prior immunomodulatory and PI treatment.

ISS=International Staging System

Source: Adapted from CSR-205678 Table 9, Table 10, Table 12, Table 13 (ADSL, ADDC, ADCTX); DREAMM-2, ITT Population, Cut-off date of 21JUN2019

The FDA's Position

The FDA generally agrees with the Applicant's assessment of baseline demographic and disease characteristics. Demographic characteristics were similar between the 2.5mg/kg cohort and 3.4 mg/kg cohort. Subjects in the 2.5 mg/kg cohort had slightly more advanced disease (ISS stage III at baseline 43%, high risk cytogenetics 27%) and were more heavily pretreated with a median of 7 prior lines of therapies. As stated in Section 2.3.1.1.1, the DREAMM-2 trial enrolled a younger patient population compared to the representative population with RRMM and patients with extramedullary disease comprised only a small subset of the total population.

9.3.2 DREAMM-2 Efficacy Results for 3.4 mg/kg Cohort

9.3.2.1 Primary Endpoint: IRC-Assessed Overall Response Rate (ORR) for 3.4 mg/kg Cohort

Table 27: Best Confirmed Response Based on Independent Review Committee (2.5 mg/kg and 3.4 mg/kg Cohorts)

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

[a] Could be due to response not confirmed or inadequate baseline assessment/ no postbaseline assessment.
Source: CSR-205678 Table 17 (ADSL, ADRS); DREAMM-2, ITT Population, Cut-off date of 21JUN2019

The FDA's Position

The FDA generally agrees with the Applicant's assessment of best confirmed response based on independent review.

9.3.2.2 Secondary Endpoint: Duration of Response (DoR) for the 3.4 mg/kg Cohort

Table 28: DoR Based on IRC assessment (2.5 mg/kg and 3.4 mg/kg Cohorts)

	Belantamab Mafodotin	
	2.5 mg/kg (n=97)	**3.4 mg/kg (n=99)**
Number of patients, N	30	34
Progressed or died due to PD (event)	7 (23)	11 (32)
Censored, follow-up ended	3 (10)	4 (12)
Censored, follow-up ongoing	20 (67)	19 (56)
Event summary		
Death due to PD	0	0
Disease progression	7 (23)	11 (32)
Estimates for DoR (months)		
1st quartile	4.2	4.7
95% CI	(1.4, -)	(2.5, 6.2)
Median	NA	NA
95% CI	(-, -)	(4.9, -)
Probability of Maintaining Response		
Time-to-Event Endpoint at 4 Months	0.78	0.87
95% CI	(0.57, 0.89)	(0.69, 0.95)

Source: CSR-205678 Table 18 (ADSL, ADTTE); DREAMM-2, ITT Population, Cut-off date of 21JUN2019

9.3.2.3 Secondary Endpoint: Progression-Free Survival (PFS) for the 3.4 mg/kg Cohort

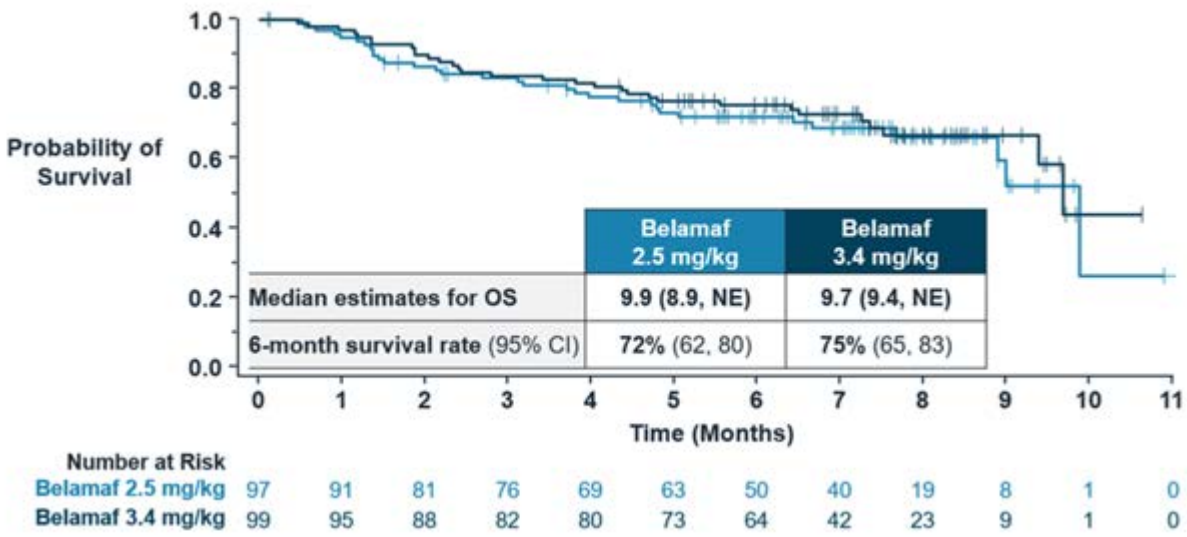
Table 29: PFS Based on IRC Assessment (2.5 mg/kg and 3.4 mg/kg Cohorts)

	Belantamab Mafodotin	
	2.5 mg/kg (N=97)	**3.4 mg/kg (N=99)**
Number of patients, n (%)		
Progressed or died (event)	56 (58)	55 (56)
Censored, follow-up ended	15 (15)	15 (15)
Censored, follow-up ongoing	26 (27)	29 (29)
Event summary, n (%)		
Disease progression	50 (52)	47 (47)
Death	6 (6)	8 (8)
Estimates for time variable (months)		
1st quartile	0.9	0.9
95% CI	(0.8, 1.5)	(0.8, 1.4)
Median	2.9	4.9
95% CI	(2.1, 3.7)	(2.3, 6.2)
3rd quartile	NA	NA
95% CI	(6.2, -)	(6.9, -)
Progression-free survival probability		
Time-to-event endpoint at 6 months	0.35	0.42
95% CI	(0.25, 0.46)	(0.31, 0.52)

Source: CSR-205678 Table 20 (ADSL, ADTTE); DREAMM-2, ITT Population, Cut-off date of 21JUN2019

9.3.2.4 Secondary Endpoint: Overall Survival (OS) for the 3.4 mg/kg Cohort

Figure 14: Kaplan-Meier Curve of Overall Survival (2.5 mg/kg and 3.4 mg/kg Cohorts)



Source: Adapted from CSR-205678 Figure 8 (ADSL, ADTTE); DREAMM-2, ITT Population, Cut-off date of 21JUN2019

The FDA's Position

FDA concurs with the results presented in 9.3.2. The median PFS was 2.9 months in the 2.5 mg/kg cohort and 4.9 months in 3.4 mg/kg cohort. The OS data was not mature at the time of analysis. As of the data cut-off, the 6-month overall survival rates were 72% and 75%. However, single-arm trials using time-to-event endpoints are difficult to interpret and unlikely to constitute supportive evidence because the inconsistent definition of time intervals across studies creates a biased estimate, and comparison to historical controls is also prone to bias. The efficacy evaluation was based on the clinical cut-off date for the primary analysis. The 9-month update was mainly for safety evaluation and additional efficacy analysis based on this data is considered exploratory.

9.3.3 DREAMM-2 Ocular Adverse Events

9.3.3.1 Keratopathy (MECs) by CTCAE Grading

MedDRA preferred terms were collated as representing events of keratopathy. The most common ocular AE was the preferred term keratopathy, which includes the "microcyst-like epithelial keratopathy" event that was reported by the investigators to correspond with corneal findings on the ocular eCRF, as instructed by the Sponsor.

In DREAMM-2 at the time of the data cut-off for the primary analysis, 71% of patients in the 2.5 mg/kg cohort and 75% of patients in the 3.4 mg/kg cohort experienced keratopathy (MECs). Grade 3 keratopathy AEs occurred in 27% and 20% of patients in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. One patient in the 3.4 mg/kg cohort had a Grade 4 keratopathy event. None of the keratopathy events were reported as SAEs. 14% of patients in the 2.5 mg/kg cohort and 17% of patients in the 3.4 mg/kg cohort experienced more than one occurrence of keratopathy.

Among patients for whom recovery data were available at the primary analysis data cut-off, 42% (28 of 67) of patients in the 2.5 mg/kg cohort with a keratopathy (MECs) event recovered,

with or without sequelae; 51% had not recovered/resolved. In the 3.4 mg/kg cohort, 30% (22 of 74) of patients with keratopathy events recovered with or without sequelae; 54% of patients with a keratopathy event had not recovered. Most patients with keratopathy had a dose delay (67% and 65% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively) and approximately one-third had a dose reduction (33% and 36% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively). Treatment was discontinued due to keratopathy for 2% of patients in the 2.5 mg/kg cohort and 3% of patients in the 3.4 mg/kg cohort.

As of the updated data cut-off for the 9-Month Update, there was no change in the proportion of patients who experienced a keratopathy event compared with the primary analysis. A higher proportion of patients' keratopathy events had recovered/resolved with or without sequelae compared with the primary analysis.

The FDA's Position

FDA's position on the limitations of CTCAE grading in assessing severity of keratopathy and ocular toxicities is outlined in Section 3.1.1.2.7.2. Nearly 60% (58/95) of patients had events of keratopathy Grade 2 or higher by CTCAE grading at the 3.4 mg/kg dose (Table 18). FDA notes that CTCAE Grade 2 or 3 (Eye Disorder, Other v4.03) includes patients assessed by the clinician as having moderate or severe symptoms including symptoms limiting age appropriate instrumental activities of daily living (Grade 2) or activities of daily living (Grade 3).

FDA agrees with the calculated rates of keratopathy in the AE dataset presented by the Applicant above. However, FDA does not agree with the Applicant's statement that 14% of patients in the 2.5 mg/kg cohort and 17% of patients in the 3.4 mg/kg cohort experienced more than one occurrence of keratopathy. FDA analysis based on the preferred term of keratopathy grouped with 1 occurrence each of the preferred terms keratitis and corneal epithelium defect, from the AE dataset, showed that 41/95 (43%) patients in the 2.5 mg/kg cohort and 45/99 (45%) patients in the 3.4 mg/kg cohort had 2 or more events of keratopathy, and the FDA analysis is consistent with the numbers presented in the Applicant's DREAMM-2 CSR. Therefore, a substantial proportion of patients experienced recurrent events of keratopathy.

The rates of resolution for keratopathy events were not significantly different from the rates of resolution of corneal events based on KVA grading with more than half the patients reporting continued events of keratopathy even with 9 months of follow up (Section 3.1.1.2.7.3).

9.3.3.2 Patient-Reported Corneal Events by CTCAE Grading: Blurred Vision

The MedDRA preferred terms collated as representing blurred vision events were blindness, diplopia, glare, halo vision, night blindness, vision blurred, visual acuity reduced, visual acuity tests abnormal, visual field defect, and visual impairment.

In DREAMM-2 at the time of the data cut-off for the primary analysis, 22% of patients in the 2.5 mg/kg cohort and 30% of patients in the 3.4 mg/kg cohort experienced blurred vision events (Table 30). Most AEs were Grade 1 or Grade 2 (13% and 15% of patients in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively) and none were SAEs. Grade 3 events occurred in 4% of patients in the 2.5 mg/kg and 2% of patients 3.4 mg/kg cohort. Patients with an event generally experienced only 1 event (76% and 70% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively).

Dose delays due to blurred vision events occurred for 24% of patients with an event in the 2.5 mg/kg and 30% in the 3.4 mg/kg cohort; dose reductions occurred in 10% of patients with an event in both cohorts. No patient discontinued treatment due to blurred vision.

For patients with blurred vision events, the event was unresolved in 38% of the patients in the 2.5 mg/kg cohort and 37% of the patients in the 3.4 mg/kg cohort.

As of the 9-Month Update, 23% of patients in the 2.5 mg/kg cohort and 32% of patients in the 3.4 mg/kg cohort experienced blurred vision events. The results are similar to what was reported for the primary analysis. Among patient with dry eye events, 36% and 31% in the 2.5 mg/kg and 3.4 mg/kg cohorts were not resolved as of the last follow up.

Table 30: DREAMM-2 Characteristics of Blurred Vision Events (CTCAE)

	Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		9-Month Update (20Sep19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Patients with Event, n (%)	21 (22)	30 (30)	22 (23)	32 (32)
Number of Events	29	43	34	45
Event Characteristics, n/N (%)				
Serious	0/95	0/99	0/95	0/99
Study treatment related	17/95 (18)	29/99 (29)	18/95 (19)	31/99 (31)
Number of events, n/N (%)				
One	16/21 (76)	21/30 (70)	15/22 (68)	23/32 (72)
Two	3/21 (14)	6/30 (20)	4/22 (18)	6/32 (19)
Three or more	2/21 (10)	3/30 (10)	3/22 (14)	3/32 (9)
Worst Outcome, n/N (%)				
Recovered/Resolved	10/21 (48)	14/30 (47)	11/22 (50)	14/32 (44)
Recovered/Resolved with Sequelae	0/21	1/30 (3)	0/22	2/32 (6)
Recovering/Resolving	3/21 (14)	4/30 (13)	3/22 (14)	6/32 (19)
Not Recovered/Not Resolved	8/21 (38)	11/30 (37)	8/22 (36)	10/32 (31)
Fatal	0/21	0/30	0/22	0/32
Maximum Grade, n/N (%)				
Grade 1	12/95 (13)	15/99 (15)	12/95 (13)	16/99 (16)
Grade 2	5/95 (5)	13/99 (13)	6/95 (6)	13/99 (13)
Grade 3	4/95 (4)	2/99 (2)	4/95 (4)	3/99 (3)
Grade 4	0/95	0/99	0/95	0/99
Grade 5	0/95	0/99	0/95	0/99
Action Taken [b], n/N (%)				
Study treatment withdrawn	0/21	0/30	2/22 (9)	0/32
Dose reduced	2/21 (10)	3/30 (10)	2/22 (9)	3/32 (9)
Dose not changed	16/21 (76)	27/30 (90)	17/22 (77)	28/32 (88)
Dose interrupted/delayed	5/21 (24)	9/30 (30)	5/22 (23)	10/32 (31)
Dose reduced or interrupted/delayed	6/21 (29)	9/30 (30)	6/22 (27)	10/32 (31)

a. Source: 9-Month Update Table 3.0182 (ADSL, ADAE)
CTCAE: Common Terminology Criteria for Adverse Events.
b. Patients could have more than 1 Action Taken and be represented more than once.

The FDA's Position

FDA clarifies that this description of blurred vision is not a "patient-reported outcome" as PRO are based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. In this section, blurred vision was interpreted by clinicians and reported by MedDRA preferred term. For discussion of the PRO-CTCAE blurred vision refer to the FDA analysis in section 3.1.1.2.7.5. Among the list of MedDRA terms provided by the Applicant, preferred terms that were present in the DREAMM-2 AE dataset were diplopia, vision blurred,

visual acuity decreased, and vision impaired. FDA agrees with the data presented by the Applicant for the AEs of blurred vision. FDA notes that although the overall rates of were low, significant proportion of patients with blurred vision (52%) did not have complete resolution of symptoms in both the dose levels and two patients in the 2.5 mg/kg cohort discontinued treatment due to blurred vision with extended follow-up at 9 months.

9.3.3.3 Patient-Reported Corneal Events by CTCAE Grading: Dry Eye

To provide a comprehensive evaluation of dry eye, events in this section include the following MedDRA AE preferred terms considered to be related to dry eye: dry eye, ocular discomfort, eye pruritus, and foreign body sensation in eyes.

Dry eye was experienced by 14% of patients in the 2.5 mg/kg cohort and 23% of patients in the 3.4 mg/kg cohort (Table 31). Most occurrences of dry eye were Grade 1 or Grade 2 (12% and 23% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively) and none were SAEs. One patient in the 2.5 mg/kg cohort had Grade 3 dry eye events. Patients with an event generally experienced only 1 occurrence of dry eye (92% and 91% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively).

For patients with dry eye, more patients in the 3.4 mg/kg cohort than in the 2.5 mg/kg cohort had dry eye that was not resolved at the time of the data cut off (38% and 65% in the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively). Dose delays due to dry eye occurred in 23% of patients with an event in the 2.5 mg/kg cohort and 13% in the 3.4 mg/kg cohorts. No patient had a dose reduction or discontinuation of treatment due to dry eye.

Of note, 20% of patients reported a history of dry eye prior to starting belantamab mafodotin. These patients were statistically more prone to develop keratopathy (MECs) compared with patients without a history of dry eye.

As of the 9-Month Update, 14% of patients in the 2.5 mg/kg cohort and 24% in the 3.4 mg/kg cohort experienced dry eye events. The results are similar to what was reported for the primary analysis. Among patient with dry eye events, 31% and 58% in the 2.5 mg/kg and 3.4 mg/kg cohorts were not resolved as of the last follow up.

Table 31: DREAMM-2 Characteristics of Dry Eye Events (CTCAE)

	Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		9-Month Update (20Sep19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Patients with Event, n (%)	13 (14)	23 (23)	13 (14)	24 (24)
Number of Events	15	25	16	26
Event Characteristics, n/N (%)				
Serious	0/95	0/99	0/95	0/99
Study treatment related	13/95 (14)	23/99 (23)	13/95 (14)	24/99 (24)
Number of Events, n/N (%)				
One	12/13 (92)	21/23 (91)	12/13 (92)	22/24 (92)
Two	0/13	2/23 (9)	0/13	2/99 (8)
Three or more	1/13 (8)	0/23	1/13 (8)	0/99
Worst Outcome, n/N (%)				
Recovered/Resolved	8/13 (62)	3/23 (13)	9/13 (69)	5/24 (21)
Recovered/Resolved with Sequelae	0/13	3/23 (13)	0/13	3/24 (13)
Recovering/Resolving	0/13	2/23 (9)	0/13	2/24 (8)
Not Recovered/Not Resolved	5/13 (38)	15/23 (65)	4/13 (31)	14/24 (58)
Fatal	0/13	0/23	0/13	0/24
Maximum Grade, n/N (%)				
Grade 1	8/95 (8)	16/99 (16)	8/95 (8)	16/99 (16)
Grade 2	4/95 (4)	7/99 (7)	4/95 (4)	8/99 (8)
Grade 3	1/95 (1)	0/99	1/95 (1)	0/99
Grade 4	0/95	0/99	0/95	0/99
Grade 5	0/95	0/99	0/95	0/99
Action Taken [a], n/N (%)				
Study treatment withdrawn	0/13	0/23	0/13	0/24
Dose reduced	0/13	0/23	0/13	0/24
Dose not changed	10/13 (77)	20/23 (87)	10/13 (77)	21/24 (88)
Dose interrupted/delayed	3/13 (23)	3/23 (13)	3/13 (23)	3/24 (13)
Dose reduced or interrupted/delayed	3/13 (23)	3/23 (13)	3/13 (23)	3/24 (13)

a. Source: 9-Month Update Table 3.0181 (ADSL, ADAE)

CTCAE: Common Terminology Criteria for Adverse Events.

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

The FDA's Position

FDA clarifies that this description of dry eye is not a "patient-reported outcome" as PRO are based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. In this section, dry eye reported by patients was interpreted by clinicians and reported by MedDRA preferred term. FDA agrees with the rates of dry eye presented by the Applicant in Table 31 and notes that despite events being Grade 1 or 2, dose modifications were instituted for managements of these events. The FDA does not agree with the Applicant's statement that patients with history of dry eye are statistically more prone to develop keratopathy compared to those without. The small number of patients with history of dry eye at baseline and lack of any formal hypothesis testing precludes this conclusion.

9.3.4 DREAMM-2 AEs of Special Interest

9.3.4.1 Adverse Events of Special Interest: Thrombocytopenia

The events reported in this section include the preferred terms thrombocytopenia and platelet count decreased. Thrombocytopenia was considered an AESI based on preclinical findings, reports in the literature using auristatin-containing ADCs, and clinical data from DREAMM-1. An

analysis of these events needs to take into consideration that patients with RRMM frequently present with thrombocytopenia and that patients with pre-existing thrombocytopenia (CTCAE Grade ≤2) were permitted to enroll in DREAMM-2. A total of 10% of patients in the 2.5 mg/kg cohort and 22% in the 3.4 mg/kg cohort had thrombocytopenia at screening.

Thrombocytopenia was one of the most common AEs associated with belantamab mafodotin and one of the most frequently reported Grade ≥3 events.

In the primary analysis, overall, 35% of patients in the 2.5 mg/kg and 59% of patients in the 3.4 mg/kg cohort had a thrombocytopenic event (Table 32). In the 2.5 mg/kg cohort, Grade ≥3 events occurred in 20% of patients, and 1% of patients had an SAE. In the 3.4 mg/kg cohort, Grade ≥3 events occurred in 34% of patients, and 3% of patients had an SAE. There was 1 fatal event of cerebral hemorrhage in the 3.4 mg/kg cohort. This patient was also categorized as discontinuing treatment for a thrombocytopenic event.

Thrombocytopenic events led to dose reduction in 15% of patients with events in the 2.5 mg/kg cohort and 22% of patients with events in the 3.4 mg/kg cohort. Thrombocytopenic events led to dose delays in 0 and 10% of patients with events. Among patients with an event, the thrombocytopenic events were not resolved in 64% of patients in the 2.5 mg/kg cohort and 66% of patients in the 3.4 mg/kg.

In the 9-Month Update, the results are similar to the primary analysis data. One additional fatal event of cerebral hemorrhage was reported for 3.4 mg/kg cohort. As of the last follow-up, 66% of patients with an event in the 2.5 mg/kg cohort and 61% in the 3.4 mg/kg cohort had unresolved thrombocytopenia.

Table 32: DREAMM-2 Characteristics of Thrombocytopenic Events (CTCAE)

	Belantamab Mafodotin Q3W			
	Primary Analysis (21Jun19)		9-Month Update (20Sep19)	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Patients with Event, n (%)	33 (35)	58 (59)	35 (37)	56 (57)
Number of Events	46	88	51	91
Event Characteristics, n/N (%)				
Serious	1/95 (1)	3/99 (3)	1/95 (1)	5/99 (5)
Study treatment related	19/95 (20)	38/99 (38)	21/95 (22)	38/99 (38)
Number of Events, n/N (%)				
One	22/33 (67)	42/58 (72)	23/35 (66)	40/56 (71)
Two	9/33 (27)	11/58 (19)	8/35 (23)	7/56 (13)
Three or more	2/33 (6)	5/58 (9)	4/35 (11)	9/56 (16)
Worst Outcome, n/N (%)				
Recovered/Resolved	9/33 (27)	16/58 (28)	10/35 (29)	16/56 (29)
Recovered/Resolved with Sequelae	0/33	0/58	0/35	0/56
Recovering/Resolving	3/33 (9)	3/58 (5)	2/35 (6)	4/56 (7)
Not Recovered/Not Resolved	21/33 (64)	38/58 (66)	23/35 (66)	34/56 (61)
Fatal	0/33	1/58 (2)	0/35	2/56 (4)
Maximum Grade, n/N (%)				
Grade 1	10/95 (11)	10/99 (10)	12/95 (13)	10/99 (10)
Grade 2	4/95 (4)	14/99 (14)	3/95 (3)	12/99 (12)
Grade 3	8/95 (8)	11/99 (11)	8/95 (8)	9/99 (9)
Grade 4	11/95 (12)	22/99 (22)	12/95 (13)	23/99 (23)
Grade 5	0/95	1/99 (1)	0/95	2/99 (2)
Action Taken [b], n/N (%)				
Study treatment discontinued	0/33	1/58 (2)	0/35	2/56 (4)
Dose reduced	5/33 (15)	13/58 (22)	6/35 (17)	13/56 (23)
Dose not changed	24/33 (73)	46/58 (79)	26/35 (74)	45/56 (80)
Dose delayed	0/33	6/58 (10)	2/35 (6)	6/56 (11)
Dose reduced or delayed	5/33 (15)	15/58 (26)	7/35 (20)	15/56 (27)

a. Source: 9-Month Update Table 3.0280 (ADSL, ADAE)
b. Patients could have more than 1 Action Taken and be represented more than once.

The FDA's Position

FDA generally agrees with the rates and characteristics of thrombocytopenia presented by the Applicant above based on the preferred terms thrombocytopenia and platelet count decreased in the AE dataset. FDA notes that while the overall incidence of thrombocytopenia in the 2.5 mg/kg cohort based on the AE dataset was 35%, capture of these types of events based on AE reporting may be an underrepresentation of the incidence of laboratory abnormalities. Based on FDA's shift analysis of the laboratory dataset from DREAMM-2, the incidence of thrombocytopenia of any grade in the 2.5 mg/kg cohort was 62% and the incidence of Grade ≥3 thrombocytopenia in the 2.5 mg/kg cohort was 21%.

9.3.4.2 Adverse Events of Special Interest: Infusion Related Reactions

Infusion-related reactions were evaluated as an AESI because IRRs are expected with a biologic agent such as belantamab mafodotin. To provide a comprehensive evaluation of IRRs, GSK used a list of 65 MedDRA dictionary derived AE terms to identify all AEs that might suggest or be compatible with an IRR.

In the primary analysis, the most frequent (≥3%) preferred terms overall representing IRRs were IRR (17% in the 2.5 mg/kg cohort and 10% in the 3.4 mg/kg cohort) and pyrexia (5% in the 2.5 mg/kg cohort and 6% in the 3.4 mg/kg cohort). Most IRRs were Grade 1 and Grade 2. Grade 3 events occurred in 3% of patients in the 2.5 mg/kg cohort and 1% of patients in the 3.4 mg/kg

cohort. No Grade 4 or Grade 5 IRRs were reported. SAEs of IRR were reported for 6 patients (4 patients in the 2.5 mg/kg cohort and 2 patients in the 3.4 mg/kg cohort).

As of the data cut-off for the 9-Month Update, no additional patients experienced IRR events.

The FDA's Position

FDA generally agrees with the Applicant's assessment of IRRs above. FDA notes that based on grouping of adverse events considered by the investigator to be part of an IRR, the overall incidence of IRRs was 21% in the 2.5 mg/kg cohort and 16% in the 3.4 mg/kg cohort.

9.4 Appendix 4: FDA Clinical Appendices

9.4.1 Dose Modification Guidelines for Corneal Events from the DREAMM-2 Protocol

	Grade 1 per GSK Scale[a]	Grade 2 per GSK Scale[a]	Grade 3 per GSK Scale[a]	Grade 4 per GSK Scale[a]
GSK2857916 Dosing Actions	Continue treatment with current dose of GSK2857916.	If **either** ophthalmic exam findings **or** visual acuity findings are **Grade 1**, continue dosing with GSK2857916 at current dose. If visual acuity **and** exam findings are **both** Grade 2, **HOLD** GSK2857916. • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with current dose	Hold GSK2857916 • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with 25% dose reduction* (* for participants receiving 1.92 mg/kg dose-continue at 1.92 mg/kg) In case of recurring ≥Gr3 events, consult GSK Medical monitor	Stop treatment with GSK2857916. Additional topical treatment may be prescribed, as recommended by ophthalmologist* Treatment re-start may be possible after discussion and agreement between the treating ophthalmologist*, treating physician, the GSK Medical Monitor and possibly a GSK ophthalmologist *or optometrist, if an ophthalmologist is not available

Source: Applicant's DREAMM-2 (Study 205678) Protocol, page 61).

9.4.2 Differences in Incidences of Certain AEs Based on FDA Analyses

There were additional differences in the rates of certain AEs presented by the Applicant due to differences in grouping of preferred terms as summarized below. As the majority were for non-ocular toxicities, these differences are not considered to be a concern for discussion given the focus of the ODAC on ocular toxicity.

Table 11: AEs Leading to Dose Delays in ≥2 Patients in Any Dose

- Based on grouping of related terms vision blurred, diplopia, visual acuity reduced, and visual impairment, the incidence of vision blurred leading to dose delays in the FDA analysis was 5% in the 2.5 mg/kg cohort and 9% in the 3.4 mg/kg cohort (discussed in Section 3.1.1.2.3).
- Based on grouping of related terms pneumonia, lung infection, and the incidence of pneumonia leading to dose delays in the FDA analysis was 6% in the 3.4 mg/kg cohort.
- Based on the grouping of related terms thrombocytopenia and platelet count decreased, the incidence of thrombocytopenia leading to dose delays in the FDA analysis was 6% in the 3.4 mg/kg cohort.
- Based on grouping of related terms sepsis, Staphylococcal sepsis, and Staphylococcal bacteremia, the incidence of sepsis leading to dose delays in the FDA analysis was 2% in the 3.4 mg/kg cohort.
- Based on grouping of related terms upper respiratory tract infection, nasopharyngitis, rhinovirus infection, and sinusitis, the incidence of upper respiratory tract infection leading to dose delays in the FDA analysis was 3% in the 2.5 mg/kg cohort.

Table 12: AEs Leading to Dose Reduction in ≥2% of Patients in Any Dose

- Based on the grouping of related terms thrombocytopenia and platelet count decreased, the incidence of thrombocytopenia leading to dose reductions in the FDA analysis was 5% in the 2.5 mg/kg cohort and 13% in the 3.4 mg/kg cohort.

Table 13: AEs Leading to Permanent Discontinuation of Study Treatment

- Based on the grouping of related terms pneumonia, lung infection, and the incidence of pneumonia leading to discontinuation of study treatment in the FDA analysis was 1% in the 2.5 mg/kg cohort.

Table 14: SAEs in ≥2 Patients in Any Dose:

- Based on grouping of related terms pneumonia, lung infection, and the incidence of SAEs of pneumonia in the FDA analysis was 7% in the 2.5 mg/kg cohort and 14% in the 3.4 mg/kg cohort.
- Based on grouping of related terms sepsis, Staphylococcal sepsis, and Staphylococcal bacteremia, the incidence of SAEs of sepsis in the FDA analysis was 4% in the 2.5 mg/kg cohort and 3% in the 3.4 mg/kg cohort.
- Based on grouping of related terms upper respiratory tract infection, nasopharyngitis, rhinovirus infection, and sinusitis, the incidence of SAEs of upper respiratory tract infection in the FDA analysis was 3% in the 3.4 mg/kg cohort.
- Based on grouping of related terms acute kidney injury, renal impairment, and renal failure, the incidence of SAEs of acute kidney injury in the FDA analysis was 4% in the 2.5 mg/kg cohort and 1% in the 3.4 mg/kg cohort.

- Based on the grouping of related terms confusional state, delirium, and mental status changes, the incidence of SAEs of confusional state in the FDA analysis was 2% in the 2.5 mg/kg cohort.

9.4.3 FDA Analysis of Chemistry Laboratory Shift Data from DREAMM-2

FDA analysis based on laboratory shift analysis is shown below in Table 33. In general, the incidence of most chemistry laboratory abnormalities was lower in the 2.5 mg/kg cohort, and the incidence of Grade ≥3 abnormalities was low in both cohorts.

Table 33: FDA Analysis of Chemistry Laboratory Abnormalities Worsened from Baseline in ≥15% of Patients

Laboratory Parameter	Belantamab mafodotin			
	All Grades, n (%)		Grade ≥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)
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
Calcium increased	16 (18)	12 (13)	3 (3)	0
Magnesium decreased	15 (16)	12 (13)	0	0
Phosphorus decreased	11 (12)	16 (17)	4 (4)	6 (6)

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

9.4.4 FDA Grouping of Preferred Terms

The following grouped preferred terms were utilized in the FDA analyses presented in Table 7, Table 10, Table 19, and Table 20:

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

9.4.5 Subgroup Analyses of Specific Populations in DREAMM-2

As discussed in Section 2.3.1.1.1, 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. 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.

The key findings of the FDA analysis of efficacy and safety of belantamab mafodotin based on demographic age subgroups are summarized below.

Table 34: FDA Analysis of Patient Demographics (Age)

Age Category	**Belantamab mafodotin**	
	2.5 mg/kg (N=97)	3.4 mg/kg (N=99)
Median (range), years	65 (39-85)	67 (34-84)
Age Group		
18 to <65 years	45 (46)	36 (36)
65 to <75 years	39 (40)	46 (46)
75 years and above	13 (13)	17 (17)

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

9.4.5.1 Analysis of Efficacy in DREAMM-2 by Age

FDA analysis of ORR (the primary endpoint in DREAMM-2) by age for DREAMM-2 is shown in Table 35.

Table 35: FDA Analysis of ORR by Age

Age Group	**Belantamab mafodotin**	
	2.5 mg/kg (N=97) ORR, n (%) (97.5% CI)	3.4 mg/kg (N=99) ORR, n (%) (97.5% CI)
18 to <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 and above	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 overall 2.5 mg/kg cohort was 31% (97.5% CI: 20.8, 42.6). In the 2.5 mg/kg cohort the ORR in patients aged 18 to <65 years and 65 to <75 years is similar to the overall ORR. Although FDA notes that the ORR data in the 75 years and above 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%.

9.4.5.2 Analysis of Safety in DREAMM-2 by Age

FDA analysis of overall safety by age for DREAMM-2 is shown in Table 36.

Table 36: FDA Analysis of DREAMM-2 Safety Overview by Age

Adverse Event Category **Age Subgroup**	**Belantamab mafodotin**	
	2.5 mg/kg (N=95) n (%)*	3.4 mg/kg (N=99) n (%)*
All Grade TEAEs (all ages)	93 (98)	99 (100)
18 to <65 years	42 (98)	36 (100)
65 to <75 years	39 (100)	46 (100)
75 years and above	12 (92)	17 (100)
Grade 3-4 TEAEs (all ages)	76 (80)	75 (76)
18 to <65 years	36 (84)	30 (83)
65 to <75 years	33 (85)	35 (76)
75 years and above	9 (69)	16 (94)
Serious TEAEs (all ages)	38 (40)	47 (48)
18 to <65 years	17 (40)	15 (42)
65 to <75 years	17 (44)	22 (48)
75 years and above	4 (31)	10 (59)
Fatal TEAEs (all ages)	3 (3)	7 (7)
18 to <65 years	1 (2)	2 (6)
65 to <75 years	2 (5)	4 (9)
75 years and above	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 AEs appear to be similar for the 18 to <65 and 65 to <75 subgroups. Due to the small number of patients within the 75 years and above subgroup, definitive conclusions cannot be drawn; however, there does not appear to an increased incidence of AEs in this subgroup.

FDA analysis of ocular toxicity by age is shown in Table 37.

Table 37: FDA Analysis of DREAMM-2 Ocular Toxicity by Age

Adverse Event Age Subgroup	Belantamab mafodotin	
	2.5 mg/kg (N=95) n (%)*	3.4 mg/kg (N=99) n (%)*
Keratopathy† (all ages)	67 (71)	76 (77)
18 to <65 years	29 (67)	32 (89)
65 to <75 years	31 (79)	32 (70)
75 years and above	7 (54)	12 (71)
Change in BCVA† (all ages)	50 (53)	48 (48)
18 to <65 years	20 (47)	17 (47)
65 to <75 years	23 (59)	19 (41)
75 years and above	7 (54)	12 (71)
Vision blurred♦ (all ages)	21 (22)	30 (30)
18 to <65 years	8 (19)	12 (33)
65 to <75 years	11 (28)	11 (24)
75 years and above	2 (15)	7 (41)
Dry eye♦ (all ages)	13 (14)	21 (21)
18 to <65 years	6 (14)	10 (28)
65 to <75 years	4 (10)	9 (20)
75 years and above	3 (23)	4 (24)

*For each age subgroup, the denominator is based on the number of patients in that subgroup
†Based on KVA scale
♦Based on grouped terms (Appendix Section 9.4.4)
Source: FDA Analysis (ADSL, ADAE, ADOCGSK, and ADOCDVA datasets; DREAMM-2 Safety Population; 21JUN2019 Data Cut-off)

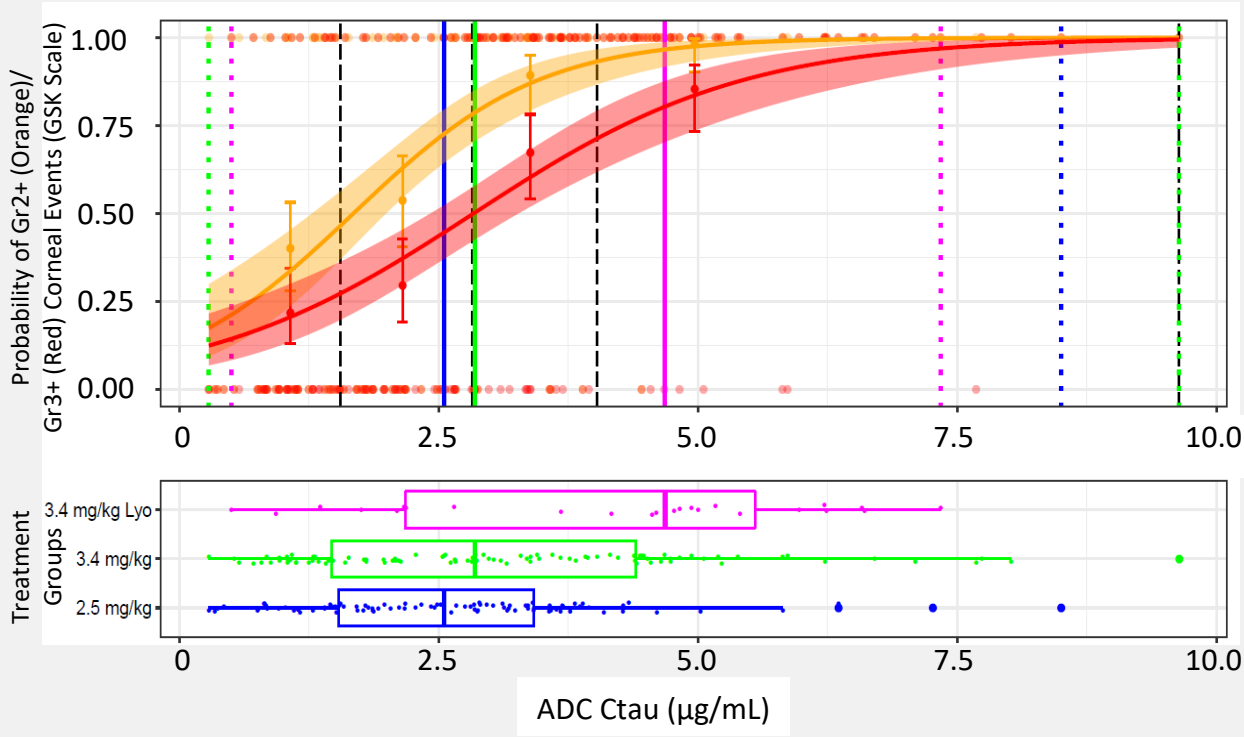
There does appear to be an increased incidence of ocular toxicity in the 65-74 years old group and 75 years and above age group compared to the 18 to <65 years age group. Due to the small number of patients within the 75 years and above subgroup, definitive conclusions cannot be drawn.

9.4.6 Dose Justification

Exposure-response (E-R) analysis for efficacy using data from DREAMM-2 showed that there was no clear relationship between efficacy endpoints (ORR and PFS) and exposures of belantamab mafodotin after adjusting for key baseline disease characteristics, such as sBCMA and β2 microglobulin. However, the E-R analyses for safety indicate that increasing doses,

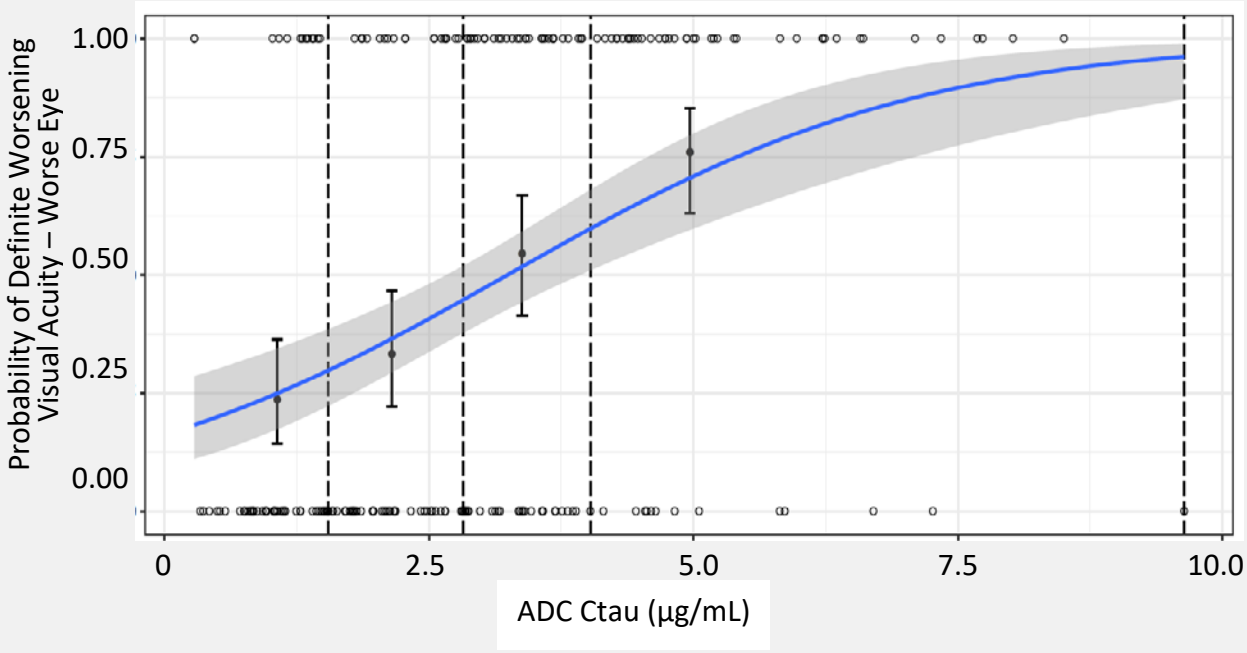
increasing trough concentration (C_{tau}) and average concentration (C_{avg}) at cycle 1 of belantamab mafodotin were significantly associated with increasing probability of Grade 2+ or 3+ corneal AEs on the GSK scale (Figure 15) and probability of increasing definite worsening visual acuity (Figure **16**). Belantamab mafodotin C_{max} at Cycle 1 may also be associated with an increased risk of ocular toxicity as well.

Figure 15: Probability of Grade 2+ and Grade 3+ Corneal Event using GSK Scale by Cycle 1 ADC Ctau (DREAMM-2)



Open dots: Observations. Closed dots and bars: Calculated proportional and 95%CI for each ADC C_{tau} quartile. Lines and areas: Logistic regression fit curves and 95% CI. Color code: Orange for grade 2+ corneal event and red for grade 3+ corneal event.
Source: FDA Analysis

Figure 16: Probability of Definite Worsening Visual Acuity in the Worse Eye by Cycle 1 ADC C_{tau} (DREAMM-2)



Open Dots: Observations. Closed Dots: Calculated Proportion (95% CI) for Quartile. Blue Line: Logistic Regression Fit (95% CI)

Source: FDA Analysis

In addition, the FDA noted that there was a significant impact of baseline sBCMA on belantamab mafodotin C_{tau} at Cycle 1 (Figure 17), and grade 2+ or 3+ corneal AE (Figure 18). The groups with lower baseline sBCMA were associated with higher belantamab mafodotin exposure and higher incidence of corneal AEs, compared to those with higher baseline sBCMA.

Figure 17: Effect of baseline soluble BCMA on Cycle 1 ADC C_{tau} (pooled population PK analyses)

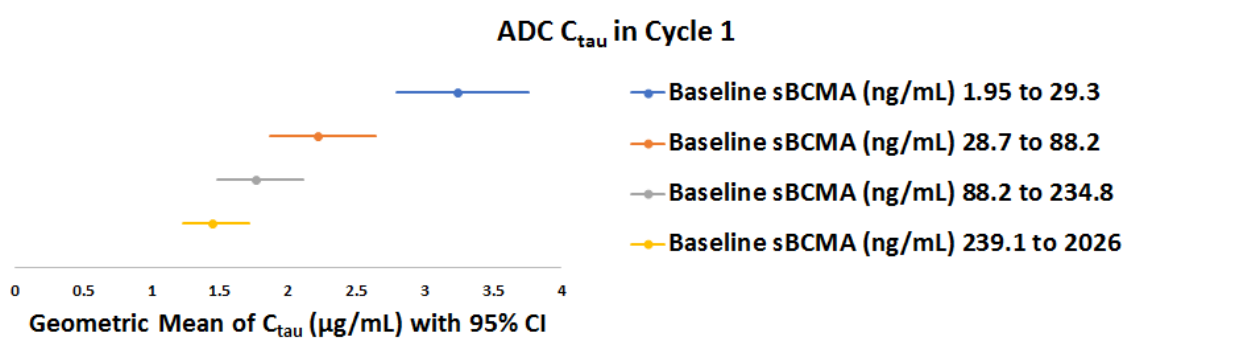
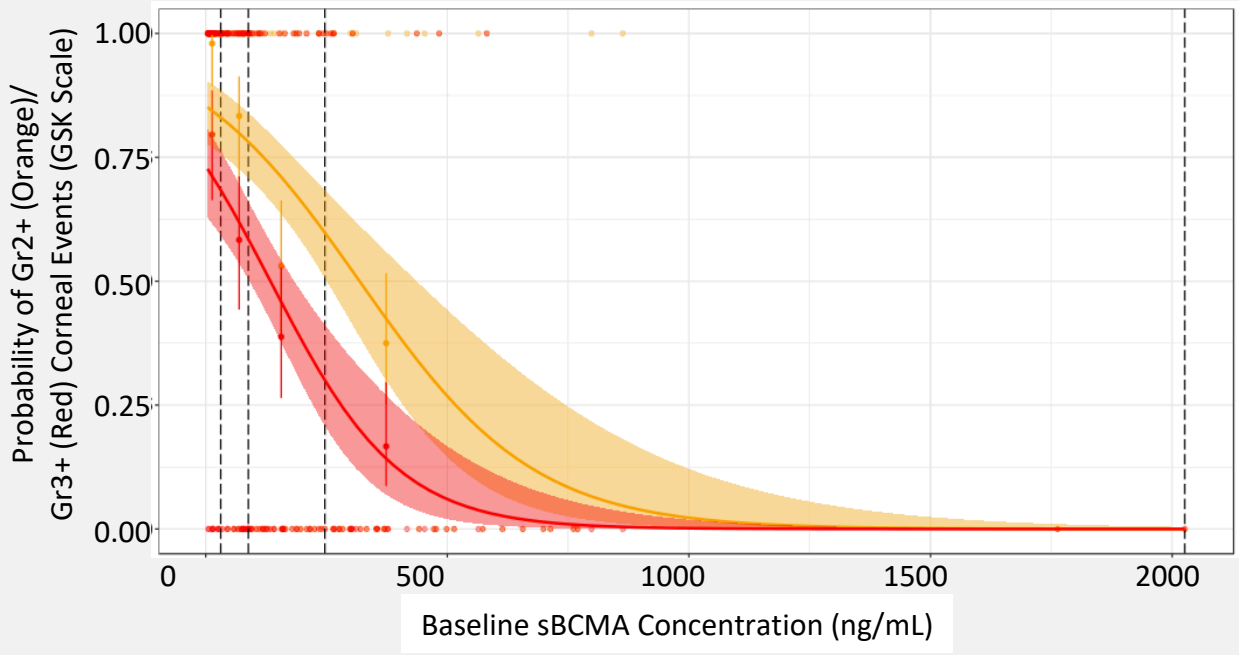


Figure 18: Probability of Grade 2+ and Grade 3+ Corneal Event using GSK Scale by Baseline sBCMA (DREAMM-2 - Frozen Liquid Presentation)



Open dots: Observations. Closed dots and bars: Calculated proportional and 95%CI for each ADC C_{tau} quartile. Lines and areas: Logistic regression fit curves and 95% CI. Color code: Orange for grade 2+ corneal event and red for grade 3+ corneal event.
Source: FDA Analysis

Using data from the 2.5 mg/kg Q3W cohort in DREAMM-2, FDA conducted a subgroup analysis to compare the safety in two groups of patients stratified by median baseline sBCMA value of 93.1 ng/mL.

Table 38: Subgroup Analysis of Belantamab Mafodotin Safety in Patients with RRMM and High Baseline sBCMA Administered Frozen Liquid Presentation 2.5 mg/kg Q3W in DREAMM-2

Frozen liquid formulation 2.5 mg/kg Q3W	Low sBCMA 19.8 [3.74, 93.1] ng/mL (n = 47)	High sBCMA 237 [93.1, 2026] ng/mL (n = 48)
Grade 2+ corneal events	92%	35%
Grade 3+ corneal events	72%	23%
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%
AEs leading to dose reduction, n (%)	43%	17%

Source: FDA Analysis

As seen in Table 38, patients with low baseline sBCMA 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.

Given the remarkable impact of baseline sBCMA on belantamab mafodotin PK and safety in the 2.5 mg/kg Q3W cohort, and positive E-R relationship for corneal AEs after adjusting for baseline disease characteristics, a lower dose may mitigate the risk of corneal toxicity without clinically significant impact on efficacy, particularly in patients with lower baseline sBCMA.

9.4.7 FDA References

Myeloma, N. S. (n.d.). Retrieved from https://seer.cancer.gov/statfacts/html/mulmy.html