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FDA Briefing Document

BLA 761440

Drug name: Blenrep (belantamab mafodotin)

Applicant: GlaxoSmithKline LLC

Oncologic Drugs Advisory Committee Meeting

July 17, 2025

Division of Hematologic Malignancies II/Office of Oncologic Diseases

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Table of Contents

Table of Tables

Table of Figures

Glossary

AC	Advisory Committee
ADC	antibody drug conjugate
AE	adverse event
BCMA	B-cell maturation antigen
BCVA	best-corrected visual acuity
BLA	biologic licensing application
BPd	Belantamab mafodotin, pomalidomide and dexamethasone
BTD	Breakthrough Therapy Designation
BVd	Belantamab mafodotin, bortezomib and dexamethasone
CCOD	clinical cut-off date
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
DVd	Daratumumab, bortezomib and dexamethasone
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module
EOT	end of treatment
ETASU	Elements to Assure Safe Use
FACT-GP5	Functional Assessment of Cancer Therapy – General Population Item #5
FDA	Food and Drug Administration
HR	hazard ratio
IA	interim analysis
IF	information fraction
IMID	immunomodulatory agent
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenously
KM	Kaplan-Meier
KVA	Keratopathy and Visual Acuity

mAb	monoclonal antibody
MM	multiple myeloma
MRD	minimal residual disease
NE	not estimable
ODAC	Oncologic Drugs Advisory Committee
ORR	overall response rate
OS	overall survival
OSDI	Ocular Surface Disease Index
PD	progressive disease
PI	proteasome inhibitor
PK/PD	pharmacokinetic/pharmacodynamic
PFS	progression-free survival
PMR	post-marketing requirement
PR	partial response
PVd	Pomalidomide, bortezomib and dexamethasone
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
Q3W	once every 3 weeks
Q4W	once every 4 weeks
Q6W	once every 6 weeks
Q8W	once every 8 weeks
Q12W	once every 12 weeks
REMS	Risk Evaluation and Mitigation Strategy
RRMM	relapsed or refractory multiple myeloma
SAP	Statistical Analysis Plan
TEAE	treatment-emergent adverse event
VGPR	very good partial response

1 Introduction

1.1 Proposed Indications

The proposed indications for belantamab mafodotin are:

For the treatment of adults with multiple myeloma

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

The proposed dosing regimen in combination with bortezomib and dexamethasone is belantamab mafodotin 2.5 mg/kg of actual body weight intravenously (IV) once every 3 weeks.

The proposed dosing regimen in combination with pomalidomide and dexamethasone is belantamab mafodotin 2.5 mg/kg of actual body weight IV once on Cycle 1 followed by 1.9 mg/kg IV once every 4 weeks starting on Cycle 2.

In both regimens, belantamab mafodotin is continued until disease progression or unacceptable toxicity. The dosages of the other drugs in combination with belantamab mafodotin in each regimen are detailed in Section 6.1.

1.2 Executive Summary

Belantamab mafodotin is a B-cell maturation antigen (BCMA)-directed antibody drug conjugate (ADC) that is proposed for the treatment of adults with relapsed or refractory multiple myeloma (RRMM), for the specific indications described in Section 1.1 above.

Belantamab mafodotin was previously granted accelerated approval as monotherapy on August 5, 2020, for the treatment of patients with RRMM who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent, and was subsequently withdrawn on February 6, 2023, due to failure of the confirmatory trial to meet its progression-free survival (PFS) primary endpoint. The previously approved monotherapy dosage of belantamab mafodotin was 2.5 mg/kg IV once every 3 weeks (Q3W).

The current application is based on data from two phase 3 trials:

- DREAMM-7 is a phase 3, randomized, open-label, 2-arm, multicenter trial that evaluated belantamab mafodotin, bortezomib, and dexamethasone (BVd) versus daratumumab, bortezomib, and dexamethasone (DVd), in patients with RRMM who had received at least 1 prior line of therapy.
    - Belantamab mafodotin dosage: 2.5 mg/kg Q3W
- DREAMM-8 is a phase 3, randomized, open-label, 2-arm, multicenter trial that evaluated belantamab mafodotin, pomalidomide, and dexamethasone (BPd) versus pomalidomide, bortezomib, and dexamethasone (PVd), in patients with RRMM who had received at least 1 prior line of therapy including lenalidomide.
    - Belantamab mafodotin dosage: 2.5 mg/kg once in Cycle 1, followed by 1.9 mg/kg Q4W

For both trials, the primary endpoint was PFS, and key secondary endpoints were overall survival (OS), duration of response (DOR), and minimal residual disease (MRD)-negativity rate.

The FDA's analysis of efficacy is based on the randomized intent-to-treat (ITT) population in each trial (DREAMM-7: BVd n=243, DVd n=251; DREAMM-8: BPd n=155, PVd n=147). The analysis of safety is based on all participants who were randomized and received at least one dose of study treatment (DREAMM-7: BVd n=242, DVd n=246; DREAMM-8: BPd n=150, PVd n=145).

Efficacy

DREAMM-7

- As of the clinical cutoff date (CCOD) of October 2, 2023, at the time of the PFS interim analysis (IA) with a median follow-up of 29.9 months, a total of 249 PFS events per independent review committee (IRC) assessment (BVd 91 [37%]; DVd 158 [63%]) were observed. The median PFS was 37 months (95% Confidence Interval (CI): 28, not estimable (NE)) in the BVd arm and 13 months (95% CI: 11, 18) in the DVd arm. The hazard ratio (HR) was 0.41 (95% CI: 0.31, 0.53); 2-sided p<0.0001.
- As of the CCOD of October 7, 2024, at the second IA for OS with a median follow-up of 41.8 months, a total of 171 OS events (BVd 68 [28%]; DVd 103 [41%]) were observed. The HR was 0.58 (95% CI: 0.43, 0.79); 2-sided p=0.0005.

DREAMM-8

- As of the CCOD of January 29, 2024, at the time of PFS IA2 with a median follow-up of 26.5 months, a total of 142 PFS events per IRC assessment (BPd 62 [40%]; PVd 80 [54%]) were observed. The median PFS was not reached (95% CI: 21, NE) in the BPd arm and 13 months (95% CI: 9, 19) in the PVd arm. The HR was 0.52 (95% CI: 0.37, 0.73; 2-sided p=0.0001.
- As of the same CCOD, at the first IA for OS, a total of 105 OS events (BPd 49 [32%]; PVd 56 [38%]) were observed. The HR was 0.77 (95% CI: 0.53, 1.14). While subsequent OS analyses are planned, OS for DREAMM-8 is not expected to be adequately powered.

Safety (DREAMM-7 and DREAMM-8)

- Despite differences in the dosing regimens of belantamab mafodotin between trials, the safety findings were generally similar.
- There were higher rates of Grade 3-4 treatment-emergent adverse events (TEAEs) on the belantamab mafodotin-containing arm of each study (DREAMM-7: BVd 95% vs. DVd 76%; DREAMM-8: BPd 92% vs. PVd 74%).
- There were higher rates of dose interruptions due to TEAEs on the belantamab mafodotin-containing arm of each study (DREAMM-7: BVd 94% vs. DVd 75%; DREAMM-8: BPd 91% vs. PVd 75%)
- The most common TEAEs with BVd (≥20%) were vision blurred, peripheral neuropathy, dry eye, photophobia, foreign body sensation in the eye, eye irritation, upper respiratory tract infection, eye pain, pneumonia, fatigue, musculoskeletal pain, COVID-19 infection, and cataract.
- The most common TEAEs with BPd (≥20%) were vision blurred, dry eye, foreign body sensation, eye irritation, photophobia, upper respiratory tract infection, pneumonia,

COVID-19 infection, fatigue, eye pain, cataract, musculoskeletal pain, visual acuity reduced, and diarrhea.
- Based on the Sponsor's Keratopathy and Visual Acuity (KVA) scale (described in Section 7.1), 77% of patients treated with BVd and 78% of patients treated with BPd experienced Grade 3-4 KVA events.
- There were high rates of treatment interruptions due to KVA events (DREAMM-7: BVd 74%; DREAMM-8: BPd 75%).

The key issues described in this document are the high rates of ocular toxicity, including keratopathy and visual acuity changes, and poor tolerability seen with each regimen and the resulting uncertainty regarding the appropriateness of the proposed dosages of belantamab mafodotin.

1.3 Purpose/Objective of the AC Meeting

FDA is convening this Oncologic Drug Advisory Committee meeting to discuss whether an appropriate dose and schedule of belantamab mafodotin has been identified, in the context of the ocular toxicity, tolerability, and efficacy results from DREAMM-7 and DREAMM-8 in the proposed populations.

2 Brief Description of Issues

2.1 High Rates of Ocular Toxicity

The key safety issue with belantamab mafodotin is ocular toxicity, including keratopathy (changes in the corneal epithelium), visual acuity changes, and other ocular symptoms, such as blurred vision and dry eye. While ocular adverse events have been seen with other antibody-drug conjugates used for the treatment of cancer, this toxicity is unique among therapies for the treatment of multiple myeloma (MM).

Despite differences in the belantamab mafodotin dosing regimens evaluated in DREAMM-7 and DREAMM-8, there were high rates of ocular toxicity in both trials. There were high rates of Keratopathy and Visual Acuity (KVA) events, as measured by the Sponsor's KVA scale, including high-grade and recurrent toxicities, and high rates of dose modifications due to KVA events in both trials. The following observations summarize these toxicities and their impact.

- The majority of patients experienced KVA events, including high-grade events (all grade: 92% and 93% and Grade 3-4: 77% and 78%, in DREAMM-7 and DREAMM-8, respectively).
- Treatment with belantamab mafodotin was associated with severe ocular toxicities, including corneal ulcers and clinically significant decline in visual acuity, including severe vision loss.
- The majority of patients (70% in DREAMM-7 and 72% in DREAMM-8) experienced recurrent ocular toxicity events (median of 3 Grade 2 or higher KVA events)
- Over 50% of patients (58% in DREAMM-7 and 57% in DREAMM-8 had ongoing Grade 2 or higher KVA events at the data cut-off.
- There were high rates of dose modifications due to KVA events and recurrent KVA events in both trials. The majority of patients (76% in DREAMM-7 and 78% in DREAMM-8) had at least one dose modification due to a KVA event.

The corneal toxicity seen with belantamab mafodotin is a unique risk to this product and is not seen with currently available therapies for MM. There is potential for ocular toxicity to have a substantial impact on patient functioning and quality of life. These toxicity concerns, coupled with the high rates of dose modifications raise concerns about whether the dosages evaluated in DREAMM-7 and DREAMM-8 have been adequately optimized.

2.2 Uncertainty Regarding the Proposed Dosages

The doses of belantamab mafodotin evaluated in DREAMM-7 and DREAMM-8 were:

- DREAMM-7: Belantamab mafodotin 2.5 mg/kg of actual body weight IV once every 3 weeks.
- DREAMM-8: Belantamab mafodotin 2.5 mg/kg of actual body weight IV once on Cycle 1 followed by 1.9 mg/kg IV once every 4 weeks starting on Cycle 2.

Despite the differences in the dosing regimens in each trial, patients on both trials had poor tolerability of the intended dose. There were high rates of dose interruptions and dose reductions, with fewer than 50% of patients on each trial receiving the intended dose by Cycle 3 of treatment.

There was limited exploration of the belantamab mafodotin dosages in combination with bortezomib and dexamethasone (BVd regimen) and in combination with pomalidomide and dexamethasone (BPd regimen) in the respective dose finding trials, DREAMM-6 (BVd) and ALGONQUIN (BPd). While limited numbers of patients were enrolled at each dose level in each dose finding trial, the observed trends in efficacy and safety indicate that response rates were comparable, and rates of ocular toxicity were lower with lower doses and longer dosing intervals of belantamab mafodotin. Ultimately, the Applicant initiated the DREAMM-7 and DREAMM-8 studies at higher dosages that have high rates of dose modifications and ocular toxicity events.

Data from the dose optimization post-marketing requirement (PMR) study (DREAMM-14) that was issued with the initial approval of belantamab mafodotin monotherapy and data from M-protein pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation approaches also suggest that efficacy may be maintained, and tolerability may be improved with lower doses and longer dosing intervals.

Considering the poor tolerability of belantamab mafodotin in the DREAMM-7 and DREAMM-8 studies, along with supportive data from DREAMM-14 and modeling approaches, there is uncertainty regarding whether appropriate dosages have been identified for the proposed indications.

3 Background

3.1 Relapsed/Refractory Multiple Myeloma

MM is a hematologic malignancy characterized by clonal expansion of malignant plasma cells in the bone marrow and overproduction of monoclonal immunoglobulins leading to impaired hematopoiesis and immunity, lytic bone lesions and renal injury. Despite advances in the treatment of MM in recent years, it remains incurable, although recent studies have shown a median overall survival exceeding 10 years in newly diagnosed patients who are transplant-eligible.[1] In 2022, approximately 192,144 people were living with MM in the United States with an estimated 36,110 new cases and 12,030 deaths from MM in the U.S. in 2025.[2]

As shown in Table 1 below, multiple products or regimens are approved for patients who have received 1 or more prior lines of therapy, while others are approved for later-line settings. These approved regimens include multiple two-and three-drug combination regimens, BCMA-directed chimeric antigen receptor (CAR T)-cell products, and BCMA-directed and g-coupled protein receptor class C, group 5, member D (GPRC5D)-directed bispecific antibodies.

Table 1: FDA Approved Therapies for Relapsed or Refractory Multiple Myeloma

Regimen	Indication
DRd, DVd, IRd, SVd, K	≥1 prior line of therapy
DPd	≥1 prior line of therapy, including lenalidomide and a PI
Ciltacabtagene-autoleucel	≥1 prior line of therapy, including a PI and an IMID and refractory to lenalidomide
DKd, KRd, IsaKd, ERd, Kd	1 to 3 prior lines of therapy
EPd, IsaPd, Pd	≥2 prior lines of therapy including lenalidomide and a PI
Idecabtagene-vicleucel	≥2 prior lines of therapy including an IMID, a PI and an anti-CD38 mAb
Daratumumab	≥3 prior lines of therapy including a PI and an IMID or double refractory to a PI and an IMID
Teclistamab, Talquetamab, Elranatamab	≥4 prior lines of therapy including an IMID, a PI and an anti-CD38 mAb
Sd	≥4 prior lines of therapy including ≥2 PIs, ≥2 IMIDs, and an anti-CD38 mAb

Abbreviations: Proteasome Inhibitors: V=bortezomib, K=carfilzomib, I=ixazomib. Immunomodulatory Agents: R=lenalidomide, P=pomalidomide. Anti-CD38 Monoclonal Antibodies: D=daratumumab, Isa=isatuximab. Anti-SLAMF7 Monoclonal Antibody: E=elotuzumab. XPO1 Inhibitor: S=selinexor. Chimeric Antigen Receptor T-cell Therapies: ciltacabtagene autoleucel, idecabtagene vicleucel. Bispecific CD3 T-cell Engagers: teclistamab, elranatamab, talquetamab. Other: d=dexamethasone.
Source: FDA generated from US prescribing information[3]

4 Drug Description

4.1 Mechanism of Action

Belantamab mafodotin is an antibody drug conjugate (ADC) with an afucosylated, humanized B-cell maturation antigen (BCMA)-directed monoclonal antibody (mAb) conjugated to a microtubule disrupting agent, monomethyl auristatin F (MMAF). Belantamab mafodotin binds to cell surface BCMA and is internalized. Once inside the cell, cytotoxic drug with the linker attached (cys-mcMMAF) is released, disrupting the microtubule network, leading to cell cycle arrest and apoptosis. Belantamab mafodotin was also shown to mediate apoptosis of BCMA-expressing tumor cells through antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.

4.2 Potential Mechanism of Corneal Toxicity

The potential mechanism of corneal toxicity has been investigated in nonclinical studies. While BCMA is not expressed in the human eye, belantamab mafodotin was shown to enter lysosomes and cause cytotoxicity in human corneal epithelial cells in vitro. One potential mechanism for the uptake of the ADC is through macropinocytosis, a non-specific form of endocytosis. Given that the mechanism of toxicity appears to be non-specific, the ocular toxicities seen with belantamab mafodotin may be attributed to the eyes' susceptibility to even low ocular concentrations of the payload or ADC.

Non-specific ocular toxicities associated with the belantamab mafodotin payload have been observed in rabbits, including corneal epithelial single cell necrosis, superficial corneal haze and vascularization, increased mitoses in the corneal epithelium, and bilateral retinal striations. Additionally, based on systemic inflammatory responses seen in the animals, the general pro-inflammatory response seen with this payload and ADC may also contribute to the development of ocular toxicity.

5 Regulatory History

Belantamab mafodotin was granted accelerated approval as monotherapy for the treatment of patients with relapsed or refractory multiple myeloma who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent on August 5, 2020, based on the results of the single arm, phase 2 DREAMM-2 trial. On February 6, 2023, belantamab mafodotin was withdrawn from the U.S. market due to failure of the proposed confirmatory trial, DREAMM-3, which evaluated belantamab mafodotin vs. pomalidomide and dexamethasone in patients with RRMM, to meet its primary PFS endpoint (see Appendix 10.1).

A summary of the key regulatory history is presented in Table 2 below.

Table 2: Key Regulatory History

Date	Regulatory Interactions
February 2018	Type B Breakthrough Therapy Designation (BTD) Meeting • FDA expressed concerns that the 3.4 mg/kg Q3W dose does not represent the optimal dose, due to high rates of dose reductions and delays, and recommended evaluating lower dose(s).
April 2018	DREAMM-2 Protocol Amendment 1 Submitted • DREAMM-2: Single-arm trial of belantamab mafodotin monotherapy in patients with RRMM, initially evaluating a dose of 3.4 mg/kg • Sponsor amended the DREAMM-2 study protocol to add an evaluation of a lower dose (2.5 mg/kg Q3W) and include 1:1 randomization to the two dose levels (3.4 mg/kg and 2.5 mg/kg)
February 2019	Type B End-of-Phase 2 Meeting held to discuss two planned randomized phase 3 studies evaluating BVd (DREAMM-7) and BPd (DREAMM-8) in patients with RRMM • FDA expressed significant concerns with the proposed dosages for evaluation in combination, due to limited numbers of patients evaluated at lower dose levels, toxicity, and tolerability concerns. • FDA recommended additional enrollment to lower dose levels to identify the dosing regimen that adequately balances safety and efficacy.
December 2019-August 2020	BLA 761158 (seeking Accelerated Approval for patients with RRMM who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent) was submitted and subsequently approved. Key interactions include: • July 14, 2020: ODAC Meeting held to discuss impact of ocular toxicity on benefit-risk for the proposed population. ODAC advised that for the proposed population, and in the context of a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), the benefits outweighed the risks.[4]

	• August 5, 2020: Accelerated approval of belantamab mafodotin:
	  ○ Postmarketing requirement (PMR) issued to conduct a randomized phase 3 confirmatory trial to verify and describe the clinical benefit of belantamab mafodotin
	  ○ PMR issued to conduct a randomized dose finding study with lower doses or alternative dosing regimens
	  ○ REMS with ETASU A, B, D, E

April 2020	DREAMM-3 trial initiated
May 2020	DREAMM-7 trial initiated
October 2020	DREAMM-8 trial initiated
July 2022	Type C Meeting held to discuss the confirmatory trial DREAMM-3 • FDA expressed continued concerns that the proposed 2.5 mg/kg Q3W dose is not the optimal dose
November 2, 2022	Teleconference held to discuss topline results of the DREAMM-3 confirmatory trial (see Appendix 10.1) • FDA noted that the trial failed to meet the primary endpoint of PFS; additionally, there was no difference between arms in the secondary endpoint of ORR, and the OS HR (48% information fraction) was >1 • FDA asked about the Sponsor's plans for withdrawal of belantamab mafodotin given the results of DREAMM-3
February 6, 2023	Belantamab mafodotin withdrawn from U.S. market following failure of the confirmatory trial to meet the PFS primary endpoint • DREAMM-3: Phase 3 study of belantamab mafodotin vs. pomalidomide and dexamethasone in patients with RRMM • Belantamab mafodotin dosage: 2.5 mg/kg Q3W • PFS HR 1.03 [95% CI: 0.72, 1.47]; p=0.558
May 10, 2023	Type D Meeting held to discuss the Sponsor's OS analysis plans for DREAMM-7 and DREAMM-8 • FDA expressed significant concerns with the Sponsor's proposed OS analysis plans • FDA stated that each study will independently need to demonstrate an improvement in PFS and OS and include sufficient OS information to support the benefit-risk assessment for the respective indications • The Agency noted the limitations with the proposed assumptions for the OS analyses and stated that the HR assumptions for both studies should be based on the assumed median OS for the respective control arms based on literature references and previous study results
May 25, 2023	Type C Meeting held to discuss the Sponsor's proposal to submit a BLA based on DREAMM-7 and DREAMM-8 • FDA stated that the submission should include sufficient OS information for both studies to adequately assess OS as both an efficacy and safety endpoint

	• FDA stated each study will need to independently demonstrate a significant improvement in PFS and OS to support registration of belantamab mafodotin for the respective indications
February 2, 2024	Teleconference held to provide preliminary advice on the Sponsor's proposal to submit a request for BTD based on the DREAMM-7 study results • FDA stated it would be challenging to seek BTD in patients who have received at least 1 prior line of therapy given the number of effective therapies in this setting, including regimens with a demonstrated OS benefit • FDA recommended against submitted a formal BTD request based on DREAMM-7 due to lack of substantial improvement over existing therapies
April 3, 2024	Type B pre-BLA Meeting held to discuss topline results from DREAMM-7 and the Sponsor's proposal to submit a BLA based on the results of DREAMM-7 and DREAMM-8 • FDA noted the immature (40% information fraction) OS data from DREAMM-7 and reiterated the need to demonstrate significant improvement in both PFS and OS to support registration. In response, the Sponsor proposed to provide results from the 2nd pre-specified OS interim analysis (~50% information fraction) at the time of the safety update • FDA expressed concerns regarding the high rates of ocular toxicity and dose modifications due to ocular toxicity • FDA stated it is within the Sponsor's discretion to submit a BLA based on DREAMM-7 and DREAMM-8; the BLA should be materially complete, and any additional data submitted during the review cycle may trigger a major amendment
July 11, 2024	Type D Meeting to discuss the Sponsor's proposal to submit a BLA based on DREAMM-7 and DREAMM-8 and the proposed timeline for submission of updated OS data • FDA stated it is at the Sponsor's discretion to submit a BLA based on the results of DREAMM-7 and DREAMM-8 • FDA stated whether the totality of data supports a determination of favorable benefit-risk for each proposed indication will be determined on review

Abbreviations: BTD=Breakthrough Therapy Designation, Q3W=once every 3 weeks, BVd=belantamab mafodotin in combination with bortezomib and dexamethasone, BPd=belantamab mafodotin in combination with pomalidomide and dexamethasone, BLA=Biologic Licensing Application, REMS=Risk Evaluation and Mitigation Strategy, ETASU=Elements to Assure Safe Use, PMR=post-marketing requirement, PFS=progression-free survival, ORR=overall response rate, OS=overall survival, HR=hazard ratio.
Source: FDA generated

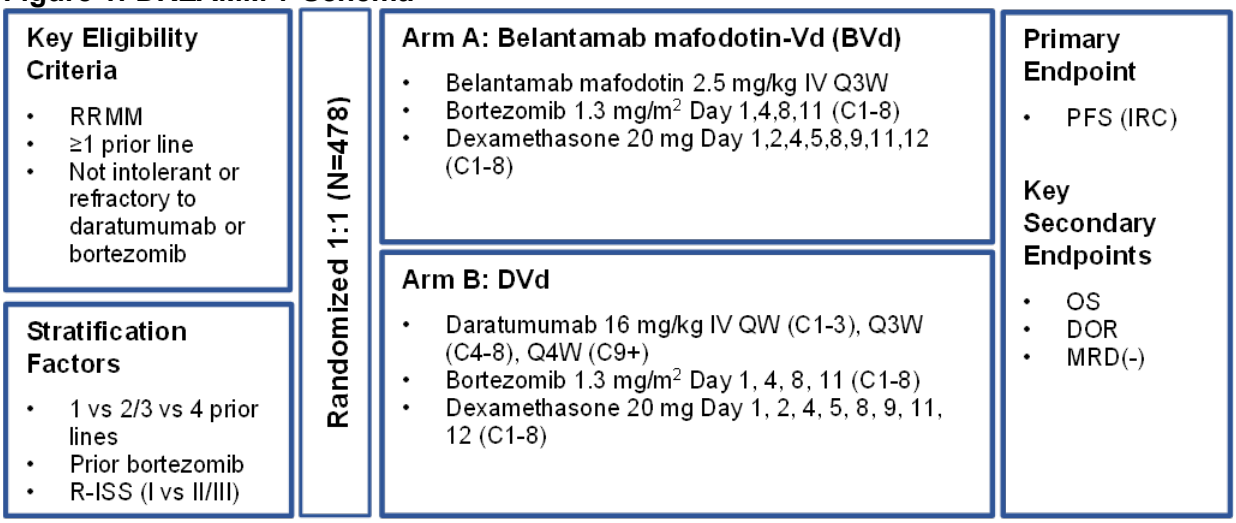
6 DREAMM-7 and DREAMM-8 Trials

6.1 Trial Designs

6.1.1 DREAMM-7

DREAMM-7 is a phase 3, randomized, open-label, 2-arm, multicenter trial evaluating belantamab mafodotin, bortezomib, and dexamethasone (BVd) versus daratumumab, bortezomib, and dexamethasone (DVd), in patients with RRMM who had received at least 1 prior line of therapy. Treatment was continued until disease progression, unacceptable toxicity, or death. The DREAMM-7 trial schema is presented in Figure 1.

Figure 1: DREAMM-7 Schema

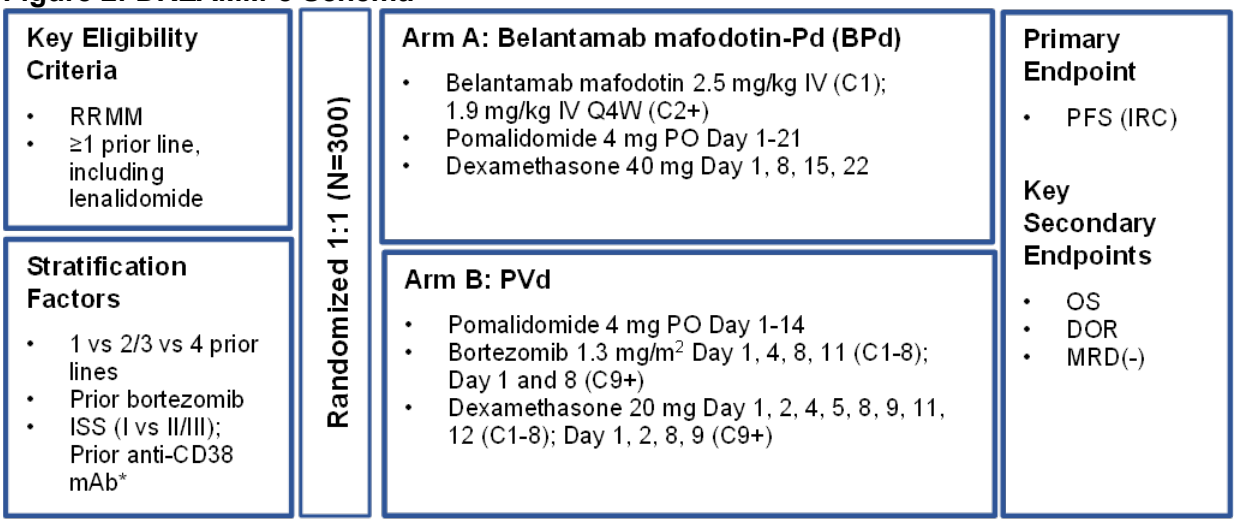


Abbreviations: R-ISS=Revised International Staging System, Q3W=once every 3 weeks, C=cycle, Q4W=once every 4 weeks, PFS=progression-free survival, IRC=Independent Review Committee, OS=overall survival, DOR=duration of response, MRD(-)=minimal residual disease negativity rate.
Source: FDA generated

6.1.2 DREAMM-8

DREAMM-8 is a phase 3, randomized, open-label, 2-arm, multicenter trial evaluating belantamab mafodotin, pomalidomide, and dexamethasone (BPd) versus pomalidomide, bortezomib, and dexamethasone (PVd), in patients with RRMM who had received at least 1 prior line of therapy including lenalidomide. Treatment was continued until disease progression, unacceptable toxicity, or death. The DREAMM-8 trial schema is presented in Figure 2.

Figure 2: DREAMM-8 Schema



*ISS status (I vs II/III) was replaced by prior anti-CD38 treatment (yes/no) after Protocol Amendment 1.
Abbreviations: ISS=International Staging System, Q4W=once every 4 weeks, C=cycle, PFS=progression-free survival, IRC=Independent Review Committee, OS=overall survival, DOR=duration of response, MRD(-)=minimal residual disease negativity rate.
Source: FDA generated

6.2 Key Eligibility Criteria

Eligible participants for both DREAMM-7 and DREAMM-8 were adults with diagnosis of multiple myeloma with at least one aspect of measurable disease (refer to Appendix 10.2 for specific criteria) and who were previously treated with at least 1 prior line of MM therapy, with documented disease progression during or after their most recent therapy.

Patients with prior BCMA-directed therapy, those with intolerance or refractoriness to bortezomib, or those with current corneal epithelial disease (except for mild punctate keratopathy) were excluded from both DREAMM-7 and DREAMM-8.

Key exclusion criteria specific to DREAMM-7 included:

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

Key exclusion criteria specific to DREAMM-8 included:

- Prior treatment with pomalidomide

Additional key protocol eligibility criteria are included in Appendix 10.2.

6.3 Statistical Analysis Plans

The primary endpoint of both DREAMM-7 and DREAMM-8 was progression-free survival (PFS), defined as the time from randomization until the earliest date of progressive disease (PD) based on Independent Review Committee (IRC)-assessment per International Myeloma Working Group (IMWG) criteria, or death due to any cause.

The key secondary endpoints were:

- Duration of response (DOR), defined as time from first documented evidence of partial response (PR) or better until the earliest date of PD, or death due to any cause.
    - This endpoint was considered exploratory by FDA due to considerations detailed in Appendix 10.3.
- Overall survival (OS), defined as the interval of time from randomization to the date of death due to any cause.
    - DREAMM-8 is not expected to be adequately powered for OS due to a reduction in the planned sample size implemented in Protocol Amendment 2 (refer to Appendix 10.3).
- Minimal residual disease (MRD)-negativity rate, defined as the percentage of participants who achieve MRD negative status (as assessed by NGS at 10^{-5} threshold) at least once during the time of confirmed complete response (CR) or better based on IRC-assessment per IMWG criteria.

DREAMM-7 was designed to target a total of 280 PFS events and 355 OS events. One interim analysis (IA) for efficacy was planned for PFS at 89% information fraction (IF). Three interim analyses were planned for OS at 40% (at the time of the PFS IA), 50%, and 75% IF.

DREAMM-8 was designed to target a total of 173 PFS events and 217 OS events. Two interim analyses were planned for PFS at 25% (potential for harm) and 84% IF (for efficacy). Three interim analyses were planned for OS at 50% (at the time of PFS IA2), 60% and 75% IF.

Details of the sample size justification, interim analyses of PFS and OS, and multiplicity control in each study are provided in Appendix 10.3.

6.4 Trial Results

6.4.1 Demographics

As shown in Table 3, baseline demographics were balanced between the arms in DREAMM-7 and DREAMM-8. However, there was limited representation of older adults; on the belantamab mafodotin containing arms, 15% of patients in DREAMM-7 and 12% in DREAMM-8 were age 75 or older, whereas in the U.S., 33% of patients diagnosed with MM are aged 75 and older.[2] There was also limited enrollment of Black or African American patients (5% in DREAMM-7 and none in DREAMM-8), whereas the prevalence of MM in Black or African Americans in the U.S. is approximately twice that of non-Hispanic Whites.[2]

While both studies were multiregional, the majority of enrollment was in Europe, with fewer than 5% of patients in each trial enrolled in the U.S.

Table 3: DREAMM-7 and DREAMM-8 Baseline Demographics

	DREAMM-7		DREAMM-8	
	BVd N=243 n (%)	**DVd N=251** n (%)	**BPd N=155** n (%)	**PVd N=147** n (%)
Age				
Median (Range), in years	65 (35, 87)	65 (33, 89)	66 (40, 82)	68 (34, 86)
Age group				
18 to <65	121 (50)	126 (50)	64 (41)	53 (36)
65 to <75	85 (35)	95 (38)	72 (47)	59 (40)
≥75	37 (15)	30 (12)	19 (12)	35 (24)
Sex				
Male	128 (53)	144 (57)	99 (64)	82 (56)
Female	115 (47)	107 (43)	56 (36)	65 (44)
Race				
White	203 (81)	206 (85)	133 (86)	127 (86)
Asian	33 (13)	28 (12)	20 (13)	17 (12)
Black or African American	12 (5)	8 (3.3)	0	0
Native Hawaiian or Pacific Islander	0	0	1 (0.6)	2 (1.4)
Multiple	1 (0.4)	0	1 (0.6)	0
Not Reported	2 (0.8)	1 (0.4)	0	1 (0.7)
Ethnicity				
Hispanic or Latino	30 (12)	41 (16)	10 (6)	17 (12)
Not Hispanic or Latino	213 (88)	208 (83)	145 (94)	139 (95)
Not Reported	0	2 (0.8)	0	1 (0.7)
Region				
Europe	126 (52)	120 (48)	105 (68)	109 (74)
Northeast Asia	26 (11)	28 (11)	18 (12)	14 (10)
North America	10 (4.1)	18 (7)	4 (2.6)	1 (0.7)
Rest of the World*	81 (33)	85 (40)	28 (18)	23 (16)

*Rest of the World includes Australia, Brazil, Israel, and New Zealand.
Source: FDA analysis

6.4.2 Baseline Disease Characteristics

Baseline disease characteristics, including International Staging System (ISS) stage, cytogenetic risk status, and presence or absence of extramedullary disease, were generally balanced between arms in each study, as shown in Table 4. The majority of patients on both trials had ISS stage I or II disease, standard risk cytogenetics, and no extramedullary disease, all of which are generally associated with good prognosis in MM.

Table 4: DREAMM-7 and DREAMM-8 Baseline Disease Characteristics

	DREAMM-7		DREAMM-8	
	BVd N=243 n (%)	DVd N=251 n (%)	BPd N=155 n (%)	PVd N=147 n (%)
ISS Stage				
I	102 (42)	103 (41)	93 (60)	85 (58)
II	130 (54)	132 (53)	39 (25)	40 (27)
III	9 (3.7)	14 (6)	22 (14)	22 (15)
Unknown	2 (0.8)	2 (0.8)	1 (0.6)	0
Cytogenetics				
High Risk*	67 (28)	69 (27)	52 (34)	47 (32)
Standard Risk	175 (72)	175 (70)	72 (46)	75 (51)
Missing	1 (0.4)	7 (2.8)	31 (20)	25 (17)
Extramedullary Disease				
Present	13 (5)	25 (10)	20 (13)	11 (7)
Absent	230 (95)	226 (90)	135 (87)	136 (93)

*Patients were considered high risk if they had at least one of the following: t(4;14), t(14;16), 17p13del.
Abbreviations: ISS=International Staging System.
Source: FDA analysis

6.4.3 Prior Therapies

Prior therapies received by patients enrolled in DREAMM-7 and DREAMM-8 are summarized in Table 5. Approximately half of patients on each study received 1 prior line of therapy. The majority of patients on both trials had received both a prior proteosome inhibitor (PI) and immunomodulatory drug (IMID). Approximately a quarter of patients on DREAMM-8 had received a prior anti-CD38 monoclonal antibody (mAb) and were triple class (PI, IMID, and anti-CD38 mAb) exposed. While the control arm in DREAMM-7 included daratumumab, patients with prior daratumumab were allowed per the eligibility criteria (see Appendix 10.2) as long as they were not intolerant or refractory to daratumumab or another anti-CD38 therapy; however, fewer than 1% of patients enrolled had received a prior anti-CD38 mAb. In DREAMM-8, approximately 26% of patients enrolled had received a prior anti-CD38 mAb. The limited data with BVd and BPd in patients who have received a prior anti-CD38 mAb may limit applicability to the current U.S. patient population, given the increasing usage of anti-CD38 mAb-containing regimens in earlier line settings, including the frontline newly diagnosed setting.

Table 5: DREAMM-7 and DREAMM-8 Prior Therapies

	DREAMM-7		DREAMM-8	
	BVd N=243 n (%)	**DVd N=251** n (%)	**BPd N=155** n (%)	**PVd N=147** n (%)
Prior Lines of Therapy				
Median (Range)	1 (1, 7)	2 (1, 7)	1 (1, 6)	1 (1, 9)
1	125 (51)	125 (50)	82 (53)	77 (52)
2-3	88 (36)	99 (39)	54 (35)	48 (33)
≥4	30 (12)	27 (11)	19 (12)	22 (15)
Prior Proteosome Inhibitor				
Yes	218 (90)	216 (86)	140 (90)	136 (93)
No	25 (10)	35 (14)	15 (10)	11 (7)
Prior Immunomodulatory Drug				
Yes	198 (81)	216 (86)	155 (100)	147 (100)
No	45 (19)	35 (14)	0	0
Prior Anti-CD38 Monoclonal Antibody				
Yes	3 (1)	4 (2)	38 (25)	42 (29)
No	240 (99)	247 (98)	117 (75)	105 (71)
Triple Class Exposed				
Yes	2 (<1)	2 (<1)	34 (22)	39 (27)
No	241 (99)	249 (99)	121 (78)	108 (73)
Prior Autologous Stem Cell Transplant				
Yes	164 (67)	173 (69)	99 (64)	82 (56)
No	79 (33)	78 (31)	56 (36)	65 (44)

Source: FDA analysis

6.4.4 Efficacy Results

6.4.4.1 Primary Endpoint: Progression-Free Survival

The primary endpoint in both DREAMM-7 and DREAMM-8 was PFS, defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause.

The PFS results for DREAMM-7 and DREAMM-8 are summarized in Table 6.

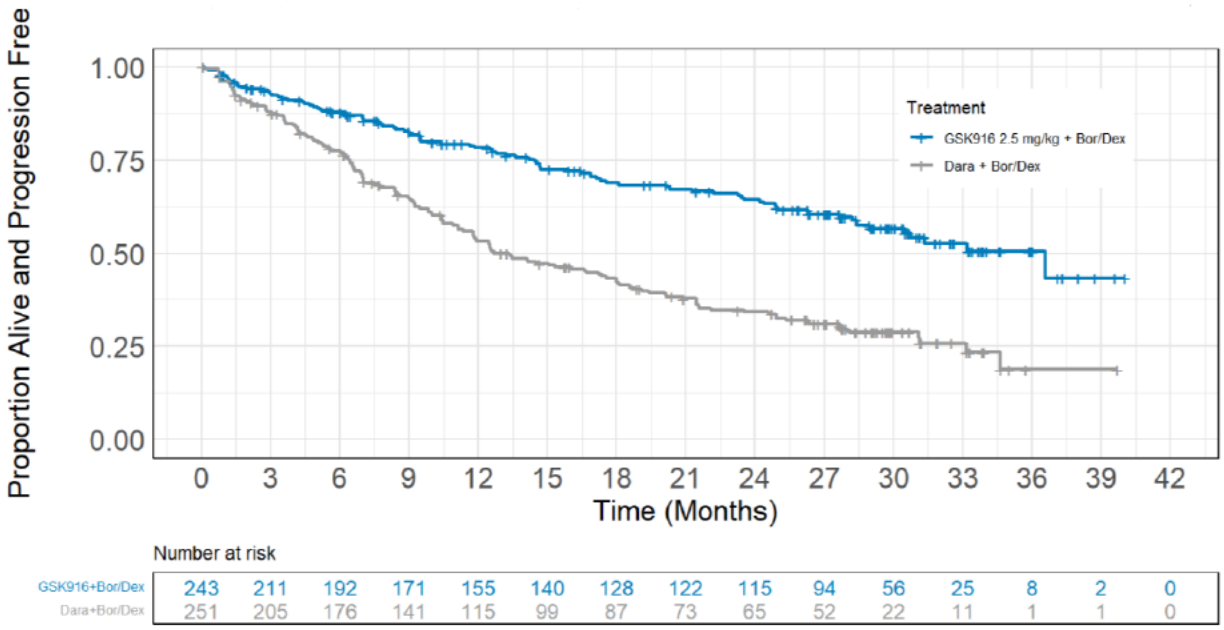
In DREAMM-7, PFS met statistical significance at IA1 (89% IF; median follow up of 29.9 months) and in DREAMM-8, PFS met statistical significance at IA2 (82% IF; median follow up of 26.5 months). The Kaplan-Meier (KM) curves of PFS are shown in Figure 3 and Figure 4 for DREAMM-7 and DREAMM-8, respectively.

Table 6: DREAMM-7 and DREAMM-8 PFS by IRC Results

	DREAMM-7 PFS IA1		DREAMM-8 PFS IA2	
	BVd N=243	DVd N=251	BPd N=155	PVd N=147
Number of events (%)	91 (37.4%)	158 (62.9%)	62 (40.0%)	80 (54.4%)
Median (months) (95% CI)	36.6 (28.4, NE)	13.4 (11.1, 17.5)	NE (20.6, NE)	12.7 (9.1, 18.5)
Hazard Ratio[1] (95% CI)	0.41 (0.31, 0.53)		0.52 (0.37, 0.73)	
P-value[2]	<0.0001		0.0001	

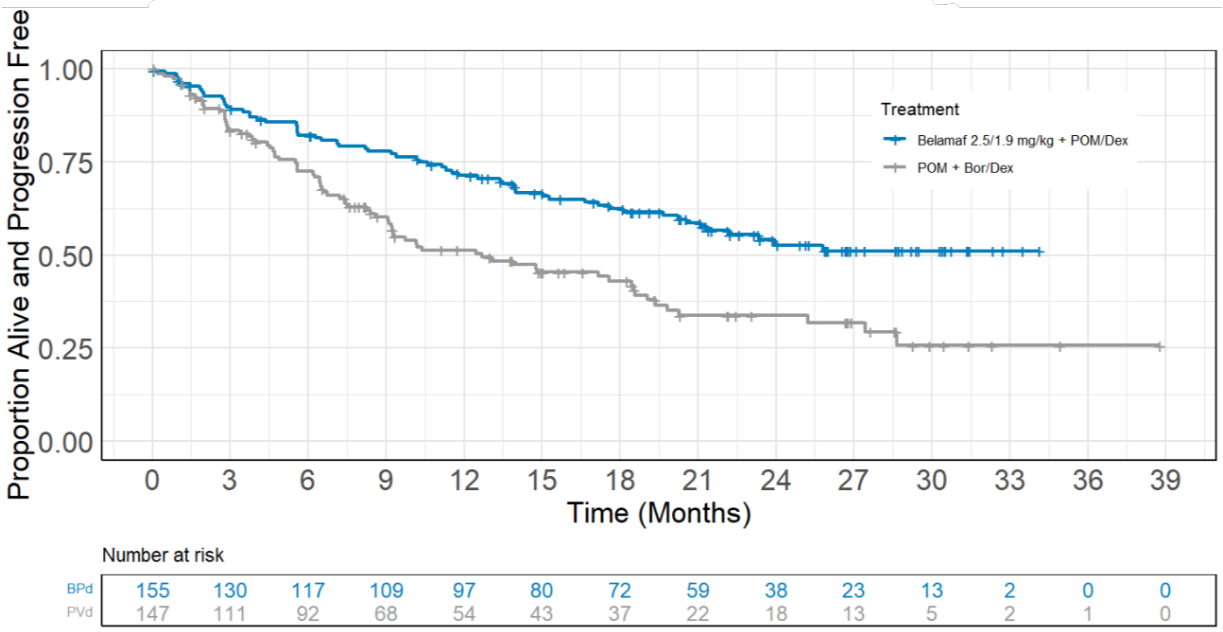
Source: FDA analysis
Abbreviations: PFS=progression-free survival, IRC=Independent Review Committee, IA=interim analysis, CI=confidence interval, NE=not estimable, ITT=intent-to-treat, HR=hazard ratio.
ITT analysis based on IRC assessment.
DREAMM-7: PFS IA1 was based on the data with clinical cut-off date (CCOD) of 02 October 2023.
DREAMM-8: PFS IA2 was based on the data with CCOD of 29 January 2024.
[1]DREAMM-7: HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and revised ISS (R-ISS) at screening (I vs. II/III). DREAMM-8: HRs were estimated using a Cox Proportional Hazards model stratified by number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no).
[2]DREAMM-7: 2-sided p-value boundary =0.034924; DREAMM-8: 2-sided p-value boundary=0.026722.

Figure 3: DREAMM-7 KM Curve of PFS by IRC (IA1)



Source: FDA analysis
Abbreviations: KM=Kaplan Meier, PFS=progression-free survival, IRC=Independent Review Committee, GSK916=belantamab mafodotin, Dara=daratumumab, Bor=bortezomib, Dex=dexamethasone, ITT=intent-to-treat.
ITT analysis based on IRC assessment.
Based on CCOD of 02 October 2023.

Figure 4: DREAMM-8 KM Curve of PFS by IRC (IA2)



Source: FDA analysis
Abbreviations: KM=Kaplan Meier, PFS=progression-free survival, IRC=Independent Review Committee, Belamaf=belantamab mafodotin, POM=pomalidomide, Bor=bortezomib, Dex=dexamethasone, ITT=intent-to-treat.
ITT analysis based on IRC assessment.
Based on CCOD of 29 January 2024.

Sensitivity analyses for PFS were conducted based on investigator assessment and using alternative censoring rules for both studies. Results of DREAMM-7 and DREAMM-8 sensitivity analyses were consistent with the primary analysis results (Refer to Appendix 10.4 for these results).

Subgroup analyses for PFS were performed, and overall, PFS subgroup results were also consistent with PFS results in the ITT population. Given the post-hoc nature of these analyses and small sample sizes in some subgroups (e.g., Black or African American subgroup and North American region subgroup), all subgroup analysis results are considered exploratory and hypothesis-generating.

6.4.4.2 Key Secondary Endpoint: Overall Survival

OS was a key secondary endpoint in both DREAMM-7 and DREAMM-8 and was tested after PFS.

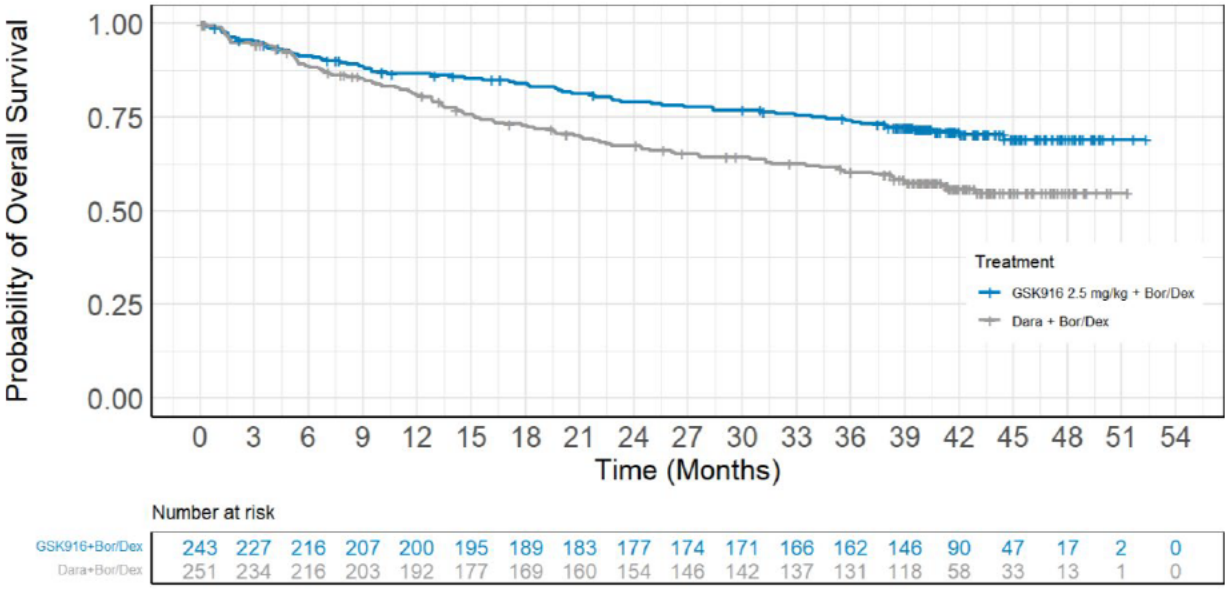
For DREAMM-7, OS IA2 (48%IF), which was conducted at the time of the primary PFS analysis, met the efficacy boundary. DREAMM-7 OS results at IA2 are summarized in Table 7 and the KM curve of OS at IA2 is shown in Figure 5.

Table 7: DREAMM-7 OS Results (IA2)

	DREAMM-7	
	BVd N=243	DVd N=251
Number of events (%)	68 (28.0%)	103 (41.0%)
Median (months) (95% CI)	NE (NE, NE)	NE (41.0, NE)
Stratified Hazard Ratio[1] (95% CI)	0.58 (0.43, 0.79)	
P-value[2]	0.0005	

Source: FDA analysis
Abbreviations: OS=overall survival, IA=interim analysis, NE=not estimable, ITT=intent-to-treat, HR=hazard ratio.
ITT analysis.
OS IA2 was based on the data with CCOD of 07 October 2024.
[1]DREAMM-7: HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III).
[2]OS IA2: 2-sided p-value boundary = 0.002246.

Figure 5: DREAMM-7 KM Curve of OS at IA2



Source: FDA analysis
Abbreviations: KM=Kaplan Meier, OS=overall survival, IA=interim analysis, GSK916=belantamab mafodotin, Dara=daratumumab, Bor=bortezomib, Dex=dexamethasone, ITT=intent-to-treat.
ITT analysis.
Based on CCOD of 07 October 2024.

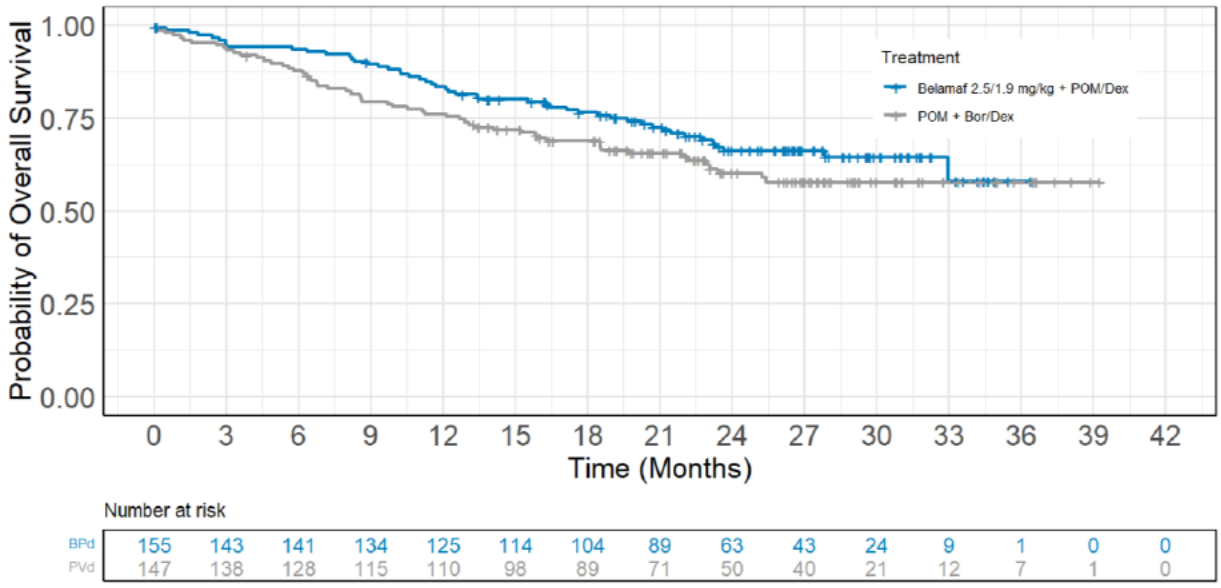
For DREAMM-8, OS IA1 (48% IF), which was conducted at the time of PFS IA2, did not meet the efficacy boundary. A descriptive OS analysis at 54% OS IF based on approximately an additional 8 months of follow up was conducted. DREAMM-8 OS IA1 results and descriptive OS results are summarized in Table 8 and Table 9, with the respective KM curves shown in Figure 6 and Figure 7. The OS analysis at 54% OS IF, while considered descriptive, reveals that the KM curves for the BPd and PVd arms overlap and cross after 36 months.

Table 8: DREAMM-8 OS Results (IA1)

	DREAMM-8	
	BPd N=155	**PVd N=147**
Number of events (%)	49 (31.6%)	56 (38.1%)
Median (months) (95% CI)	NE (33.0, NE)	NE (25.2, NE)
Stratified Hazard Ratio[1] (95% CI)	0.77 (0.53, 1.14)	
P-value[2]	0.1896	

Source: FDA analysis
Abbreviations: OS=overall survival, IA=interim analysis, NE=not estimable, ITT=intent-to-treat, HR=hazard ratio. ITT analysis.
Based on CCOD of 29 January 2024.
[1]DREAMM-8: HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no).
[2]OS IA1: 2-sided p-value boundary = 0.0025.

Figure 6: DREAMM-8 KM Curve of OS at IA1



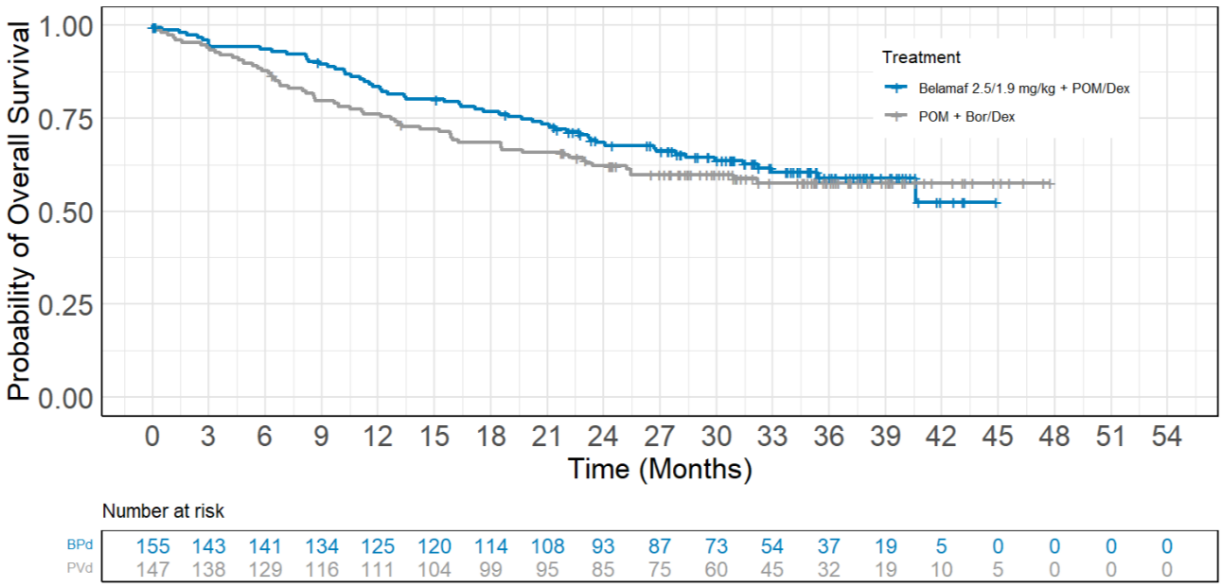
Source: FDA analysis
Abbreviations: KM=Kaplan Meier, OS=overall survival, IA=interim analysis, Belamaf=belantamab mafodotin, POM=pomalidomide, Bor=bortezomib, Dex=dexamethasone, ITT=intent-to-treat.
ITT analysis.
Based on CCOD of 29 January 2024.

Table 9: DREAMM-8 OS Results (Descriptive)

	DREAMM-8	
	BPd N=155	**PVd N=147**
Number of events (%)	58 (37.4%)	60 (40.8%)
Median (months) (95% CI)	NE (35.4, NE)	NE (32.2, NE)
Stratified Hazard Ratio[1] (95% CI)	0.86 (0.60,1.24)	

Source: FDA analysis
Abbreviations: OS=overall survival, NE=not estimable, ITT=intent-to-treat, HR=hazard ratio.
ITT analysis.
Based on CCOD of 07 October 2024.
[1]DREAMM-8: HRs were estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no).

Figure 7: DREAMM-8 KM Curve of OS (Descriptive)



Source: FDA analysis
Abbreviations: KM=Kaplan Meier, OS=overall survival, Belamaf=belantamab mafodotin, POM=pomalidomide, Bor=bortezomib, Dex=dexamethasone, ITT=intent-to-treat.
ITT analysis.
Based on CCOD of 07 October 2024.

Subgroup analyses for OS were performed, and overall, OS subgroup results were also consistent with OS results in the ITT population for both studies, except for age subgroups in DREAMM-7.

In DREAMM-7, the OS HR in the subgroup of patients ≥75 years of age (based on 37 patients on the BVd arm and 30 patients on the DVd arm ≥75 years of age) was 1.21 (95% CI: 0.58 to 2.54) (Appendix 10.5, Table 33). Of note, the OS HR for the subgroup of patients ≥75 years of age in DREAMM-8 was consistent with the results in the ITT population. Given the post-hoc nature of these analyses, all subgroup analysis results are considered exploratory and hypothesis-generating.

6.4.4.3 Other Key Secondary Endpoints

Other key secondary endpoints in DREAMM-7 and DREAMM-8 were DOR and MRD-negative CR rate. Refer to Appendix 10.5 for results of these endpoints.

DOR was included in the hierarchical testing procedure for DREAMM-7, but not in DREAMM-8. FDA considers the analyses of DOR for both studies to be descriptive only, as this comparison is based on a comparison of responders only, removing the balance between arms ensured by randomization.

6.5 Safety Results

The assessment of safety in DREAMM-7 and DREAMM-8 was based on patients who received at least one dose of study treatment (DREAMM-7: BVd n=242, DVd n=246; DREAMM-8: BPd

n=150, PVd n=145). This section provides an overview of the safety profile of belantamab mafodotin in the proposed combination regimens, while the focused review of the key issue of ocular toxicity is presented in Section 7.1.

The FDA's analysis of treatment emergent adverse events (TEAEs) was based on grouped related adverse event terms for selected adverse events as indicated in the tables below.

The overall median duration of treatment (based on longest duration of any component of the regimen) was 15.9 months in the BVd arm vs. 12.8 months in the DVd arm in DREAMM-7 and 15.9 months in the BPd arm vs. 8.5 months in the PVd arm in DREAMM-8.

6.5.1 Safety Overview

An overview of TEAEs and dose modifications due to TEAEs is provided in Table 10.

In the belantamab mafodotin-containing arms of both DREAMM-7 and DREAMM-8, over 90% of patients experienced Grade 3-4 TEAEs and approximately 10% of patients experienced fatal TEAEs. The rates of Grade 3-4 TEAEs and serious TEAEs were higher in the belantamab mafodotin-containing arms as compared to the comparator arm in both studies. There were high rates of dose modifications in the belantamab mafodotin-containing arms in both DREAMM-7 and DREAMM-8, which were notably higher than the rates on the comparator arms. The majority of patients who received a belantamab mafodotin-containing regimen required dose interruptions or reductions due to TEAEs, and 31% and 15% required discontinuation of study treatment due to TEAEs in DREAMM-7 and DREAMM-8, respectively.

The most common reasons for dose modification on the BVd arm in DREAMM-7 were thrombocytopenia, blurred vision, and peripheral neuropathy. The most common reasons for dose modification on the BPd arm in DREAMM-8 were blurred vision, neutropenia, and pneumonia. As described in Section 7.2.1, ocular toxicities, specifically due to keratopathy and visual acuity changes, were the leading cause of dose interruptions on the belantamab mafodotin-containing arms of DREAMM-7 and DREAMM-8.

Table 10: DREAMM-7 and DREAMM-8 Safety Overview

	DREAMM-7		DREAMM-8	
AE Category, n (%)	**BVd N=242**	**DVd N=246**	**BPd N=150**	**PVd N=145**
Any Grade TEAEs	242 (100)	246 (100)	149 (99)	139 (96)
Grade 3-4 TEAEs	229 (95)	187 (76)	138 (92)	107 (74)
Grade 5 TEAEs	23 (10)	19 (8)	17 (11)	17 (11)
Serious TEAEs	121 (50)	90 (37)	95 (63)	65 (45)
TEAEs leading to any dose modification	236 (98)	220 (89)	136 (91)	124 (86)
TEAEs leading to dose interruption	228 (94)	185 (75)	136 (91)	109 (75)
TEAEs leading to dose reduction	182 (75)	146 (59)	92 (61)	88 (61)
TEAEs leading to discontinuation	75 (31)	46 (19)	22 (15)	18 (12)

Abbreviations: TEAE=treatment-emergent adverse event.
Source: FDA analysis

6.5.2 Deaths

An overview of deaths by study arm on each study is presented in Table 11. In each study, the rates of fatal TEAEs were comparable between treatment arms. The most common fatal TEAEs in patients who received BVd in DREAMM-7 were pneumonia (2%), sepsis (2%), and COVID-19 infection (1%). The most common fatal TEAEs in patients who received BPd in DREAMM-8 were pneumonia (3%), cardiovascular causes (2%), and COVID-19 infection (1%).

Table 11: DREAMM-7 and DREAMM-8 Summary of Deaths

	DREAMM-7		DREAMM-8	
Death Category, n (%)	**BVd N=242**	**DVd N=246**	**BPd N=150**	**PVd N=145**
Total Deaths (Safety Population)	55 (23)	85 (35)	48 (32)	55 (38)
Deaths within 30 days	17 (7)	22 (9)	14 (9)	16 (11)
Deaths due to TEAEs	17 (7)	19 (8)	11 (7)	13 (9)
Deaths due to PD	0	3 (1)	3 (2)	3 (2.1)
Deaths >30 days	38 (16)	63 (26)	34 (23)	39 (27)

Abbreviations: TEAE=treatment-emergent adverse event, PD=progressive disease.
Source: FDA analysis, based on FDA adjudication

6.5.3 Serious Adverse Events

As shown in Table 12 and Table 13 for DREAMM-7 and DREAMM-8, respectively, there were higher rates of serious TEAEs in the belantamab mafodotin-containing arms as compared to the comparator arms. The most common serious TEAE reported in the belantamab mafodotin-containing arms of each trial was pneumonia.

Table 12: DREAMM-7 Serious TEAEs

	DREAMM-7	
AE Category, n (%)†	**BVd N=242**	**DVd N=246**
Any Serious TEAEs	121 (50)	90 (37)
Pneumonia*	43 (18)	20 (8)
Pyrexia*	12 (5)	10 (4.1)
COVID-19	11 (4.6)	10 (4.1)

†SAEs with ≥5% incidence in either arm reported.
*Includes grouped related adverse event terms.
Abbreviations: TEAE=treatment-emergent adverse event.
Source: FDA analysis

Table 13: DREAMM-8 Serious TEAEs

	DREAMM-8	
AE Category, n (%)†	**BPd N=150**	**PVd N=145**
Any Serious TEAEs	95 (63)	65 (45)
Pneumonia*	49 (33)	20 (14)
Upper Respiratory Tract Infection*	11 (7)	5 (3.5)
COVID-19	10 (7)	4 (2.8)

†SAEs with ≥5% incidence in either arm reported.
*Includes grouped related adverse event terms.
Abbreviations: TEAE=treatment-emergent adverse event.
Source: FDA analysis

6.5.4 Common TEAEs

The most common TEAEs (at least 20% incidence in either arm), excluding laboratory abnormalities (see Section 6.5.5 below) are shown in Table 14 and Table 15 for DREAMM-7 and DREAMM-8, respectively. The most common TEAEs were similar in both trials. Eye disorders, including blurred vision and other ocular symptoms, were the most commonly reported TEAEs in the belantamab mafodotin-containing arms in each trial. Additionally, there were higher rates, including for Grade 3-4 events, of pneumonia and hepatotoxicity in the BVd arm compared to the DVd arm in DREAMM-7, and higher rates, including for Grade 3-4 events, of upper respiratory tract infections, pneumonia and COVID-19 in the BPd arm compared to the PVd arm in DREAMM-8.

Table 14: DREAMM-7 Common TEAEs

TEAE, n (%)†	DREAMM-7			
	BVd N=242		DVd N=246	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Eye disorders				
Vision blurred	160 (66)	53 (22)	26 (11)	2 (0.8)
Dry eye*	123 (51)	16 (7)	18 (7)	0
Photophobia	114 (47)	5 (2.1)	6 (2.4)	0
Foreign body sensation*	107 (44)	8 (3.3)	10 (4.1)	0
Eye irritation	103 (43)	12 (5)	13 (5)	0
Eye pain*	79 (33)	2 (0.8)	9 (3.7)	1 (0.4)
Cataract*	59 (24)	19 (8)	34 (14)	8 (3.3)
Nervous system disorders				
Peripheral neuropathy*	128 (53)	10 (4.1)	122 (50)	16 (7)
Infections				
Upper respiratory tract infection*	93 (38)	5 (2.1)	88 (36)	6 (2.4)
Pneumonia*	62 (26)	33 (14)	41 (17)	13 (5)
COVID-19	58 (24)	11 (4.6)	49 (20)	6 (2.4)
Hepatobiliary disorders				
Hepatotoxicity*Δ	81 (33)	34 (14)	39 (16)	6 (2.4)
Gastrointestinal disorders				
Diarrhea	78 (32)	9 (3.7)	77 (31)	10 (4.1)
Constipation	46 (19)	2 (0.8)	56 (23)	1 (0.4)
General disorders				
Fatigue*	63 (26)	14 (6)	67 (27)	9 (3.7)
Musculoskeletal pain*	58 (24)	4 (1.7)	87 (35)	9 (3.7)

†TEAEs with ≥20% incidence in either arm reported.
*Includes grouped related adverse event terms.
ΔIncludes adverse event terms reported based on laboratory abnormalities.

Abbreviations: TEAE=treatment-emergent adverse event.
Source: FDA analysis

Table 15: DREAMM-8 Common TEAEs

TEAE, n (%)†	DREAMM-8			
	BPd N=150		PVd N=145	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Eye disorders				
Vision blurred	119 (79)	26 (17)	22 (15)	0
Dry eye*	91 (61)	12 (8)	14 (10)	0
Foreign body sensation*	91 (61)	9 (6)	11 (8)	0
Eye irritation	75 (50)	6 (4)	13 (9)	0
Photophobia	66 (44)	5 (3.3)	6 (4.1)	0
Eye pain*	51 (34)	3 (2)	7 (4.8)	0
Cataract*	49 (33)	12 (8)	19 (13)	7 (4.8)
Visual acuity reduced	34 (23)	20 (13)	8 (6)	1 (0.7)
Infections				
Upper respiratory tract infection*	66 (44)	10 (7)	46 (32)	5 (3.5)
Pneumonia*	62 (41)	43 (29)	32 (22)	16 (11)
COVID-19	56 (37)	8 (5)	31 (21)	1 (0.7)
General disorders				
Fatigue*	55 (37)	12 (8)	50 (35)	13 (9)
Musculoskeletal pain*	39 (26)	2 (1.3)	37 (26)	3 (2)
Edema*	24 (16)	3 (2)	32 (22)	5 (3.5)
Gastrointestinal disorders				
Constipation	23 (15)	2 (1.3)	33 (23)	2 (1.4)
Diarrhea	35 (23)	2 (1.3)	33 (23)	10 (7)
Nervous system disorders				
Peripheral neuropathy*	19 (13)	1 (0.6)	60 (41)	5 (3.5)

†TEAEs with ≥20% incidence in either arm reported.
*Includes grouped related adverse event terms.
Abbreviations: TEAE=treatment-emergent adverse event.
Source: FDA analysis

6.5.5 Laboratory Abnormalities

A summary of hematology and chemistry laboratory abnormalities that worsened from baseline with ≥30% incidence in DREAMM-7 and DREAMM-8 is provided in Appendix 10.6. The rates of thrombocytopenia (all grades and Grades 3-4) were higher in the belantamab mafodotin-containing arms as compared to the comparator arms in both trials. The rates of all-grade AST and ALT elevation were higher in the belantamab mafodotin-containing arms as compared to the comparator arms in both trials; however, the rates of Grade 3-4 AST and ALT elevation were low overall.

7 Issues for the AC

7.1 High Rates of Ocular Toxicity

Ocular toxicity is a key safety concern with belantamab mafodotin. As described in Section 4, the ocular toxicity observed with belantamab mafodotin is primarily related to the nonspecific uptake of the MMAF payload into corneal epithelial cells, while other factors, such as a systemic inflammatory response may also contribute. Corneal toxicity may be asymptomatic, particularly in earlier stages, in part due to the lack of pain receptors in the eye and due to the potential for one eye to compensate for loss of vision in the other eye. Additionally, many clinically relevant ocular toxicities are not necessarily symptomatic, but may be considered serious because they may 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.

7.1.1 Grading of Ocular Toxicity (KVA Scale)

Given the factors described above, there are limitations with the use of the Common Terminology Criteria for Adverse Events (CTCAE) grading scale, which is based on symptoms and interference with activities of daily living, for the identification and grading of corneal toxicity. Therefore, the Sponsor developed the Keratopathy and Visual Acuity (KVA) scale, with input from the FDA (see Appendix 10.7). The KVA scale incorporates slit-lamp eye examination findings and best corrected visual acuity (BCVA); the worse grade by either examination method is used to inform the grade of the KVA event.

Table 16 shows the corneal exam findings and BCVA changes, according to the visual acuity chart, that inform the KVA grade and the recommended dosage modifications of belantamab mafodotin based on the grade of KVA event in each study. BCVA is defined as the highest level of vision an eye can achieve using corrective lenses like glasses or contacts.

For determination of the overall KVA grade, the more severe finding of the corneal exam and BCVA change was used. Dosage modifications were recommended for Grade ≥2 KVA events on both studies. While the dosage modification guidance in DREAMM-7 included one potential dose reduction, the dosage modification guidance in DREAMM-8 included multiple potential reductions in dose and/or dosing frequency.

Table 16: Keratopathy and Visual Acuity (KVA) Grading Scale

	Grade 1	Grade 2	Grade 3	Grade 4
Keratopathy and Visual Acuity (KVA) Scale Grading				
Corneal exam findings	Mild superficial keratopathy	Moderate superficial keratopathy	Severe superficial keratopathy	Corneal epithelial defect
Change in BCVA (from baseline)	Decline of 1 line	Decline of 2 or 3 lines and not worse than 20/200	Decline by >3 lines and not worse than 20/200	Worse than 20/200
Recommended Dosage Modifications for Belantamab Mafodotin				
DREAMM-7	Continue current dose	Hold until Grade ≤1; resume at current dose	Hold until Grade ≤1; resume at reduced dose (1.9 mg/kg Q3W)	Permanently discontinue
DREAMM-8	Continue current dose	Hold until Grade ≤1; resume at reduced dose: • Prior to Cycle 2: 1.9 mg/kg Q4W • Cycle 2+: reduce to 1.9 mg/kg Q8W		Hold until Grade ≤1; discuss benefit-risk; resume at reduced dose (1.4 mg/kg Q8W)

Abbreviations: BCVA=best corrected visual acuity, Q#W=once every # weeks.
Source: FDA generated table based on DREAMM-7 and DREAMM-8 Study Protocols

Other ocular adverse event data was also collected by investigators and graded using the CTCAE version 5.0 (see Section 7.1.5). Patient reported outcomes (PRO) data (see Section 7.1.6) was collected using the PRO-CTCAE, Ocular Surface Disease Index (OSDI), and Functional Assessment of Cancer Therapy – General Population Item #5 (FACT-GP5) scales to evaluate symptomatic toxicities, visual symptoms and function, and overall side effect bother, respectively.

The clinical trial protocols specified that ophthalmic exams were to be performed at screening/baseline, at least prior to each of the first 6 doses, and at the end of treatment (EOT), with additional exams as clinically indicated. In patients who did not experience visual symptoms, changes in vision, or corneal exam findings up to and including the time of the 6th dose of belantamab mafodotin, ophthalmic exam frequency could be reduced to once every 3 months. Patients with ocular events at the EOT were to have ophthalmic exams once every 3 months until resolution or up to 1 year.

7.1.2 Other Ocular Toxicity Mitigation Strategies Evaluated

Earlier in the development of belantamab mafodotin, the Applicant evaluated additional potential strategies (e.g., steroid eye drops, bandage contact lenses) to mitigate the risk of ocular toxicity. The phase 2, single arm DREAMM-2 trial, which supported the initial approval of belantamab mafodotin monotherapy, included an ocular sub-study to evaluate the effect of topical corticosteroids on the development of corneal events in approximately 30 participants (n=17 in the 2.5 mg/kg cohort; n=13 in the 3.4 mg/kg cohort) who received monocular topical corticosteroids during the first 4 cycles of treatment. No differences were observed in the incidence or time to onset of corneal events with topical corticosteroid treatment in the ocular sub-study. The phase 3 randomized DREAMM-3 trial, which evaluated belantamab mafodotin

monotherapy vs. pomalidomide and dexamethasone, also included an exploratory ocular sub-study to assess whether the use of bandage contact lenses in patients who develop Grade 2 or higher KVA events could mitigate the risk of higher-grade ocular toxicity through resolution of corneal epithelial lesions. Approximately 60 participants were planned for 1:1 randomization to receive bandage contact lenses or routine management per a qualified eye care specialist; however, only 25 patients were enrolled, and only 9 patients were randomized to the bandage contact lenses group. Due to the small number of participants enrolled, no conclusions could be drawn on whether the use of bandage contact lenses may help mitigate the risk of higher grades of ocular toxicity. Therefore, the available data do not suggest that either of these strategies have been efficacious in mitigating the ocular toxicity seen with belantamab mafodotin. The only currently identified mitigation strategy for the ocular toxicity and the only strategy incorporated in the DREAMM-7 and DREAMM-8 trials was the implementation of dose modifications based on ophthalmic exam and visual acuity findings.

7.1.3 Corneal Toxicity (by KVA Scale)

7.1.3.1 KVA Event Summary

High rates of corneal toxicity, as measured by the KVA scale, were seen in the belantamab mafodotin-containing arms of DREAMM-7 and DREAMM-8, as shown in Table 17. Over 75% of patients who received belantamab mafodotin in each study experienced Grade 3-4 KVA events. High rates of dose modifications due to KVA events also occurred on both studies, with approximately 75% of patients requiring dose interruptions due to a KVA event in each study. There were higher rates of dose reductions due to KVA events on DREAMM-8 (57%) as compared to DREAMM-7 (30%).

Table 17: DREAMM-7 and DREAMM-8 Overview of KVA Events

	DREAMM-7	DREAMM-8
Adverse Event Category, n (%)	**BVd N=242**	**BPd N=150**
Any Grade KVA event	222 (92)	140 (93)
Grade 1	13 (5)	9 (6)
Grade 2	22 (9)	15 (1)
Grade 3	136 (56)	103 (69)
Grade 4	51 (21)	13 (9)
Any dose modification due to KVA event	185 (76)	117 (78)
Dose interruption due to KVA event	179 (74)	113 (75)
Dose reduction due to KVA event	72 (30)	86 (57)
Discontinuation due to KVA event	15 (6)	11 (7)

Abbreviations: KVA=keratopathy and visual acuity (i.e., event per KVA scale).
Source: FDA Analysis

Table 18 provides an analysis of the maximum toxicity grade by patient for each of the two components of the KVA scale, corneal exam findings and change in BCVA. As described in Section 7.1, the most severe finding of the two components, corneal exam findings or BCVA change, was used to derive the KVA grade. The results from analysis of the individual

components demonstrate that both corneal exam findings and BCVA changes contributed to the overall KVA grade.

Table 18: DREAMM-7 and DREAMM-8 KVA Event Category

	DREAMM-7	DREAMM-8
Type of KVA Event, n (%)	**BVd N=242**	**BPd N=150**
Grade 1		
Corneal exam	10 (4)	10 (7)
BCVA	22 (9)	13 (9)
Grade 2		
Corneal exam	23 (10)	27 (18)
BCVA	56 (23)	34 (23)
Grade 3		
Corneal exam	130 (54)	84 (56)
BCVA	125 (52)	86 (57)
Grade 4		
Corneal exam	45 (19)	9 (6)
BCVA	13 (5)	4 (2.7)

Abbreviations: KVA=keratopathy and visual acuity (i.e., event per KVA scale), BCVA=best corrected visual acuity.
Source: FDA Analysis

The majority of patients on the belantamab mafodotin-containing arms of DREAMM-7 and DREAMM-8 had multiple KVA events. A summary of the number of occurrences in each patient by study is provided in Table 19.

Table 19: DREAMM-7 and DREAMM-8 Number of KVA Occurrences

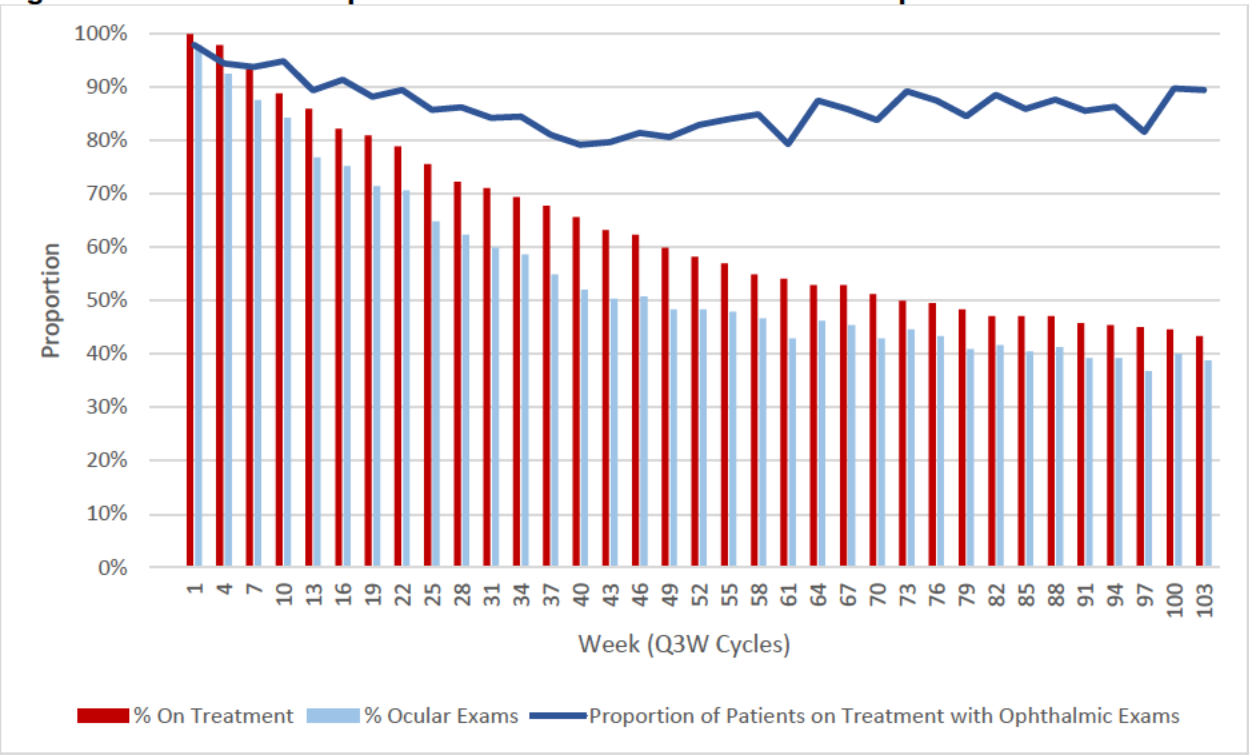
	DREAMM-7	DREAMM-8
Number of KVA Events, n (%)	**BVd N=242**	**BPd N=150**
Median (range)	3 (1,11)	3 (1,10)
Number of events (%)		
1	63 (30)	36 (27)
2	35 (17)	20 (15)
3 or more	111 (53)	75 (57)

Abbreviations: KVA=keratopathy and visual acuity (i.e., event per KVA scale).
Source: FDA Analysis

7.1.3.2 Ophthalmic Exams in DREAMM-7 and DREAMM-8

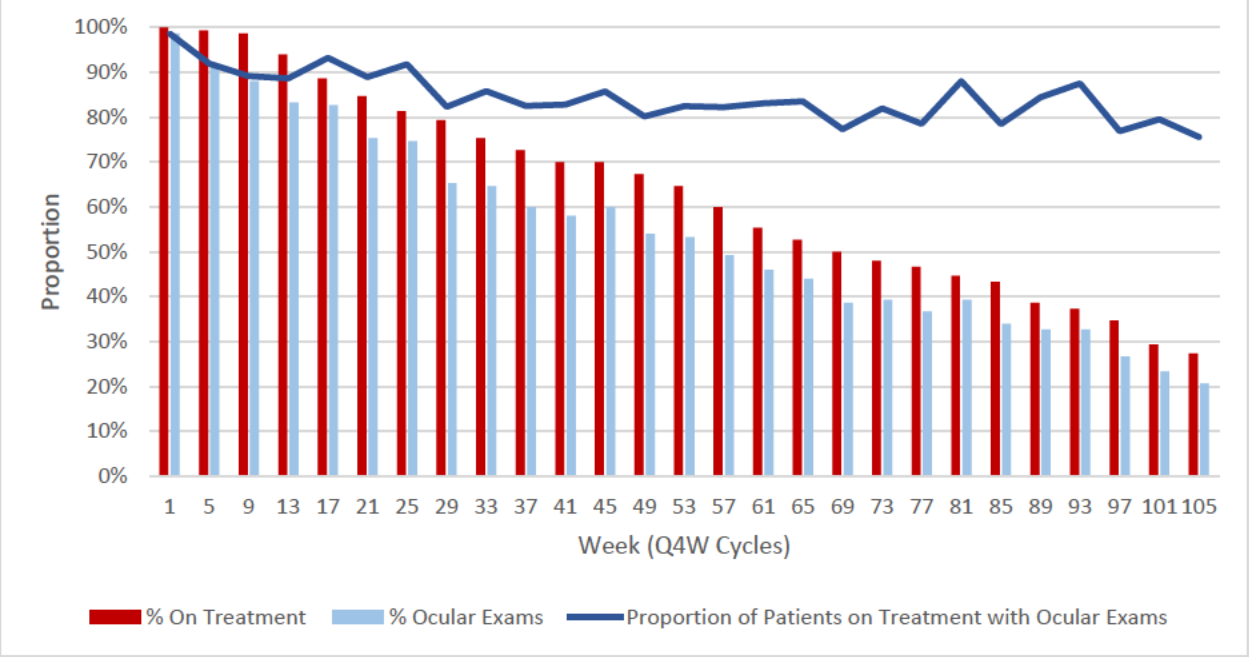
FDA's analysis of the frequency of ophthalmic exams conducted on the belantamab mafodotin-containing arms of the DREAMM-7 and DREAMM-8 studies, as shown in Figure 8 and Figure 9, respectively, demonstrate that the majority of patients on treatment (i.e., >80% of patients at most timepoints in both studies) underwent ophthalmic exams at various timepoints throughout treatment. As ophthalmic exams were routinely performed at least prior to each of the first 6 doses, per protocol, with subsequent exams performed as clinically indicated, these findings further highlight the high rates of ocular toxicity and frequent occurrences of ocular toxicity that necessitated ophthalmic exam monitoring throughout the duration of treatment.

Figure 8: DREAMM-7 Proportion of Patients on Treatment with Ophthalmic Exams



Abbreviations: Q3W=once every 3 weeks.
Source: FDA analysis; Applicant's Response to FDA Information Request dated February 7, 2025

Figure 9: DREAMM-8 Proportion of Patients on Treatment with Ophthalmic Exams



Abbreviations: Q4W=once every 4 weeks.
Source: FDA analysis; Applicant's Response to FDA Information Request dated February 7, 2025

7.1.3.3 Timing and Outcomes of KVA Events

The time to onset and number of occurrences of KVA events are summarized in Table 20. The majority of patients who experienced Grade ≥2 KVA events had initial onset within the first 2 months of study treatment, however there was a large range in time-to-onset, with 26% and 22% of events occurring after 2 months from the start of treatment in DREAMM-7 and DREAMM-8, respectively. For events that resolved (based on improvement to Grade 1 or better), the median duration was approximately 3 months.

Table 20: Timing and Duration of Grade ≥2 KVA Events

	DREAMM-7	DREAMM-8
	BVd N=242	BPd N=150
Grade ≥2 KVA event, n (%)	209 (86)	131 (87)
Onset (1st event), median (range), in days	43 (15, 611)	32 (18, 533)
0-2 months	154 (74)*	102 (78)
2-4 months	38 (18)	19 (14)
4-6 months	7 (3)	4 (3)
6 months and beyond	10 (5)	6 (5)
Duration (all events), median (range), in days	85 (5, 813)	85 (2, 746)

*Includes 1 patient with Grade 2 KVA findings at baseline.
Abbreviations: KVA=keratopathy and visual acuity (i.e., event per KVA scale).
Source: FDA analysis

Table 21 summarizes the outcomes of the last Grade ≥2 KVA event (based on the cut-off date) in patients treated on the belantamab mafodotin-containing arms of DREAMM-7 and DREAMM-8. Data presented includes that from patients who were currently receiving belantamab mafodotin and those who had discontinued treatment at the time of data cut-off.

While the Applicant has provided data regarding resolution of the first event, data regarding resolution of the last KVA event is particularly important, given the high rates of recurrent KVA events experienced by patients treated on the DREAMM-7 and DREAMM-8 trials. As rates and time to recovery may differ between a first and last KVA event in a given patient, and given the importance of characterizing the longer-term outcomes of the toxicity including after completion of study treatment, the FDA analyzed the outcome of the last Grade ≥2 KVA event.

The Applicant's definition of resolution of a Grade ≥2 KVA event was based on improvement to Grade 1 or baseline. Therefore, patients with mild superficial keratopathy or decline of 1 line on the visual acuity chart would have been considered to have "resolved" toxicity in the analysis. Additionally, patients were eligible to resume treatment with belantamab mafodotin after improvement in either corneal examination findings or changes in BCVA to Grade 1 or better in DREAMM-7 and after recovery to Grade ≤1 per the KVA scale in DREAMM-8. The KVA scale did not include a category for "Grade 0" (i.e., clear cornea and normal/baseline visual acuity); therefore, data regarding complete resolution of KVA events is not available. The lack of information regarding resolution to normal corneal exam and visual acuity findings represents a limitation in interpreting the following results regarding KVA event resolution.

As shown in Table 21, over 50% of patients who experienced Grade ≥2 KVA events had ongoing events at the data cut-off. Among the patients with ongoing KVA events at the data cut-off, approximately 50% had discontinued study treatment.

Table 21: Outcome of Current or Last Grade 2 KVA Event

	DREAMM-7	DREAMM-8
	BVd N=242	BPd N=150
Grade ≥2 KVA event, n (%)	209 (86)	131 (87)
Outcome (last event), n (%)		
Resolved (Grade ≤1)	87 (42)	56 (43)
Ongoing	122 (58)	75 (57)
Ongoing study treatment	56 (27)	38 (29)
Discontinued treatment, follow-up ongoing	31 (15)	12 (9)
Discontinued treatment, follow-up ended	35 (17)	25 (19)

Abbreviations: KVA=keratopathy and visual acuity (i.e., event per KVA scale).
Source: FDA analysis

In patients with ongoing KVA events following treatment discontinuation (66 patients in DREAMM-7 and 37 patients in DREAMM-8), only approximately one-third of patients had ocular exams following EOT. In those who had ocular exams following treatment discontinuation, median time from the EOT to the last ocular exam date was 60.5 days (range 2 – 442) in DREAMM-7 and 22 days (range 2 – 726) in DREAMM-8. Therefore, the assessment of outcomes post-treatment discontinuation may be limited by the relatively short median duration of follow-up after treatment discontinuation in both studies.

7.1.3.4 Additional Analyses of KVA Events

Patient-Level Outcomes in Patients with Ongoing KVA Events After Treatment Discontinuation

A detailed assessment of patient-level data in patients who had an ongoing KVA event at the EOT was requested from the Applicant and is summarized in Appendix 10.8. Interpretation of the data regarding rates of resolution of KVA events in these patients is limited by missing exams post-treatment discontinuation and by limited duration of follow up in certain patients. However, it is notable that there are patients who continued to have the same grade of toxicity at the time of their off-study ocular exams and that some patients had stable or worsening of their ocular toxicity after treatment discontinuation. In DREAMM-7 and DREAMM-8, of those with a KVA event at the EOT, 16% and 14%, respectively had stable KVA events and 8% and 11%, respectively, had worsening of the toxicity at their last ocular exam.

Age Subgroup Analyses

To evaluate whether age impacted the incidence and severity of corneal toxicity, analyses of KVA events by age subgroup (<65, 65 to 74, and ≥75) were conducted. No clear differences in the rates, number of occurrences, timing of onset, or outcomes of Grade ≥2 KVA events were seen across these subgroups in DREAMM-7 or DREAMM-8. Refer to Table 38 in Appendix 10.8 for results of these analyses.

7.1.4 Visual Acuity Changes

Visual acuity changes that are considered to be clinically significant are those that result in a change of 3 lines on the eye chart. For patients with 20/20 baseline vision, a change of 3 lines

corresponds to 20/50 vision. Therefore, for the following analyses, clinically significant changes in visual acuity correspond to changes to 20/50 or worse.

For reference, simulations for each of the levels of visual acuity described (20/20, 20/50, 20/100, and 20/200) are provided in Figure 10.

Figure 10: Simulations of 20/20, 20/50, 20/100, and 20/200 Vision

Source: Sight-Sim™ Software Tool accessed at https://www.sight-sim.scot.nhs.uk

A summary of the rates of clinically significant visual acuity changes (unilateral worsening to 20/50, 20/100 or 20/200) is provided in Table 22 and Table 23 for DREAMM-7 and DREAMM-8, respectively. As these analyses summarize BCVA of 20/50 *or worse*, 20/100 *or worse,* and 20/200 *or worse*, certain patients may be represented in multiple columns corresponding to different levels of BCVA changes.

There are limitations to these analyses, as they do not capture bilateral events (*20/50 or worse in both eyes)*, and therefore, may underrepresent of the severity/duration of clinically meaningful changes in BCVA. Further, considering the Applicant's definition of duration, which was defined as the time from onset of any worsening of BCVA to the specified threshold in only one eye until the occurrence is resolved (BCVA better than the threshold in both eyes*) or the start of a bilateral event (e.g., 20/50 or worse in both eyes)*, unilateral events that later worsened to bilateral were considered as "ending".

Despite these limitations, the analyses demonstrate that in both trials, there were high rates of clinically meaningful changes in BCVA, with median duration of approximately 3 weeks for the majority of BCVA changes in DREAMM-7 and approximately 4 weeks in DREAMM-8.

Table 22: DREAMM-7 Clinically Meaningful Unilateral Changes in Visual Acuity

	DREAMM-7		
	BVd N=242		
	20/50 or Worse	20/100 or Worse	20/200 or Worse
N (%)	155 (64)	68 (28)	27 (11)
Median time to first onset (range), in days	84 (15-925)	101 (15-798)	105 (17-676)
Duration of all events, in days	23 (3-766)	22 (5-766)	22 (4-766)

Source: DREAMM-7 Clinical Study Report, Applicant's Response to FDA Information Request dated June 12, 2025

Table 23: DREAMM-8 Clinically Meaningful Unilateral Changes in Visual Acuity

	DREAMM-8		
	BPd N=150		
	20/50 or Worse	20/100 or Worse	20/200 or Worse
N (%)	95 (63)	41 (27)	19 (13)
Median time to first onset (range), in days	91 (24-764)	114 (26-761)	5 (26-871)
Duration of all events, in days	29 (5-302)	29 (3-338)	58 (26-450)

Source: DREAMM-8 Clinical Study Report, Applicant's Response to FDA Information Request dated June 12, 2025

7.1.5 Other Ocular Toxicities

Data regarding other ocular toxicities that were collected by investigators and graded by CTCAE are presented in Table 24 for DREAMM-7 and in Table 25 for DREAMM-8.

There were higher rates of ocular toxicities in the belantamab mafodotin-containing arm of each trial relative to the comparator arm. In DREAMM-7, the most common ocular toxicities were blurred vision, dry eye, and photophobia. In DREAMM-8, the most common ocular toxicities were blurred vision, dry eye, and foreign body sensation.

Table 24: DREAMM-7 Ocular TEAEs by CTCAE

	BVd N=242		DVd N=246	
AE Term, n (%)	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Vision blurred	160 (66)	53 (22)	26 (11)	2 (0.8)
Dry eye*	123 (51)	16 (7)	18 (7)	0
Photophobia	114 (47)	5 (2.1)	6 (2.4)	0
Foreign body sensation in eyes*	106 (44)	8 (3.3)	10 (4.1)	0
Eye irritation	103 (43)	12 (5)	13 (5)	0
Eye pain*	79 (33)	2 (0.8)	9 (3.7)	1 (0.4)
Cataract*	59 (24)	19 (8)	34 (14)	8 (3.3)
Visual impairment	26 (11)	13 (5)	4 (1.6)	1 (0.4)
Corneal toxicity*	21 (9)	12 (5)	5 (2)	1 (0.4)
Lacrimation increased	21 (9)	2 (0.8)	7 (2.9)	0
Visual acuity reduced	14 (6)	4 (1.6)	5 (2)	1 (0.4)

*Includes grouped related adverse event terms
Abbreviations: TEAE=treatment emergent adverse event, CTCAE=Common Terminology Criteria for Adverse Events.
Source: FDA analysis

Table 25: DREAMM-8 Ocular TEAEs by CTCAE

	BPd N=145		PVd N=150	
AE Term, n (%)	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Vision blurred	119 (79)	26 (17)	22 (15)	0
Dry eye*	91 (61)	12 (8)	14 (10)	0
Foreign body sensation in eyes*	91 (61)	9 (6)	9 (6)	0
Eye irritation	75 (50)	6 (4)	13 (9)	0
Photophobia	66 (44)	5 (3.3)	6 (4.1)	0
Corneal toxicity*	56 (37)	26 (17)	2 (1.4)	1 (0.7)
Eye pain*	51 (34)	3 (2)	7 (4.8)	0
Cataract*	49 (33)	12 (8)	19 (13)	7 (4.8)
Visual acuity reduced	34 (23)	20 (13)	8 (6)	1 (0.7)
Visual impairment	23 (15)	15 (10)	2 (1.4)	1 (0.7)
Lacrimation increased	9 (6)	1 (0.7)	4 (2.8)	0

*Includes grouped related adverse event terms
Abbreviations: TEAE=treatment emergent adverse event, CTCAE=Common Terminology Criteria for Adverse Events.
Source: FDA analysis

7.1.6 Patient-Reported Outcomes

Patient-reported outcomes can provide additional details about tolerability, complementing clinician observed safety data. In DREAMM-7 and DREAMM-8, the Applicant collected patient-reported outcomes primarily using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC-QLQ-C30), specific items from the EORTC item library to assess myeloma disease symptoms, a selection of Patient-Reported Outcomes Version of the CTCAE (PRO-CTCAE) items, the Functional Assessment of Cancer Therapy – General Population Item #5 (FACT-GP5), and the Ocular Surface Disease Index (OSDI). The FDA's review focused on the PRO-CTCAE (blurred vision), OSDI, and FACT-GP5 results to better characterize the safety and tolerability of the belantamab mafodotin-containing regimens in DREAMM-7 and DREAMM-8.

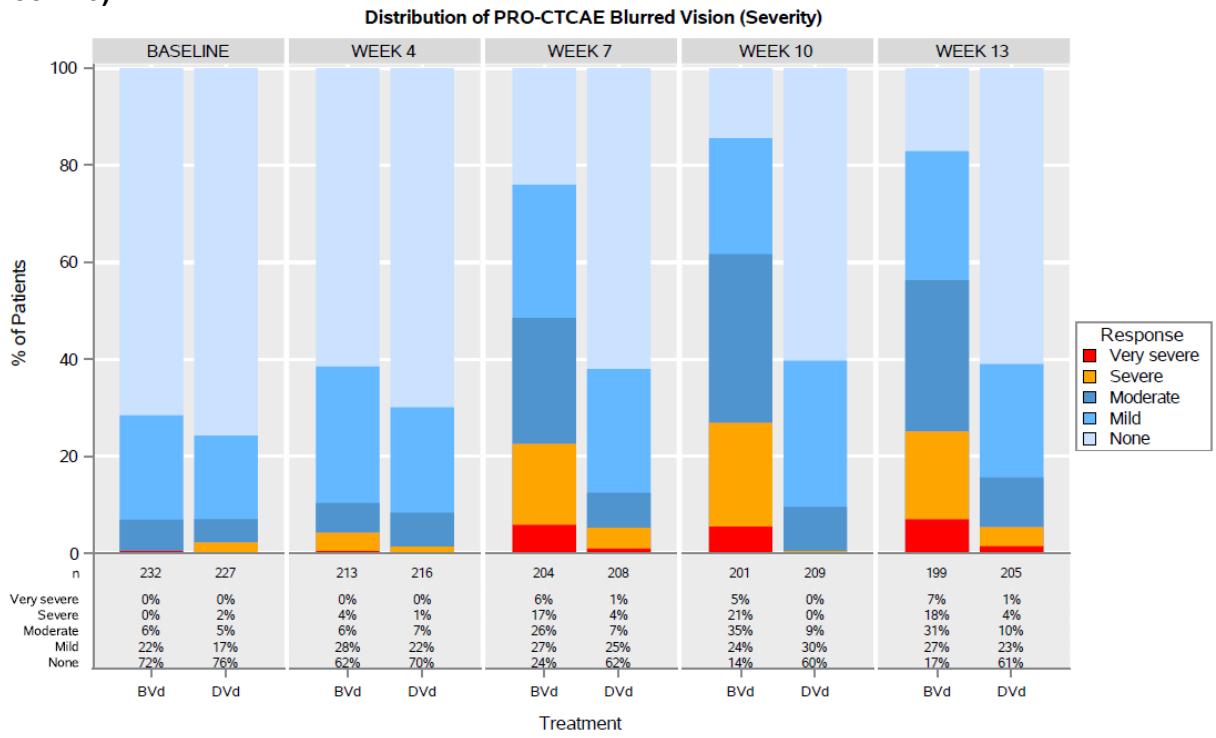
PRO-CTCAE, OSDI, and FACT-GP5 were assessed every three weeks in DREAMM-7 and every four weeks in DREAMM-8 until end of treatment. The FDA's review was focused on the results from baseline to week 28 in DREAMM-7 and week 29 in DREAMM-8. In general, the data quality for these PROs through these timepoints was amenable to interpretation, with compliance rates (the proportion of patients who actually provided a response out of those expected to provide a response at a given timepoint) above 70% at most timepoints within the time period of interest for the FDA PROs of interest. One exception was the data quality for the OSDI in DREAMM-7, with some timepoints between baseline and week 28 with compliance rates in the 50-60% range.

The figures below were generated by the Applicant, in response to the FDA's request for additional characterization of PRO data; the FDA's assessment of these results is provided.

DREAMM-7 and DREAMM-8 PRO-CTCAE Blurred Vision Results

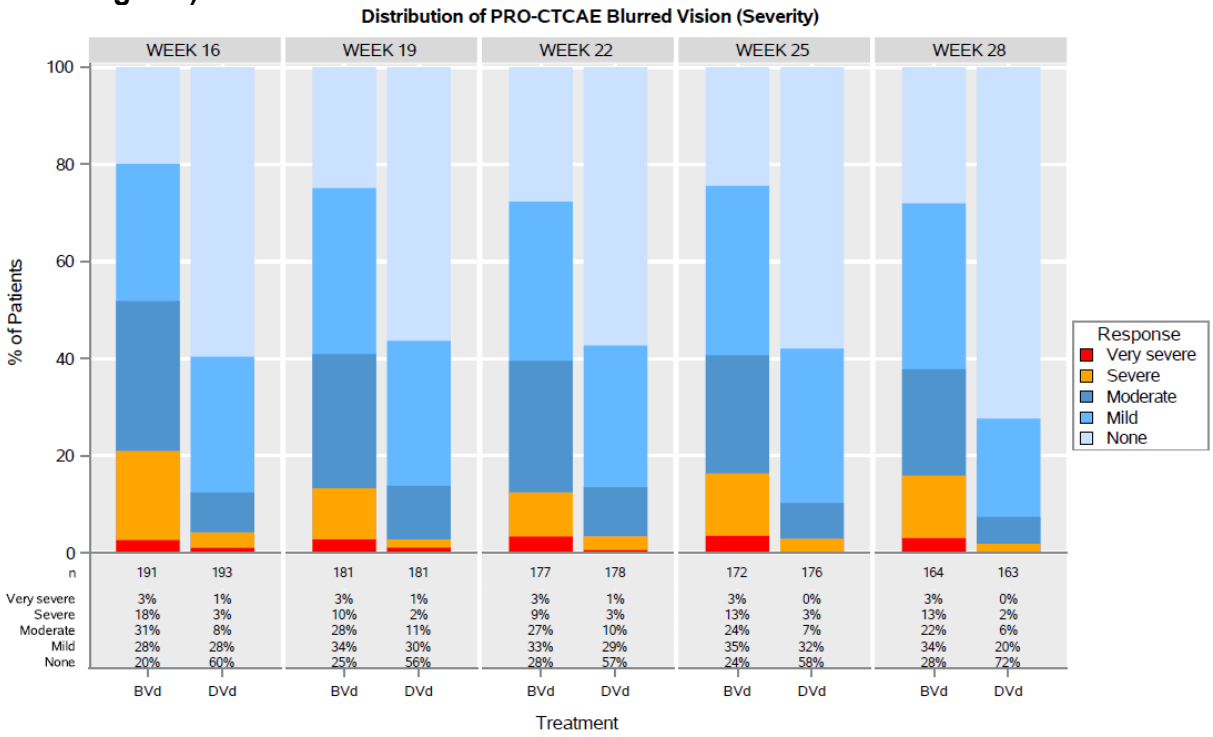
The PRO-CTCAE blurred vision item asks, "In the last 7 days, what was the severity of your blurry vision at its worst?" Presented below are the PRO-CTCAE results for blurred vision in DREAMM-7. Figure 11 and Figure 12 show the severity results from DREAMM-7 through Week 28.

Figure 11: DREAMM-7 PRO-CTCAE Blurred Vision (Severity) results (Baseline through Week 13)



Source: Applicant's Response to FDA Information Request dated March 27, 2025

Figure 12: DREAMM-7 PRO-CTCAE Blurred Vision (Severity) Results, Continued (Week 16 through 28)



Source: Applicant's Response to FDA Information Request dated March 27, 2025

Figure 21 and Figure 22 in Appendix 10.9 show the results for the branching question regarding interference with usual or daily activities for the subset of patients who responded with any severity greater than “none” at that timepoint. In DREAMM-7, over 20% of patients at timepoints between Weeks 7 through 16 responded “quite a bit” or “very much” when asked about the degree of interference.

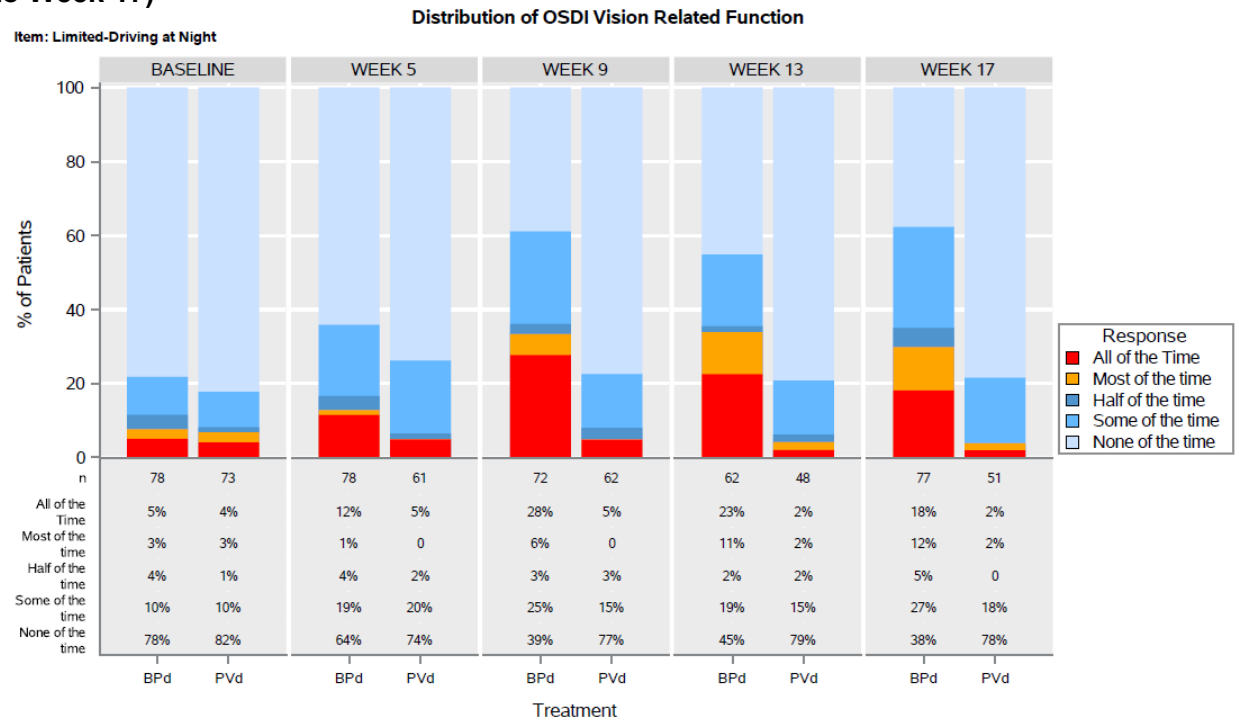
DREAMM-8 results are not presented graphically in this briefing document for brevity; however, generally the DREAMM-8 results for the belantamab mafodotin-containing arm are similar in terms of timing of onset and trajectory over time. However, PRO-CTCAE blurred vision was observed to be less severe in DREAMM-8 compared to DREAMM-7 in the belantamab mafodotin-containing arms, which may be due to the lower dose of belantamab mafodotin administered in DREAMM-8 or differences in dose modifications. For example, at week 13, 13% of PRO-CTCAE respondents in the belantamab mafodotin arm of DREAMM-8 had “very severe” or “severe” responses to the blurred vision item, less than what was observed at the same timepoint in DREAMM-7 as shown in the figure above. Nevertheless, in both DREAMM-7 and DREAMM-8, there was a subset of belantamab mafodotin treated patients who had severe blurry vision.

DREAMM-7 and DREAMM-8 OSDI Results

The OSDI is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning. Although there are multiple visual functioning items on the OSDI, the FDA focused on the results from items relating to ability to read (see Appendix 10.9, Figure 23 through Figure 26) and drive at night. Although data quality was not as high for the OSDI compared to the other PROs assessed in DREAMM-7, similar trends in onset and trajectory of visual side effects in the belantamab mafodotin-containing arms of DREAMM-7 and DREAMM-8 were observed relative to other PROs discussed in this section.

When asked “Have problems with your eyes limited you in performing any of the following during the last week:” patients in DREAMM-7 and DREAMM-8 who received belantamab mafodotin-containing regimens generally responded “all of the time” or “most of the time” more frequently compared to the control arms at almost all assessment timepoints. For example, at week 10 of DREAMM-7, 39% of OSDI respondents in the BVd arm reported limitation in driving at night “all of the time” or “most of the time”. Similarly, at weeks 9 and 13 of DREAMM-8, 34% of OSDI respondents in the BPd arm reported limitation in driving at night “all of the time” or “most of the time”. Although these improve slightly at subsequent timepoints, there remains an approximately 10-20% proportion of belantamab mafodotin treated patients at each assessment timepoint that have severe limitation in their ability to drive at night. Figure 13 below shows the DREAMM-8 OSDI “driving at night” categorical results.

Figure 13: DREAMM-8 OSDI Vision Related Function – Driving at Night Results (Baseline to Week 17)



Source: Applicant's Response to FDA Information Request dated March 27, 2025

Similar results were observed in DREAMM-7 and DREAMM-8 for the OSDI item on limitations in reading, as provided in Appendix 10.9 (Figure 23 through Figure 26).

DREAMM-7 and DREAMM-8 Overall Side Effect Bother (FACT-GP5) Results

The FACT GP5 item is a single item from the FACT-G, which assesses how bothersome the side effects of treatment are for cancer patients. The recall period is the past 7 days, and the item has a 5-category response scale ranging from "0=Not at all" to "4=Very much". In DREAMM-7 and DREAMM-8, patients in the belantamab mafodotin-containing arm reported worse overall side effect bother at all post-baseline timepoints through week 100.

The FACT-GP5 results through week 13 and 17 for DREAMM-7 and DREAMM-8 are provided in Appendix 10.9 (Figure 27 and Figure 28, respectively). Overall side effect bother was highest between Weeks 7-13 in DREAMM-7 and between Weeks 9-17 in DREAMM-8, with higher rates of side effect bother reported on the belantamab mafodotin-containing arms of each study.

Overall side effect bother improved after week 13 in both arms of DREAMM-7 (not shown in this briefing document for brevity), likely due to institution of supportive care, dose modification, or dose delay/interruption; however, the BVd arm consistently had slightly worse bother compared to DVd at assessed post-baseline timepoints.

Interpretation of Tolerability Related PRO Results from DREAMM-7 and DREAMM-8

At each assessed timepoint, there was a group of patients who experienced severe visual side effects related to belantamab mafodotin. For concepts proximal to this side effect, such as blurred vision and visual functioning, there was a growing subset of patients who experienced

severe visual symptoms between baseline through week 13-17, but fewer patients reported these symptoms following this timepoint, likely corresponding to the implementation of dose modifications and administration of supportive care. Nevertheless, approximately 5-15% of patients at each timepoint reported severe visual symptoms throughout DREAMM-7 and DREAMM-8. For example, at week 45 of DREAMM-8, 18% of patients reported “very severe” or “severe” blurred vision by PRO-CTCAE (severity).

The less specific tolerability PRO results such as those from the FACT-GP5 and the EORTC-QLQ-C30 (not discussed here) may obscure the severity of visual side effects related to treatment with belantamab mafodotin, as only a subset of patients had these severe visual side effects or limitation in function at any given timepoint. While the impact of visual side effects is limited to a subset of belantamab mafodotin treated patients at any given timepoint, the severity and interference of these visual side effects is notable, and these PRO results support the clinician reported ocular toxicity findings presented above.

7.1.7 Ocular Toxicity Summary

The key safety issue with belantamab mafodotin is ocular toxicity, with specific findings that include keratopathy, clinically significant changes in visual acuity, and other ocular TEAEs such as blurred vision, photophobia, and dry eye. Despite the differences in the dosing regimens of belantamab mafodotin in DREAMM-7 and DREAMM-8, with a reduction in dose from Cycle 2 onward in DREAMM-8, the ocular toxicity findings were generally similar across studies.

In both DREAMM-7 and DREAMM-8, there were high rates of KVA events, including Grade 3 and higher KVA events. The majority of patients experienced recurrent KVA events throughout the duration of treatment and a substantial percentage of patients experienced clinically significant unilateral changes in visual acuity. While data regarding reversibility of ocular toxicity is limited by the duration of follow up and missing eye exams following study treatment, it is notable that not all KVA events, including visual acuity changes, resolved and that a subset of patients who discontinued study treatment continued to have stable or worsening KVA events at the time of follow up examinations. These findings raise questions regarding the reversibility of the ocular toxicity seen with belantamab mafodotin, particularly towards the end of study treatment, when a patient may have already experienced multiple ocular toxicity events.

Assessment of patient reported outcomes demonstrated impairment of visual symptoms and functioning, with severe symptoms in 5-15% of patients in the majority of the post baseline assessment timepoints.

Considering the frequency and severity of the ocular toxicity seen with belantamab mafodotin at the evaluated dosages, an incomplete understanding of its reversibility, and the impacts on patient functioning and quality of life, concerns regarding the benefit-risk of belantamab mafodotin and the appropriateness of the proposed doses are raised.

7.2 Uncertainty Regarding the Proposed Dosages

The determination of an adequately optimized dose that minimizes toxicity, is tolerable, and maintains efficacy is critical to the FDA’s determination of whether a drug is safe and effective for the proposed use. Dose optimization/dose selection should ideally occur before initiation of the pivotal clinical trial, due to significant challenges that may arise with post-approval

optimization (e.g., exposure of patients to poorly tolerated dosages and challenges with feasibility of post-approval dose optimization trials).

There are concerns with the limited dose exploration of belantamab mafodotin as monotherapy and in the combination regimens evaluated in DREAMM-7 and DREAMM-8. In the context of the significant ocular toxicity and poor tolerability, there are uncertainties regarding the acceptability of the proposed dosages.

There have been challenges in identification of an appropriate dosage of belantamab mafodotin throughout its development as monotherapy and in combination with other agents. It is important to note that at significant junctures during the development of belantamab mafodotin, the FDA provided feedback and expressed concerns with the Applicant's strategies and selected dosages. Notably, at the time of original approval of belantamab mafodotin monotherapy at a dosage of 2.5 mg/kg once every 3 weeks (the lower of the two doses evaluated in the DREAMM-2 trial), these safety and tolerability concerns prompted the requirement for a post-marketing study that was designed to evaluate lower doses and alternative dosing regimens. As described in Section 5, this approval was withdrawn in 2023, after the confirmatory trial failed to show a statistically significant improvement in progression-free survival (See Appendix 10.1).

Despite these concerns with the 2.5 mg/kg Q3W dosage as monotherapy, the Applicant initiated the DREAMM-7 trial of belantamab mafodotin in combination with bortezomib and dexamethasone at the same dosage. The dosage selected for DREAMM-8 was based on the same starting dose, with a reduction to 1.9 mg/kg Q4W from Cycle 2.

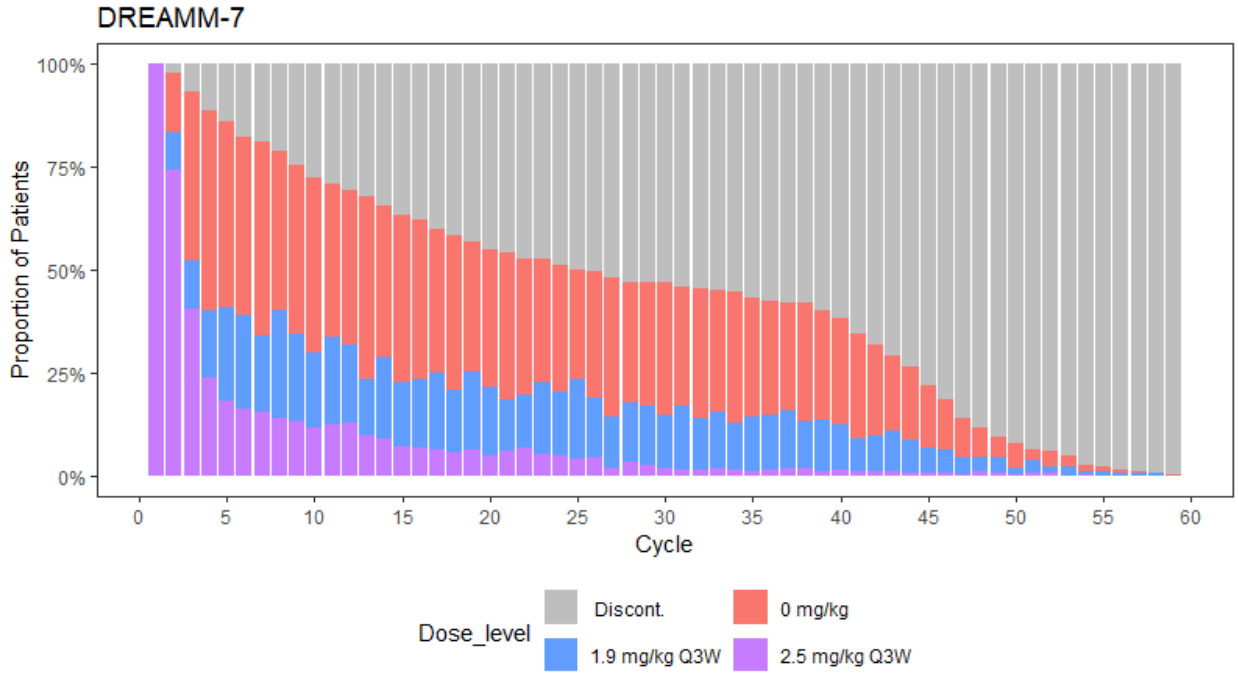
7.2.1 Dose Modifications

As described in Sections 6.5.1 and 7.1.3, the dosages of belantamab mafodotin evaluated in DREAMM-7 and DREAMM-8 were associated with high rates of dose modifications (interruptions, reductions and discontinuations) due to TEAEs and KVA events.

Figure 14 and Figure 15 represent the percentage of patients in each study who received a given dose in each cycle of treatment in DREAMM-7 and DREAMM-8, respectively. By Cycle 3, over 50% of the patients in both studies had discontinued treatment or had a dose interruption or reduction. In both trials, the percentage of patients remaining on the intended dose decreased sharply within the first 3 cycles and continued to decrease steadily over time throughout the duration of treatment.

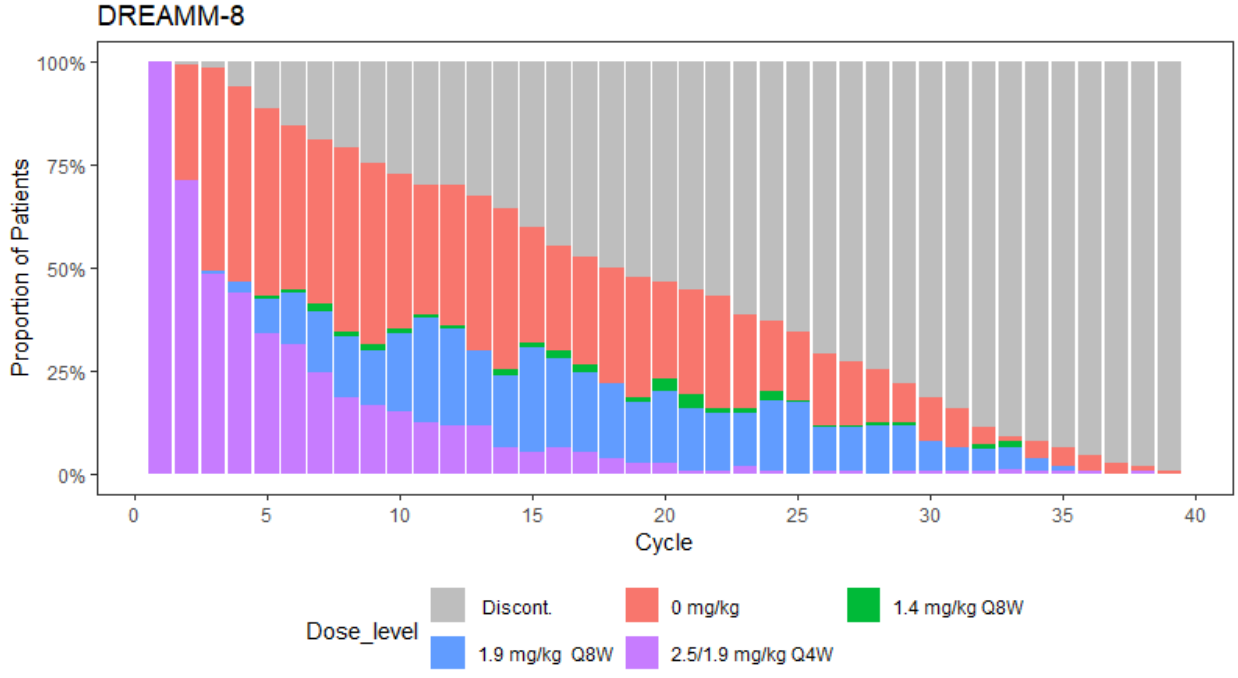
The median duration of dose delays was 54 days (range 1 – 732) in DREAMM-7 and 53 days (range 1 – 980) in DREAMM-8. The inability of the intended dosage to be administered to the majority of patients on both studies raises significant concerns regarding tolerability and the appropriateness of the doses and schedules of belantamab mafodotin.

Figure 14: DREAMM-7 Proportion of Patients Receiving Each Dose Level by Cycle



0 mg/kg reflects dose delays when no dose was given.
Source: FDA analysis

Figure 15: DREAMM-8 Proportion of Patients Receiving Each Dose Level by Cycle



0 mg/kg reflects the dose delays when no dose was given.
Source: FDA analysis

KVA events were the most common cause of dose delays, accounting for 70% and 78% of all dose delays in DREAMM-7 and DREAMM-8, respectively. Figure 29 and Figure 30, which

depict the percentage of patients who received a given dose in each cycle of treatment, with the dose modifications due to KVA events specified, for DREAMM-7 and DREAMM-8, respectively are provided in Appendix 10.10.

Figure 31 in Appendix 10.11 illustrates KVA events and dose modifications (including reductions and interruptions/delays) that occurred throughout the course of treatment in a subset of patients who were treated in DREAMM-7. While a selection of only eight patients from DREAMM-7 is shown, this figure highlights the prolonged and recurrent nature of the dose interruptions/delays that were experienced by some patients. DREAMM-8 patient profiles were not included for brevity, but findings were similar.

7.2.2 Limited Dose Exploration

For both DREAMM-7 and DREAMM-8, dose exploration was limited and was based on the previously approved monotherapy dosage. While the belantamab mafodotin dosage of 2.5 mg/kg on Day 1 followed by 1.9 mg/kg once every 4 weeks (Q4W) in combination with pomalidomide and dexamethasone that was used in DREAMM-8 provides a lower cumulative dose than the dosage evaluated in the monotherapy studies, this dosage was also selected with minimal dose finding.

For DREAMM-7, the proposed dosage for belantamab mafodotin in combination with bortezomib and dexamethasone of 2.5 mg/kg once every 3 weeks (Q3W) was based on data from DREAMM-6 (Arm B). DREAMM-6 was a dose-escalation and expansion study that was initiated in September 2018 in a small number of patients with RRMM after at least one prior line of therapy. The study evaluated 3 doses of belantamab mafodotin, two of which (2.5 mg/kg and 3.4 mg/kg), when administered Q3W, were not considered optimal dosages based on the available monotherapy data.

The results from DREAMM-6 Arm-B (BVd), for treatment groups relevant to DREAMM-7, are shown in Table 26. While interpretation of the data is limited by the small sample size at each dose level, the observed overall response rates (ORR) were similar at the 1.9, 2.5 and 3.4 mg/kg doses on the Q3W regimen. Similarly, ORR across dose levels at Q6W intervals was generally comparable.

However, it is notable that there were fewer adverse events (AEs) and dosage modifications with the 1.9 mg/kg Q6W regimen as compared to the 2.5 mg/kg Q6W regimen and the three doses evaluated at Q3W dosing intervals. Despite similar ORR and lower rates of corneal AEs (per the GSK scale) and dose modifications at the lower dose with a longer dosing interval, the 2.5 mg Q3W regimen was selected as the dosage to be evaluated in DREAMM-7. As described in Section 5 (End-of-Phase 2 Meeting in 2019), due to the toxicity and tolerability concerns at the proposed dosage, the FDA recommended further dose exploration prior to the initiation of DREAMM-7.

Table 26: DREAMM-6 Arm-B (BVd) Summary of Efficacy and Safety

	1.9 mg/kg Q6W N=12	1.9 mg/kg Q3W N=12	2.5 mg/kg then 1.9 mg/kg Q6W N=12	2.5 mg/kg Q6W N=12	2.5 mg/kg Q3W N=18	3.4 mg/kg Q3W N=16
ORR	6 (50%)	10 (83%)	11 (92%)	9 (75%)	14 (78%)	11 (69%)
Any grade AE	12 (100%)	12 (100%)	12 (100%)	12 (100%)	18 (100%)	16 (100%)
AEs leading to discontinuation	3 (25%)	1 (8%)	5 (42%)	4 (33%)	7 (39%)	7 (44%)
AEs leading to dose reduction	8 (67%)	11 (92%)	9 (75%)	11 (92%)	16 (89%)	15 (94%)
Corneal AEs by GSK Scale*						
Any grade corneal AEs	10 (83%)	11 (92%)	12 (100%)	12 (100%)	18 (100%)	16 (100%)
Grade ≥2 corneal AEs	8 (67%)	10 (83%)	12 (100%)	12 (100%)	18 (100%)	16 (100%)
Corneal AEs leading to dose reduction	0	0	0	3 (25%)	14 (78%)	7 (44%)
Corneal AEs leading to dose interruption or delay	7 (58%)	9 (75%)	12 (100%)	10 (83%)	15 (83%)	15 (94%)

*For details of the GSK scale, refer to Appendix 10.6.
Abbreviations: ORR=overall response rate, AE=adverse event.
Source: DREAMM-6 Arm B CSR; Table 60 (All AEs), Table 75 (Ocular AE by GSK scale), Table 91 (Efficacy)

The proposed dosage of belantamab mafodotin in combination with pomalidomide and dexamethasone is 2.5 mg/kg on Day 1 followed by 1.9 mg/kg every 4 weeks. This dosage was selected based on the investigator-led ALGONQUIN study; patient-level data from this study was not provided to or reviewed by the FDA and were obtained from a published article. ALGONQUIN was a dose-escalation and expansion study that evaluated 1.9 mg/kg, 2.5 mg/kg, and 3.4 mg/kg of belantamab mafodotin in combination with pomalidomide and dexamethasone (BPd) over a range of dosing schedules in patients with multiple myeloma after at least one line of therapy.

The results from ALGONQUIN, for dosages relevant to DREAMM-8 are shown in Table 27. While interpretation of data is limited by the small number of patients treated at each dosage, the overall response rates was similar across doses ranging from 1.9 mg to 3.4 mg/kg, suggesting that higher doses may not improve efficacy. Similarly, there appears to be no notable differences in efficacy with the same dose administered at intervals ranging from Q4W to Q12W.

Interpretation of trends in incidence of corneal events (by GSK scale) and decreased visual acuity is challenging due to sample size limitations; however, the overall efficacy and safety data suggest there is no clear advantage to the selection of the higher dose. In addition, prolongation of the dosing interval to Q12W appears to improve safety and tolerability. Therefore, the rationale for selection of the 2.5 mg/kg followed by 1.9 mg/kg Q4W regimen is unclear, given the data suggests that a lower dose with a longer interval may provide similar efficacy, with improved safety and tolerability. Due to the toxicity and tolerability concerns at the

proposed dosage, the FDA also recommended additional exploration the BPd dosage prior to initiation of DREAMM-8 at the time of the End-of-Phase 2 meeting in 2019.

Table 27: ALGONQUIN (BPd) Summary of Efficacy and Safety

	1.9 mg/kg Q4W N=12	**2.5 mg/kg Q4W** N=7	**2.5 mg/kg Q8W** N=12	**2.5 mg/kg Q12W** N=12	**2.5 mg/kg then 1.9 mg/kg Q4W** N=5
ORR	8/11[†] (73%)	7/7 (100%)	11/12 (92%)	11/11 (100%)	5/5 (100%)
Corneal AEs (GSK scale)	67%	100%	92%	67%	60%
Decreased visual acuity*	75%	100%	83%	83%	80%
Number of doses missed (min, max)	3 (0, 22)	14 (7, 28)	4 (0, 9)	2 (0, 4)	5 (2, 27)

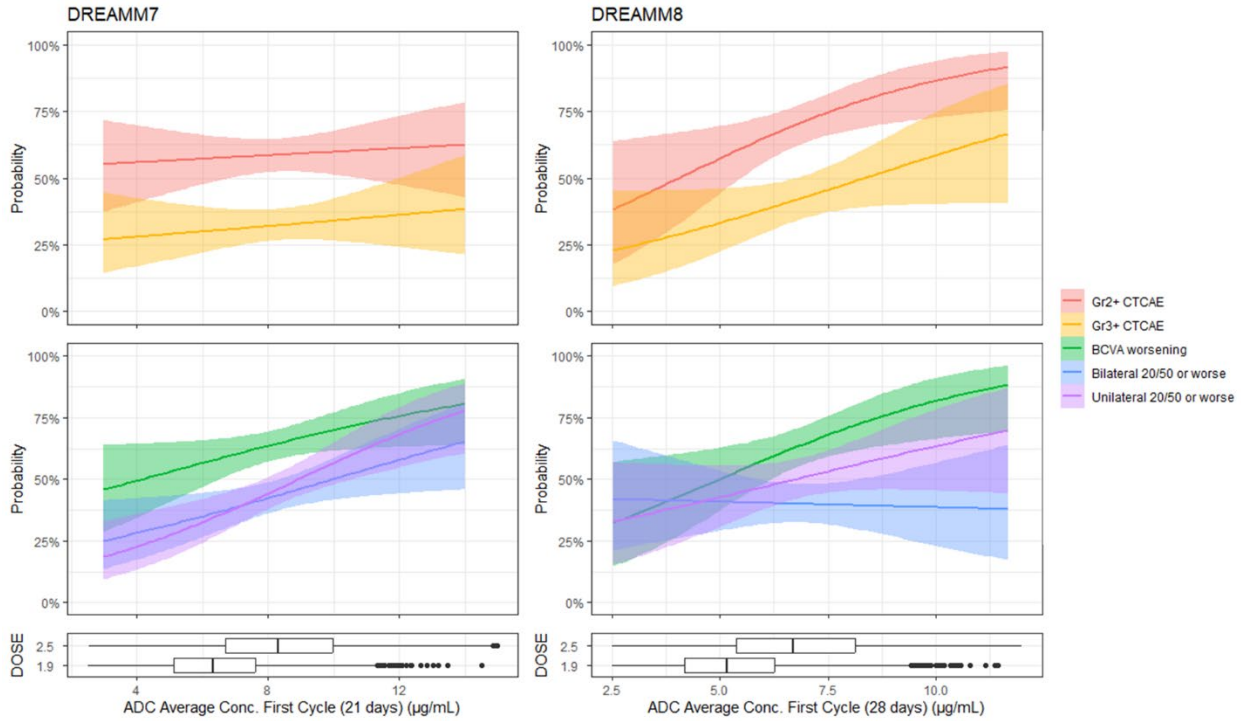
*Defined as any grade change in BCVA.
[†]Represents n responders/N evaluable for response.
Abbreviations: ORR=overall response rate, AE=adverse event, GSK=GlaxoSmithKline.
Source: Trudel et al (2024), Extended Data Table 4 (ORR), Extended Data Table 2 (Ocular AEs), and Table 3 (Belantamab mafodotin dosing)

7.2.3 Additional Data Supporting Alternative Dosing Schedules

Exposure-Response Analyses

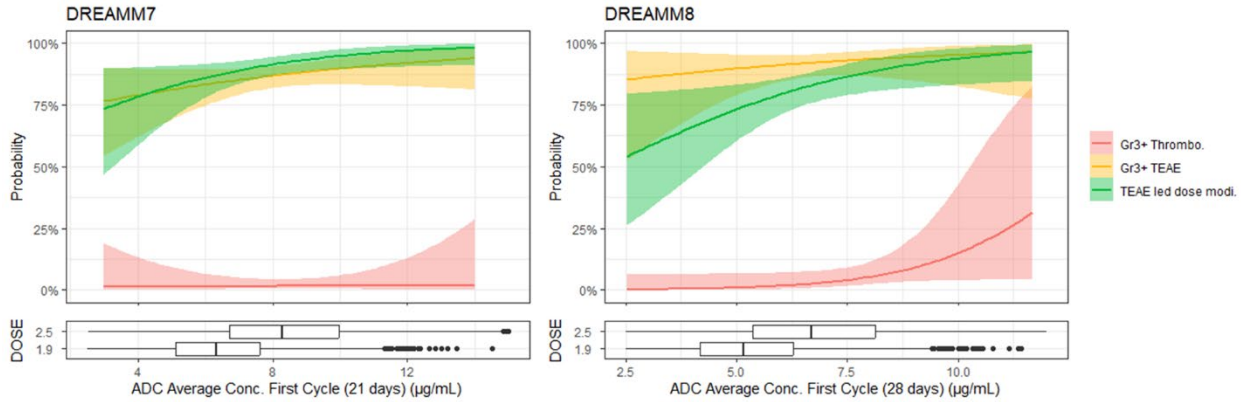
Exposure-response analyses for safety indicate that there is a relationship between drug exposure after the first cycle and ocular toxicity, Grade 3 or higher TEAEs, and TEAEs leading to dose modification for belantamab mafodotin in both combinations and a relationship between drug exposure and Grade 3 or higher thrombocytopenia for belantamab mafodotin in combination with pomalidomide and dexamethasone, as shown in Figure 16 and Figure 17. Results of this analysis indicate that lower doses may be associated with lower rates of safety events.

Figure 16: Exposure Response Relationship between Belantamab Mafodotin Average Concentration in Cycle 1 and Ocular Toxicity



Abbreviations: ADC=antibody drug conjugate (i.e., belantamab mafodotin), Gr=grade, CTCAE=Common Terminology Criteria for Adverse Events, BCVA=best corrected visual acuity.
Source: FDA analysis

Figure 17: Exposure Response Relationship between Belantamab Mafodotin Average Concentration in Cycle 1 and Other Safety Events



Abbreviations: ADC=antibody drug conjugate (i.e., belantamab mafodotin), Gr=grade, Thrombo=thrombocytopenia, TEAE=treatment emergent adverse event.
Source: FDA analysis

DREAMM-14 PMR Study

Given the ocular toxicities and tolerability concerns observed with belantamab mafodotin as monotherapy in the DREAMM-2 trial, a post-marketing requirement to conduct a dose optimization study was issued at the time of its accelerated approval in 2020. DREAMM-14, a randomized study to investigate the safety, efficacy, and PK of various dosages of belantamab

mafodotin, was conducted to address this requirement to characterize the safety and efficacy of lower doses or alternative dosages of belantamab mafodotin.

In DREAMM-14, 177 patients with RRMM who had received at least 3 prior lines of treatment were randomized to the dosages evaluated, with 160 patients randomized to dosages relevant to the current submission. An overview of the safety and efficacy data from these 160 patients are detailed in Table 28. As shown, the overall response rates observed at belantamab mafodotin doses of 1.9 mg/kg or 2.5 mg/kg at Q3W or Q6W intervals were similar, with overlapping confidence intervals. At the 1.9 mg/kg dose, the incidence of mKVA events and dose reductions appear to be substantially lower than that seen at the 2.5 mg/kg dose (refer to Appendix 10.6 for details of the mKVA scale). At the same doses administered at Q6W intervals, as compared to Q3W intervals, the increased dosing intervals appear to be associated with lower rates of adverse events and treatment modifications.

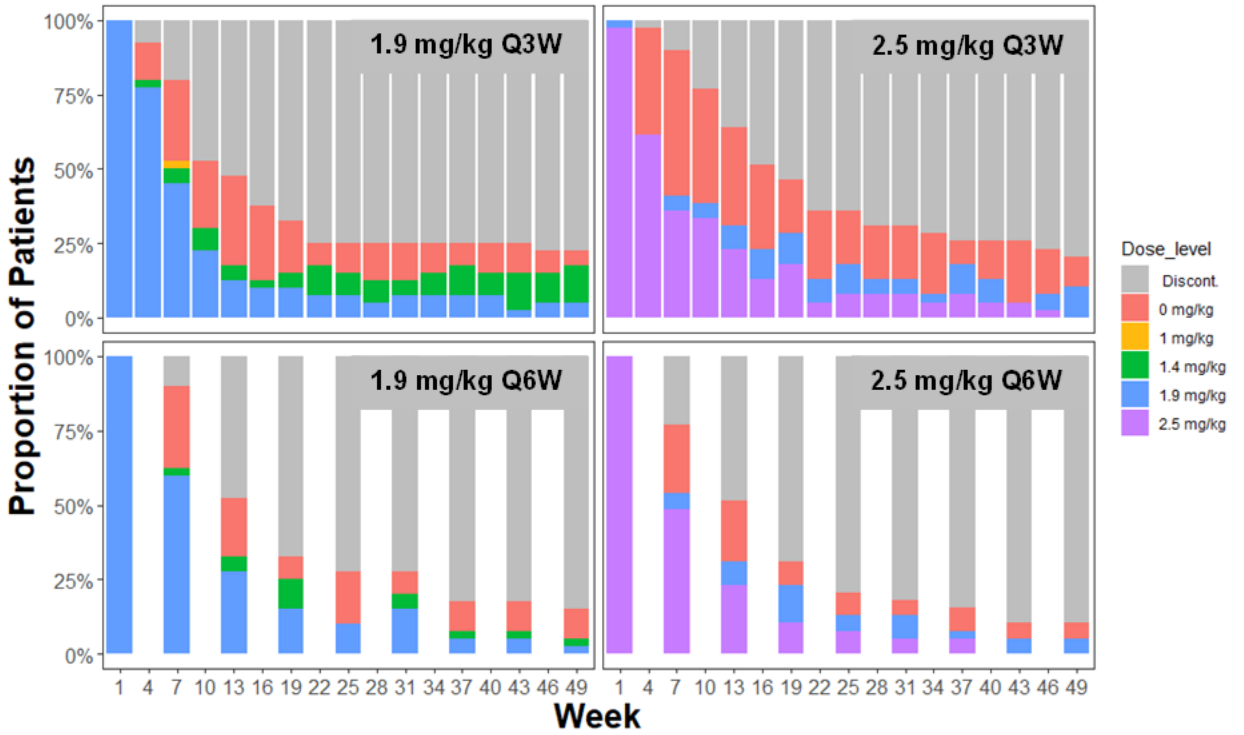
Table 28: DREAMM-14 (Belantamab Mafodotin Monotherapy) Summary of Efficacy and Safety

	1.9 mg/kg Q6W N=40	**1.9 mg/kg Q3W** N=40	**2.5 mg/kg Q6W** N=40	**2.5 mg/kg Q3W** N=40
ORR, (95% CI)	25% (12.7,41.2)	25% (12.7, 41.2)	25% (12.7, 41.2)	33% (18.6, 49.1)
Corneal AE (mKVA) Grade ≥2	38%	40%	44%	64%
Corneal AE (mKVA) leading to dose reduction	20%	28%	26%	31%
Corneal AE (mKVA) leading to dose interruption/delay	33%	35%	28%	59%

Abbreviations: ORR=overall response rate, AE=adverse event, mKVA=modified KVA scale.
Source: DREAMM-14 final CSR (05/21/2025) Table 6 (ORR), Table 64 (Ocular AEs and Dose-modifications)

Figure 18 depicts the proportion of patients by cycle receiving each dose level, separated by each relevant regimen evaluated in DREAMM-14. At the same dosing frequency, patients treated at the lower dose (1.9 mg/kg) as compared to the higher dose (2.5 mg/kg) were able to remain on the intended dosage for longer. At the same dose level (e.g., 1.9 mg/kg), patients treated with the longer dosing interval of Q6W were able to remain on the intended dosage for longer. A similar trend is seen with the comparison of dosing intervals in patients who received the 2.5 mg/kg dose. Taken together, these results suggest improved tolerability with lower doses and longer dosing intervals.

Figure 18: DREAMM-14 Dose Levels by Cycle and Dosing Regimen



Source: FDA analysis of DREAMM-14 (adexbela.xpt)

PK/PD Simulations: M-protein modeling

Biochemical marker modeling, such as M-protein modeling, can be informative when used to support dose exploration and selection objectives and may also be used to predict the effect of alternate dosages on biochemical response. Modeling approaches can be used to characterize the time-course of drug's effect and to evaluate exposure-response relationships in the context of substantial dose modifications. Simulations, based on these models, could be used to evaluate the effect of different doses and dosing schedules and support the identification of dosages for further exploration in clinical trials.

A longitudinal PK/PD serum M-protein model, briefly described in Appendix 10.12, was used to characterize the exposure-response relationship between belantamab mafodotin exposure and drug activity. This analysis also allowed for the simulated evaluation of alternate dosages of belantamab mafodotin. The analysis conducted leveraged a tumor-growth inhibition model to describe changes in serum M-protein levels using patient data from DREAMM-7 and DREAMM-8 and incorporated changes in belantamab mafodotin activity from observed data. Belantamab mafodotin was modeled as causing a reduction in serum M-protein levels by increasing the rate of elimination of M-protein generating cells. The longitudinal PK/PD model was able to describe the observed data from DREAMM-7 and DREAMM-8 well, indicating adequate performance of the model.

Using data from the patients enrolled in DREAMM-7 and DREAMM-8, simulations of the impact of several alternative regimens on biochemical response were conducted. These results are shown in Table 29. While this modeling is exploratory and the simulations do not account for dose modifications due to toxicity, results are generally consistent with the observed clinical

data from DREAMM-14, suggesting that efficacy may be maintained with lower doses and longer dosing intervals. As compared to the 2.5 mg/kg Q3W dose, in the simulations based on DREAMM-7 and DREAMM-8 data, ORR based on M-protein across various alternative regimens, including starting doses of 1.9 mg/kg and dosing intervals as long as Q8W were comparable.

Table 29: Summary of ORR Across Dosage Regimens based on M-Protein Simulation

	DREAMM-7		DREAMM-8	
Details of Dosing Regimen	ORR based on M-Protein	% change in ORR compared to reference	ORR based on M-Protein	% change in ORR compared to reference
2.5 mg/kg Q3W (Observed – DREAMM-7)	82	-*	-*	-*
2.5 mg/kg Q3W (Simulated Reference for DREAMM-7)	96.5	-*	-*	-*
2.5 mg/kg to 1.9 mg/kg Q4W (Observed DREAMM-8)	-*	-*	85.4	-*
2.5 mg/kg to 1.9 mg/kg Q4W (Simulated Reference for DREAMM-8)	-*	-*	93.2	-*
2.5 mg/kg to 1.9 mg/kg Q3W	96.5	100	-*	-*
2.5 mg/kg Q6W	96	99.5	91.3	98.8
1.9 mg/kg Q6W	94.5	97.9	91.3	96.4
2.5 mg/kg Q8W	94	97.4	90.3	93.9
1.9 mg/kg Q8W	93	96.4	90.3	89.1
2.5 mg/kg Q6W followed by 1.9 mg/kg Q6W	95	98.4	91.3	98.8
2.5 mg/kg Q8W followed by 1.9 mg/kg Q8W	93	96.4	90.3	92.8
2.5 mg/kg Q6W followed by 1.9 mg/kg Q8W	94.5	97.9	91.3	93.9

* Dosage not evaluated in clinical trial (observed) or simulated with PKPD model
Overall Response Rate (ORR) based in M-protein were calculated using serum M-protein-based response definitions from the International Myeloma Working Group (IMWG). Partial response is defined as ≥50% reduction in M-protein from baseline and very good partial response is defined as ≥90% reduction in M-protein from baseline

Source: Table 5 and Table 8 in Applicant's response to FDA Information Request dated March 07, 2025

Ongoing Development of Belantamab Mafodotin

The dosages of belantamab mafodotin that have been evaluated in pivotal trials to date, both as monotherapy and in combination, have been characterized by high rates of ocular toxicity and poor tolerability. For more recent clinical development in patients with transplant-ineligible newly diagnosed multiple myeloma (TI-NDMM), the Applicant initiated the phase 3 DREAMM-10 study in December of 2024, evaluating belantamab mafodotin, lenalidomide, and dexamethasone (BRd) versus daratumumab, lenalidomide, and dexamethasone (DRd), at a lower dose and longer dosing interval of belantamab mafodotin (NCT06679101).

Based on a dose-finding study in patients with TI-NDMM, which demonstrated similar efficacy across evaluated dose levels and mitigation of clinically meaningful changes in visual acuity in

cohorts with less frequent dosing, the Applicant has selected the 1.9 mg/kg Q8W for 24 weeks then Q12W thereafter as the dosage of belantamab mafodotin for the DREAMM-10 study.[8]

While the results of the DREAMM-10 trial may inform efficacy of a lower dose with longer dosing interval in the TI-NDMM setting and safety and tolerability of the selected dose and schedule, uncertainties remain regarding the optimal dose in the RRMM setting.

7.2.4 Dosing Summary

In summary, data from DREAMM-7 and DREAMM-8 demonstrate high rates of treatment modifications, with the majority of treatment interruptions being related to the occurrence of KVA events. In both trials, the majority of patients were unable to remain on the intended dosage as early as Cycle 3 of treatment. Additionally, there was limited exploration of doses and dosing intervals in the regimens evaluated in DREAMM-7 (BVd) and DREAMM-8 (BPd). The data from DREAMM 6 and ALGONQUIN suggest comparable outcomes for the 1.9 and 2.5 mg/kg doses, and DREAMM 14 results suggest that lower doses with longer dosing intervals may have a more favorable benefit-risk profile as compared to higher doses with shorter dosing intervals as monotherapy. The benefit-risk of lower doses with longer dosing intervals continues to be explored, with DREAMM-14 and DREAMM-10 ongoing at this time. Given the safety and tolerability data from DREAMM-7 and DREAMM-8, coupled with the limited dose exploration conducted of each combination regimen, uncertainties remain regarding the appropriateness of the proposed dosages in patients with RRMM.

8 Benefit-Risk Conclusions

Benefit-risk assessment is an integral part of the FDA's review of a drug and the demonstration of safety requires showing that benefits of the drug outweigh its risks. For the current applications, there are several important points to consider, which are described below.

The DREAMM-7 and DREAMM-8 trials each met the primary endpoint of PFS. While OS met statistical significance in DREAMM-7, DREAMM-8 did not demonstrate a statistically significant improvement in OS and is not expected to be adequately powered for OS. In both trials, there was limited enrollment in the U.S., and limited enrollment of Black or African American patients and those 75 years of age and older. The underrepresentation of these specific populations may limit applicability of the results from both trials to U.S. patients with RRMM. It is also important to note that PVd, the comparator arm in DREAMM-8, is not an approved regimen in the U.S; therefore, the applicability of DREAMM-8 findings to U.S. patients with RRMM may be further limited.

The ocular toxicity, including corneal toxicity, observed with belantamab mafodotin is a unique toxicity that is not seen with any currently available treatments for multiple myeloma. It may be asymptomatic in the early stages, and consequences of severe or inappropriately managed toxicity have the potential to be severe and could lead to loss of vision. While other mitigation measures have been explored by the Applicant throughout the development program, the only strategy that has emerged as effective has been the implementation of dose modifications. Despite standardized dose modification guidelines on the clinical trial protocols, patients experienced severe and recurrent toxicities and clinically significant visual changes. It is important to consider that stringent protocol-defined criteria for ocular toxicity monitoring and resulting dose modifications may be challenging to replicate in the post-market setting.

There were high rates of ocular toxicities, including KVA events and visual acuity changes, which were shown to have impacts on patient-reported visual symptoms and functioning. Most patients experienced recurrent KVA events and while the understanding of reversibility of the ocular findings is incomplete, particularly as it relates to a patient's last toxicity event, not all patients had demonstrated reversal of their ocular toxicities, including at timepoints following end of study treatment.

There is concern that the dosages of belantamab mafodotin have not been adequately optimized, as evidenced by the high rates of ocular toxicity and poor tolerability of the selected DREAMM-7 and DREAMM-8 dosages. On both trials, there were high rates of dose modifications; by Cycle 3, the majority of patients were not receiving the intended dosage and patients required frequent dose modifications, including interruptions, throughout the duration of treatment.

Early dose-finding trials of BVd and BPd indicated that lower doses and extended dosing intervals might enhance tolerability without compromising efficacy. However, the DREAMM-7 and DREAMM-8 studies were initiated with dosages that resulted in high rates of ocular toxicity and necessitated frequent dose modifications. Data from the DREAMM-14 trial, conducted to address the dose optimization post-marketing requirement, along with M-protein modeling approaches, further support the potential benefits (i.e., improved tolerability with similar efficacy)

of lower doses at longer intervals. Although the Applicant is currently evaluating a lower dose with extended dosing intervals in the ongoing DREAMM-10 trial in patients with TI-NDMM patients, uncertainty remains regarding the appropriateness of the BVd and BPd dosages in patients with RRMM.

While DREAMM-7 and DREAMM-8 each met their primary efficacy endpoint, the high rates of ocular toxicity and dose modifications, coupled with limited dose exploration, necessitate a careful evaluation of the risks associated with belantamab mafodotin at the proposed dosages. Given that the proposed indications are for patients who have received one or more prior lines of therapy, the benefit-risk assessment must be contextualized within the current treatment landscape for RRMM. This landscape includes multiple approved therapies, including combination regimens, bispecific antibodies, and CAR T-cell therapies.

Considering the observed efficacy results, safety and tolerability concerns, and uncertainties regarding the appropriateness of the proposed dosages, the benefit-risk profile of belantamab mafodotin for the proposed indications, based on the DREAMM-7 and DREAMM-8 studies, remains unclear.

9 References

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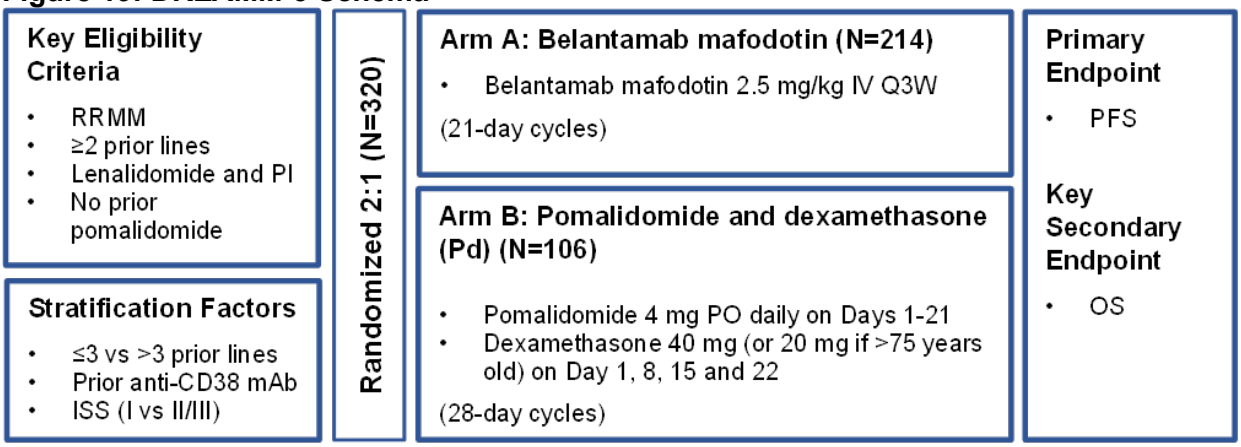
10 Appendix

10.1 DREAMM-3 Trial Results and Considerations

DREAMM-3 was a phase 3, randomized, open label, 2-arm, multicenter trial evaluating belantamab mafodotin monotherapy versus pomalidomide and dexamethasone (Pd) in patients with RRMM who had received at least 2 prior lines of therapy, including lenalidomide and a PI. Treatment was continued until disease progression, unacceptable toxicity, or death. The DREAMM-3 trial schema is presented in Figure 19.

Figure 19: DREAMM-3 Schema



Abbreviations: RRMM=relapsed or refractory multiple myeloma, PI=proteasome inhibitor, mAb=monoclonal antibody, ISS=International Staging System, Q3W=once every 3 weeks, PFS=progression-free survival, OS=overall survival.
Source: FDA generated

The primary endpoint of DREAMM-3 was PFS, defined as the time from randomization until the earliest date of PD based on investigator-assessment per IMWG criteria, or death due to any cause. The primary analysis was supported by an IRC audit in a randomly selected subset of the ITT population. OS was a key secondary endpoint.

According to the Applicant's DREAMM-3 Clinical Study Report, a total of 325 patients were randomized 2:1 to the belantamab mafodotin arm (n=218) or the Pd control arm (n=107). DREAMM-3 was designed to target a total of 151 PFS events and 250 OS events. The study did not meet its primary endpoint of PFS. At the PFS final analysis, with a median follow-up of 11.53 months and 10.78 months, respectively, in the belantamab mafodotin and Pd arms, there was no statistically significant difference in PFS between arms, with a HR of 1.03 (95% CI: 0.72, 1.47), p=0.558). The median PFS was 11.2 (95% CI: 6.4, 14.5) months in the belantamab mafodotin arm vs. 7.0 (95% CI: 4.6, 10.6) months in the Pd arm. At the time of the primary analysis, OS IA1 (122 events, 48.8% IF) showed an OS HR of 1.14 (95% CI: 0.77, 1.68), with similar median OS between arms.

Per the Clinical Study Report, the median time on study treatment was 4.14 months in the belantamab mafodotin arm and 5.19 months for pomalidomide on the Pd arm. Dose delays occurred in 12% of patients on the belantamab mafodotin arm vs. 31% for pomalidomide and 11% for dexamethasone. Dose delays on the belantamab mafodotin arm were noted to be prolonged. A total of 41% of patients on the belantamab mafodotin arm required a dose

reduction compared to 25% and 21% of patients on the Pd arm requiring dose reduction of pomalidomide or dexamethasone, respectively. The Applicant noted that most dose reductions of belantamab mafodotin occurred between Cycle 2 and Cycle 8 and that dose interruptions and reductions in the belantamab mafodotin arm were mostly driven by ocular adverse events.

FDA's analysis of the DREAMM-3 results is based on an overview of the data from the DREAMM-3 Clinical Study Report provided by the Applicant. It is notable that the DREAMM-3 trial utilized the same dose of belantamab mafodotin (2.5 mg/kg Q3W) as in the DREAMM-2 trial. The concerns with the dosing of belantamab mafodotin in DREAMM-2, including high rates of ocular toxicity and high rates of dose modifications due to ocular toxicity, necessitated issuing a PMR to conduct a randomized dose finding study with lower doses or alternative dosing regimens at the time of the previous accelerated approval of the 2.5 mg/kg Q3W dose (see Section 5 and Section 7.2). Therefore, while the reasons for the failure of the DREAMM-3 study to meet its primary endpoint are not known, it is possible that poor tolerability of the belantamab mafodotin 2.5 mg/kg Q3W dose may have impacted the efficacy of belantamab mafodotin monotherapy.

10.2 DREAMM-7 and DREAMM-8 Key Eligibility Criteria

Further details regarding key eligibility criteria discussed in Section 6.2 are provided below.

DREAMM-7 Key Inclusion Criteria

- Confirmed diagnosis of multiple myeloma as defined by the IMWG criteria [Rajkumar, 2014].
- Previously treated with at least 1 prior line of MM therapy, and must have documented disease progression during or after their most recent therapy.
- Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:
  - ASCT was >100 days prior to initiating study treatment, and
  - No active bacterial, viral, or fungal infection(s) present.
- Must have at least ONE aspect of measurable disease, defined as one the following:
  - Urine M-protein excretion ≥200 mg/24h, or
  - Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or
  - Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65).

DREAMM-7 Key Exclusion Criteria

- Intolerant to daratumumab.
- Refractory to daratumumab or any other anti-CD38 therapy (defined as progressive disease during treatment with anti-CD38 therapy, or within 60 days of completing that treatment).
- Intolerant to bortezomib, or refractory to bortezomib (defined as progressive disease during treatment with a bortezomib-containing regimen of 1.3 mg/m^2 twice weekly, or within 60 days of completing that treatment). Note: participants with progressive disease during treatment with a weekly bortezomib regimen are allowed.
- Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain.
- Prior treatment with anti-BCMA therapy.
- Current corneal epithelial disease except for mild punctate keratopathy.

DREAMM-8 Key Inclusion Criteria

- Have a confirmed diagnosis of multiple myeloma as defined by the International Myeloma Working Group (IMWG) criteria [Rajkumar, 2016].
- Have been previously treated with at least 1 prior line of MM therapy including a lenalidomide-containing regimen (lenalidomide must have been administered for at least 2 consecutive cycles) and must have documented disease progression during or after their most recent therapy. Note: Participants treated with lenalidomide ≥10 mg daily for at least 2 consecutive cycles are eligible.
- Must have at least ONE aspect of measurable disease, defined as one the following:
  - Urine M-protein excretion ≥200 mg/24 h, or
  - Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or
  - Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65) only if patient has no measurable urine or serum M spike.
- Have undergone autologous stem cell transplant (ASCT) or are considered transplant ineligible. Participants with a history of ASCT are eligible for study participation provided the following eligibility criteria are met:

- ASCT was >100 days prior to the first dose of study medication
- No active bacterial, viral, or fungal infection(s) present

DREAMM-8 Key Exclusion Criteria

- Received prior treatment with or intolerant to pomalidomide.
- Received prior BCMA targeted therapy.
- Intolerant to bortezomib or refractory to bortezomib (i.e., participant experienced progressive disease during treatment, or within 60 days of completing treatment, with a bortezomib-containing regimen of 1.3 mg/m2 twice weekly).
- Ongoing Grade 2 peripheral neuropathy with pain within 14 days prior to randomization or ≥ Grade 3 peripheral neuropathy.
- Active or history of venous and arterial thromboembolism within the past 3 months.
- Contraindications to or unwilling to undergo protocol-required anti-thrombotic prophylaxis.
- Current corneal disease except for mild punctate keratopathy.

10.3 DREAMM-7 and DREAMM-8 Statistical Analysis Plans

As discussed in Section 6.3, further details of the sample size justification, interim analyses of PFS and OS, and multiplicity control in each study are provided here.

PFS Censoring Scheme

The key censoring scheme included censoring at randomization if no adequate baseline or post-baseline assessments, censoring at last adequate assessment if no progression or death, censoring at last adequate assessment prior to new anti-myeloma therapy, censoring at last adequate assessment prior to PD/death if death/PD after an extended loss-to-follow-up time (6 weeks + 7-day window for DREAMM-7 and 8 weeks + 7-day window for DREAMM-8).

Sample Size Justification

The DREAMM-7 study was designed with a planned sample size of approximately 478 patients (239 per arm). The sample size calculation was based on a 92% power to detect a PFS hazard ratio (HR) of 0.67 (BVd vs DVd), with a 5% type I error rate (2-sided). This assumed an increase in median PFS from 16.7 months in the DVd arm to 25 months in the BVd arm. Based on these parameters, the target number of PFS events was set at 280. The study also planned for approximately 355 OS events to provide 84% power to detect an OS HR of 0.73 at the 5% significance level (2-sided), assuming a median OS of 49 months in the DVd arm and 67 months in the BVd arm.

The DREAMM-8 study was designed with a planned sample size of approximately 302 patients (151 per arm). The sample size calculation was based on a 90% power to detect a PFS hazard ratio (HR) of 0.6 (BPd vs PVd), with a 5% type I error rate (2-sided). This assumed an increase in median PFS from 12 months in the PVd arm to 20 months in the BPd arm. Based on these parameters, the target number of PFS events was set at 173. The study also planned for approximately 217 OS events to provide 83% power to detect an OS HR of 0.67 at the 5% significance level (2-sided), assuming a median OS of 44 months in the PVd arm and 65.7 months in the BPd arm.

Interim and Final Analyses

<u>DREAMM-7</u>

- Interim Analysis (IA) 1: IA1 was planned to occur after approximately 250 PFS events (~89% of targeted events) had occurred. The purpose of this analysis was to evaluate PFS for early efficacy. For OS, the SAP indicates an interim analysis is planned when approximately 142 OS events (~40% of targeted events) have occurred
- Primary PFS Analysis / OS IA2: Primary PFS Analysis is planned to occur after approximately 280 PFS events (100% of targeted events). The OS IA2 was planned to be performed when approximately 178 OS events (~50% of targeted events) have occurred.
- OS IA3: Planned to occur after approximately 266 OS events (~75% targeted events).
- OS Final Analysis (FA): To be performed at the end of the study, with an expected total of 355 OS events (100% targeted events).

<u>DREAMM-8</u>

- PFS IA1: Planned to occur after approximately 35 PFS events (~25% of the original 139 targeted events up to Protocol Amendment 3) had occurred. The purpose of this analysis was to evaluate PFS for harm and potential sample size re-estimation. No OS interim analysis was planned at this time point.
- PFS IA2 / OS IA1: PFS IA2 was planned to occur after approximately 145 PFS events (~84% of targeted events) had occurred. The purpose of this analysis was to evaluate PFS for early efficacy. OS IA1 was planned when approximately 109 OS events (~50% of targeted events) have occurred.
- Primary PFS Analysis / OS IA2: Primary PFS Analysis was planned to occur after approximately 173 PFS events (100% of targeted events). The OS IA2 was planned to be performed when approximately 130 OS events (~60% of targeted events) have occurred.
- OS IA3: Planned to occur after approximately 163 OS events (~75% targeted events).
- OS FA: To be performed at the end of the study, with an expected total of 217 OS events (100% targeted events).

Multiplicity Control

For both DREAMM-7 and DREAMM-8 studies, a hierarchical testing procedure was implemented to control the overall type I error rate at 5% (2-sided). In DREAMM-7, the testing order began with PFS. If PFS was significant, alpha was to be split between OS (4%) and DoR (1%). If DOR proved significant, its allocated alpha was to be added to OS, potentially increasing OS's alpha to 5%. MRD negativity was only to be tested if OS showed significance.

DREAMM-8 followed a similar strategy but with a simpler hierarchy of PFS, OS, and MRD negativity. In this case, if PFS was significant, the full 5% alpha was allocated to OS, with MRD negativity tested only upon OS significance. Both studies employed the Lan-DeMets O'Brien-Fleming alpha spending function for PFS and OS interim analyses, allowing for potential early efficacy stopping while maintaining the overall alpha level.

The FDA notes the following considerations regarding the statistical analysis plans for DREAMM-7 and DREAMM-8.

- DOR was included in the hierarchical testing procedure for DREAMM-7, but not in DREAMM-8. FDA considers the analyses of DOR for both studies to be descriptive only, as this comparison is based on a comparison of responders only, removing the balance between arms ensured by randomization. Therefore, for DREAMM-7, OS was to be tested at 5% alpha level if PFS was significant, regardless of the results of DOR analysis.
- For DREAMM-8, due to revisions in the sample size, OS is not expected to be adequately powered
    - In Protocol Amendment 2, the planned sample size was reduced from 450 to 302 participants. The Applicant’s rationale for this reduction was based on slow recruitment rates and updated predictions that the target number of PFS events could be achieved with fewer participants and appropriate follow-up duration.
    - The OS HR assumption was revised from 0.75 to 0.67 in SAP Version 2, based on Protocol Amendment 4, in response to regulatory feedback that the initial 69% power for OS would be insufficient. Rationale for the revision included results from the OPTIMISSM study, which reported a median OS of 35.6 months in the PVd arm.
    - The Applicant stated that these changes were implemented prior to any knowledge of aggregate study data. However, the FDA expressed concerns that the revised OS HR assumption of 0.67 appeared overly optimistic and that the OS analysis was likely to be underpowered.

10.4 DREAMM-7 and DREAMM-8 PFS Sensitivity Analyses

Table 30: Sensitivity Analyses of PFS: DREAMM-7

Primary analysis: PFS by IRC (ITT)	0.41 (0.31, 0.53)
PFS by IRC (mITT)	0.41 (0.31, 0.53)
PFS based on investigator - assessed response	0.40 (0.31, 0.52)
PFS based on investigator - assessed response (allowing use of local labs at baseline)	0.40 (0.31, 0.52)
PFS by IRC considering the minimum (date of next scheduled visit, date of death) as an event, when progression is documented between scheduled visits without extended loss-to-follow-up time (Supp 1)	0.41 (0.31, 0.53)
PFS by IRC considering new anti-myeloma therapy as an event on the start date of new anti-myeloma therapy (Supp 2)	0.45 (0.35, 0.58)
PFS by IRC considering extended loss-to-follow-up death or progression as an event on the date of death or progression (Supp 3)	0.41 (0.32, 0.53)
PFS by IRC considering treatment discontinuation due to clinical progression prior to documented progression or death as an event (Supp 4)	0.42 (0.32, 0.55)
PFS by IRC with COVID-19 censoring	0.42 (0.32, 0.55)
PFS by IRC with actual stratification (according to eCRF data)	0.40 (0.31, 0.53)
PFS by IRC excluding the 2 participants who were randomized	0.41 (0.31, 0.53)

Source: FDA analysis
Abbreviations: ITT=intent-to-treat, IRC=independent review committee, PFS= progression-free survival, Supp=Supplementary analysis.
Based on the data with CCOD 02 October 2023.

Table 31: Sensitivity Analyses of PFS: DREAMM-8

	HR (95% CI)
Primary analysis: PFS by IRC (ITT)	0.52 (0.37, 0.73)
PFS by IRC (based on pooling stratification using number of lines of prior therapy, prior bortezomib use, ISS status, and prior anti-cd38)	0.51 (0.36, 0.72)
PFS by IRC (stratified by number of lines of prior therapy and prior bortezomib use; adjusted by ISS status, and prior anti-cd38)	0.54 (0.39, 0.77)
PFS by IRC (stratified by number of lines of prior therapy and prior bortezomib assessed according to the eCRF data)	0.50 (0.36, 0.71)
PFS by IRC with COVID-19 censoring	0.49 (0.35, 0.69)
PFS based on investigator - assessed response	0.47 (0.34, 0.66)
PFS by IRC (mITT)	0.51 (0.36, 0.72)
PFS by IRC considering the minimum (date of next scheduled visit, date of death) as an event, when progression is documented between scheduled visits without extended loss-to-follow-up time (Supp 1)	0.52 (0.37, 0.73)
PFS by IRC considering new anti-myeloma therapy as an event on the start date of new anti-myeloma therapy (Supp 2)	0.48 (0.35, 0.65)
PFS by IRC considering extended loss-to-follow-up death or progression as an event on the date of death or progression (Supp 3)	0.53 (0.38, 0.73)
PFS by IRC considering treatment discontinuation due to clinical progression prior to documented progression or death as an event (Supp 4)	0.50 (0.36, 0.69)

Source: FDA analysis
Abbreviations: ITT=intent-to-treat, IRC=independent review committee, PFS= progression-free survival, ISS= international staging system, Supp=Supplementary analysis.
Based on the data with CCOD 29 January 2024.

10.5 Additional Efficacy Results

DOR was defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to any cause. DOR was included in the hierarchical testing procedure for DREAMM-7, but not in DREAMM-8. FDA considers the analyses of DOR for both studies to be descriptive only, with these analyses based on responders and due to the limitations of DOR analysis in a randomized trial.

Minimal residual disease (MRD) negativity rate was defined as the percentage of participants who achieved MRD negative status (as assessed by NGS at 10^{-5} threshold) at least once during the time of confirmed CR or better response based on IRC assessment per IMWG. For both DREAMM-7 and DREAMM-8, MRD-negative CR rate was tested hierarchically after OS. In DREAMM-7, the MRD negativity CR rate was significantly higher for the BVd group than the DVd group. In DREAMM-8, the MRD-negative CR rate was higher for the BPd group than the PVd group, however as the OS analysis result did not meet the pre-specified efficacy boundary, MRD negativity was not formally tested.

The DOR and MRD-negative CR rate results in DREAMM-7 and DREAMM-8 (discussed in Section 6.4.4.3) are summarized in Table 32.

Table 32: DREAMM-7 and DREAMM-8 Summary of Other Key Secondary Endpoints

	DREAMM-7		DREAMM-8	
	BVd N=243	**DVd N=251**	**BPd N=155**	**PVd N=147**
DOR				
N	201	179	120	106
Number of events (%)	68 (33.8%)	105 (58.7%)	39 (32.5%)	49 (46.2%)
Median (95% CI) (months)	35.6 (30.5, NE)	17.8 (13.8, 23.6)	NE (24.9, NE)	17.5 (12.1, 26.4)
MRD[-] CR rate				
n (%)	60 (24.7%)	24 (9.6%)	37 (23.9%)	7 (4.8%)
95% CI	(19.4%, 30.6%)	(6.2%,13.9%)	(17.4%, 31.4%)	(1.9%, 9.6%)
P-value	<0.0001[1]		--	
Patients achieved CR or better	84	43	62	24
MRD[-] missing rate among patients achieved CR or better, N (%)	6 (7.1%)	5 (12%)	8 (12.9%)	4 (16.7%)

Source: FDA analysis
Abbreviations: DOR=Duration of Response, MRD=Minimal Residual Disease, CR=Complete Response.
ITT analysis.
DREAMM-7: CCOD 02 October 2023; DREAMM-8: CCOD 29 January 2024.
[1]DREAMM-7: P-value is based on Cochran-Mantel-Haenszel test. The stratification factors: number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III); 2-sided significance level is 0.05.

The results for subgroup analysis by age for DREAMM-7 (discussed in Section 6.4.4.2) are presented below.

Table 33: DREAMM-7 and DREAMM-8 OS subgroup Analyses

DREAMM-7			
	BVd n events/N	**DVd n events/N**	**HR (95% CI)**
All subjects in ITT population[1]	68/243	103/251	0.58 (0.43, 0.79)
Age			
<65 years	24/121	45/126	0.46 (0.28, 0.76)
65-74 years	27/85	46/95	0.61 (0.38, 0.99)
>=75 years	17/37	12/30	1.21 (0.58, 2.54)
DREAMM-8			
	BPd n events/N	**PVd n events/N**	**HR (95% CI)**
All subjects in ITT population[2]	58/155	60/147	0.86 (0.60, 1.24)
Age			
<65 years	26/64	22/53	0.94 (0.53, 1.66)
65-74 years	26/72	24/59	0.79 (0.45, 1.38)
>=75 years	6/19	14/35	0.85 (0.33, 2.21)

Source: FDA analysis

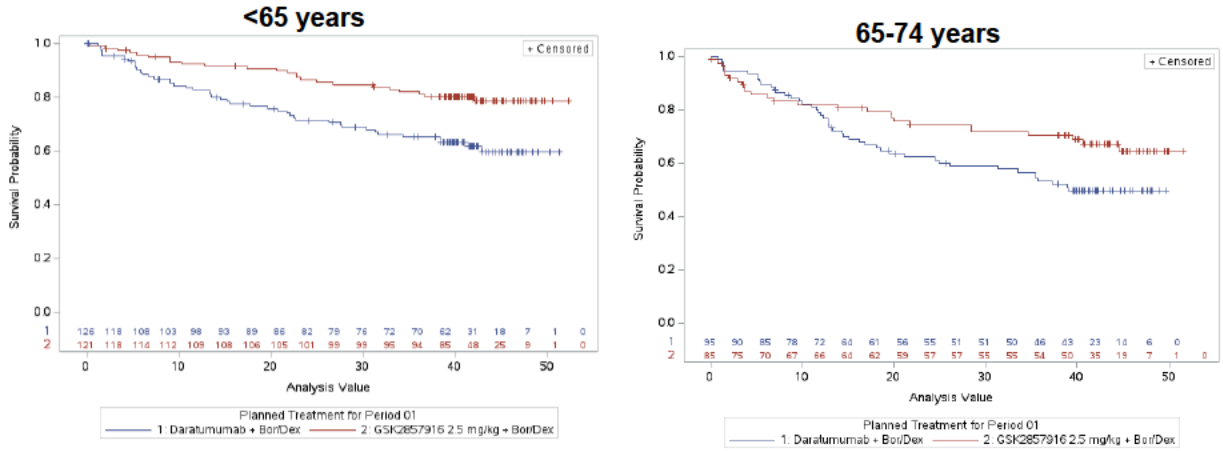
Abbreviations: OS=overall survival, ITT=intent-to-treat, HR=hazard ratio, CI=confidence interval.

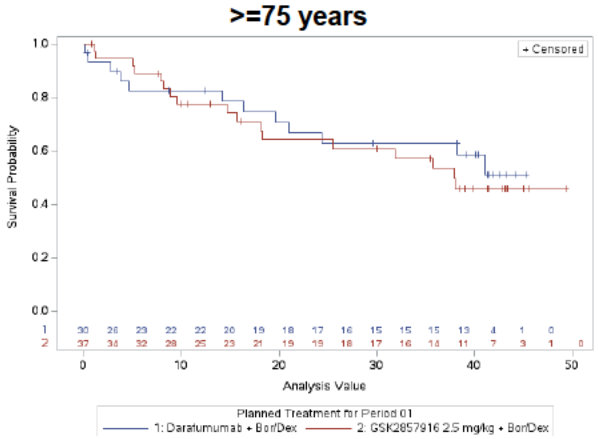
[1]HR was estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III).

[2]HR was estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no).

Based on CCOD of 07 October 2024.

Figure 20: DREAMM-7 OS KM Curve for age subgroups





Source: FDA analysis
Abbreviations: KM=Kaplan Meier, OS=overall survival, Bor=bortezomib, Dex=dexamethasone, GSK2857916=belantamab mafodotin.
ITT analysis.

Table 34: DREAMM-7 and DREAMM-8 PFS subgroup Analyses

DREAMM-7			
	BVd n events/N	**DVd n events/N**	**HR (95% CI)**
All subjects in ITT population[1]	91/243	158/251	0.41 (0.31, 0.53)
Age			
<65 years	42/121	84/126	0.39 (0.27, 0.56)
65-74 years	37/85	61/95	0.48 (0.32, 0.73)
>=75 years	12/37	13/30	0.62 (0.28, 1.38)
DREAMM-8			
	BPd n events/N	**PVd n events/N**	**HR (95% CI)**
All subjects in ITT population[2]	62/155	80/147	0.52 (0.37, 0.73)
Age			
<65 years	28/64	27/53	0.64 (0.37, 1.09)
65-74 years	29/72	34/59	0.48 (0.29, 0.79)
>=75 years	5/19	19/35	0.40 (0.15, 1.07)

Source: FDA analysis
Abbreviations: PFS=progression-free survival, ITT=intent-to-treat, HR=hazard ratio, CI=confidence interval.
[1]HR was estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs. II/III).
[2]HR was estimated using a Cox Proportional Hazards model stratified by the number of lines of prior therapy (1 vs. 2/3 vs. ≥4) and prior bortezomib use (yes or no).
DREAMM-7: CCOD of 02 October 2023.
DREAMM-8: CCOD of 29 January 2024.

10.6 Additional Safety Results (Laboratory Abnormalities)

As described in Section 6.5.5, selected laboratory abnormalities that worsened from baseline with at least 30% incidence in either arm are summarized in Table 35 and Table 36 below.

Table 35: DREAMM-7 Laboratory Abnormalities Worsened from Baseline

Laboratory Abnormality, n (%)*†	DREAMM-7			
	BVd N=242		DVd N=246	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hematology				
Decreased platelets	241 (100)	178 (74)	216 (88)	118 (48)
Decreased lymphocytes	218 (90)	127 (53)	226 (92)	138 (56)
Decreased leukocytes	141 (59)	26 (11)	165 (67)	43 (17)
Decreased neutrophils	126 (52)	41 (17)	130 (53)	33 (13)
Decreased hemoglobin	123 (51)	25 (10)	148 (60)	29 (12)
Chemistry				
AST increased	210 (88)	12 (5)	99 (40)	0
ALT increased	171 (71)	12 (5)	132 (54)	3 (1)
Alkaline phosphatase increased	144 (60)	2 (0.8)	66 (27)	1 (0.4)
Albumin decreased	119 (50)	5 (2)	132 (54)	5 (2)
Calcium increased	91 (38)	10 (4)	50 (20)	3 (1)
Calcium decreased	141 (59)	12 (5)	168 (69)	13 (5)
Creatinine increased	122 (51)	5 (2)	130 (53)	2 (0.8)

*Denominator based on number of subjects with at least one post-baseline laboratory value for each laboratory test.
†Selected laboratory abnormalities with ≥30% incidence in either arm reported.
Source: FDA analysis

Table 36: DREAMM-8 Laboratory Abnormalities Worsened from Baseline

Laboratory Abnormality, n (%)*†	DREAMM-8			
	BPd N=150		PVd N=145	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hematology				
Decreased platelets	124 (83)	60 (40)	115 (81)	43 (30)
Decreased lymphocytes	125 (87)	76 (53)	120 (88)	62 (45)
Decreased leukocytes	128 (85)	48 (32)	125 (88)	34 (24)
Decreased neutrophils	133 (94)	98 (69)	124 (90)	67 (49)
Decreased hemoglobin	81 (54)	18 (12)	94 (66)	23 (16)
Chemistry				
AST increased	90 (60)	4 (3)	37 (26)	4 (3)
ALT increased	84 (56)	4 (3)	62 (44)	5 (4)
Alkaline phosphatase increased	61 (41)	2 (1)	50 (35)	0
Albumin decreased	65 (42)	2 (1)	77 (54)	1 (0.7)
Calcium decreased	56 (38)	0	77 (56)	4 (3)
Creatinine increased	62 (41)	2 (1)	79 (56)	4 (3)
Magnesium decreased	60 (40)	2 (1)	58 (41)	0
Postassium increased	36 (24)	2 (1)	43 (30)	3 (2)

*Denominator based on number of subjects with at least one post-baseline laboratory value for each laboratory test.
†Selected laboratory abnormalities with ≥30% incidence in either arm reported
Source: FDA analysis

10.7 Description of KVA, GSK, and mKVA Scales

As described in Section 7.1.1, the KVA scale was developed by the Sponsor with input from FDA. Minor differences were present in the scales used to grade ocular toxicity due to keratopathy and changes in BCVA across studies. The key differences are summarized below in Table 37. The KVA scale was used in DREAMM-7 and DREAMM-8, while the GSK scale and mKVA scale were used in DREAMM-6 and DREAMM-14, respectively.

The GSK scale was an earlier version developed by the Sponsor with input from FDA. Differences between the GSK scale and KVA scale are limited to revisions to remove epithelial or stromal edema from the description of moderate and severe punctate keratopathy. The Sponsor revised the KVA scale further in response to FDA feedback provided at a Type C Meeting on August 30, 2021, and implemented this modified KVA (mKVA) scale in DREAMM-14. The mKVA scale incorporated a "Grade 0" category to allow for determination of baseline grade at screening, updated terminology from "keratopathy" to "keratitis" and changed recording of BCVA to logMAR units to allow for standardization across different visual acuity charts.

Table 37: Ocular Toxicity Grading Scales Used Across Studies

DREAMM Studies	CTCAE Scale DREAMM-7, -8 original protocols	GSK scale DREAMM-6 and ALGONQUIN	KVA scale DREAMM-7, -8 from Protocol Amendment 1	mKVA scale DREAMM-14
Grade 0	n/a	n/a	n/a	Clear Cornea BCVA BL or no change from BL
Grade 1	Intervention not indicated; No limitation of instrumental or self-care ADL	Mild superficial keratopathy (change from BL) BCVA: Change of 1 line from baseline*	Mild superficial keratopathy (change from BL, w/ or w/o symptoms) BCVA Decline of 1 line from baseline*	Mild (nonconfluent) SPK BCVA decrease not more than 0.1 logMAR units from baseline
Grade 2	Symptoms Limiting instrumental ADL BCVA 20/40 and better or ≤3 lines decreased vision from known baseline	Moderate punctate keratopathy[a] Change of 2 or 3 lines from baseline (BCVA not worse than 20/200)*	Moderate superficial keratopathy[c] Decline of 2 or 3 lines from baseline (BCVA not worse than 20/200)*	Presence of peripheral confluent SPK, patchy microcyst-like deposits, peripheral subepithelial haze, or peripheral stromal opacity Decrease >0.1 logMAR units, but < 0.3 logMAR units (<=1.0logMAR)
Grade 3	Symptoms Limiting self-care ADL; marked decrease in BCVA (BCVA worse than 20/40 or > 3 lines decline from baseline; but <20/200)	Severe punctate keratopathy[b] Change of >3 lines from baseline (BCVA <20/200)*	Severe superficial keratopathy[d] Decline of >3 lines from baseline (BCVA <20/200)*	Presence of central confluent SPK, diffuse (confluent) microcyst-like deposits, central subepithelial haze, or central stromal opacity Decrease >0.3 logMAR units (<=1.0logMAR)
Grade 4	BCVA 20/200 or worse	Corneal Ulcer BCVA worse than 20/200*	Corneal Epithelial Defect[e] BCVA worse than 20/200*	Corneal ulcer[f] >1.0logMAR

*Change in visual acuity should be due to corneal events. If change in vision is for reason other than corneal events, ophthalmic exam findings will drive event grading.
ADL=activities of daily living, BCVA=best corrected visual acuity; CTCAE=Common Terminology Criteria for Adverse Event; KVA=keratopathy and visual acuity, BCVA=best corrected visual acuity, BL=baseline, SPK=superficial punctate keratitis

a) and/or Mild/patchy microcysts and/or Mild/patchy Epithelial or stromal edema and/or Sub-epithelial haze (peripheral) and/or Active stromal opacity (peripheral)
b) and/or Diffuse microcysts and/or Diffuse Epithelial or stromal edema and/or Sub-epithelial haze (central) and/or Active stromal opacity (central)
c) Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
d) severe superficial keratopathy with or without diffuse microcyst-like deposits involving the central cornea, subepithelial haze (central), or a new central stromal opacity.
e) corneal epithelial defect such as corneal ulcers.
f) includes other corneal epithelial defects such as corneal erosions

Source: Applicant's Response to FDA Information Request dated June 11, 2025

10.8 Additional Analyses of KVA Events

Analysis of Patient-Level Data in Patients with KVA Events at End of Treatment (EOT)

The following results are based on patients who had KVA events at EOT in DREAMM-7 and DREAMM-8. The KVA grades at EOT and the last ocular exam in each patient are reported. Notably, there are high rates of missing ocular exams following EOT. However, as mentioned in Section 7.1.3.4, it is notable that over 20% of patients with KVA events at EOT on each trial had stable or worsening KVA events at their last ocular exam.

DREAMM-7

- Of 3 patients with Grade 1 toxicity at EOT
  - (3) 100% worsened to Grade 2
- Of 34 patients who had Grade 2 toxicity at EOT,
  - 27 (79%) had missing exams
  - 5 (15%) remained at Grade 2
  - 2 (6%) worsened to Grade 3.
- Of 22 patients who had Grade 3 toxicity at EOT
  - 13 (59%) had missing exams
  - 5 (23%) improved to Grade 2
  - 4 (18%) remained at Grade 3
- Of 4 patients who had Grade 4 toxicity at EOT
  - 2 (50%) had missing exams
  - 1 (25%) improved to Grade 3
  - 1 (25%) remained at Grade 4

Overall, 24% of patients with KVA events at EOT in DREAMM-7 had stable (16%) or worsening (8%) KVA event toxicity at the last ocular exam.

DREAMM-8

- Of 2 patients with Grade 1 toxicity at EOT
  - 2 (100%) worsened to Grade 2
- Of 21 patients who had Grade 2 toxicity at EOT
  - 17 (81%) had missing exams
  - 2 (10%) remained at Grade 2
  - 2 (10%) worsened to Grade 3
- Of 12 patients who had Grade 3 toxicity at EOT
  - 7 (58%) had missing exams
  - 2 (17%) improved to Grade 2
  - 3 (25%) remained at Grade 3
- Of 2 patients who had Grade 4 toxicity at EOT
  - 1 (50%) had missing exams
  - 1 (50%) improved to Grade 2

Overall, 24% of patients with KVA events at EOT in DREAMM-8 had stable (14%) or worsening toxicity (11%) at the last ocular exam.

The source for this analysis was the Applicant's response to FDA's Information Request (dated April 1, 2025).

Subgroup Analyses of KVA Events by Age

The analyses of KVA events by age subgroup discussed in Section 7.1.3.4 are presented below.

Table 38: DREAMM-7 and DREAMM-8 KVA Event Summary by Age Subgroups

	DREAMM-7 BVd N=242			DREAMM-8 BPd N=150		
	Age Subgroup			Age Subgroup		
	<65 N=121	65 to 74 N=84	≥75 N=37	<65 N=64	65 to 74 N=70	≥75 N=16
All Grades (KVA), n (%)	112 (93)	77 (92)	33 (89)	57 (89)	67 (96)	16 (100)
Grade 1	6 (5)	3 (4)	4 (11)	4 (6)	4 (6)	1 (6)
Grade 2	8 (7)	10 (12)	4 (11)	8 (13)	5 (7)	2 (13)
Grade 3	76 (63)	43 (51)	17 (46)	42 (66)	50 (71)	11 (69)
Grade 4	22 (18)	21 (25)	8 (22)	3 (5)	8 (11)	2 (13)

Source: FDA Analysis

Table 39: DREAMM-7 and DREAMM-8 Characterization of KVA Events by Age Subgroup

	DREAMM-7 BVd N=242			DREAMM-8 BPd N=150		
	Age Subgroup			Age Subgroup		
	<65 N=121	65 to 74 N=84	≥75 N=37	<65 N=64	65 to 74 N=70	≥75 N=16
Grade ≥2	106 (87)	74 (88)	29 (78)	53 (83)	63 (90)	15 (94)
Onset (Grade ≥2), days (range)	42 (15, 403)	43 (18, 611)	52 (16, 255)	29 (18, 533)	54 (22, 393)	32 (24, 127)
Duration of first occurrence (Grade ≥2), days (range)	85 (5, 774)	102 (15, 609)	134 (21, 481)	109 (15, 746)	86 (24, 393)	136 (57, 371)
# Occurrences						
1	28 (26)	22 (30)	13 (45)	12 (23)	18 (29)	6 (40)
2	18 (17)	13 (18)	4 (14)	9 (17)	9 (14)	2 (13)
3 or more	60 (57)	39 (53)	12 (41)	32 (60)	36 (57)	7 (47)
Outcome of Last Event						
Resolved	48 (45)	30 (41)	9 (31)	21 (40)	31 (49)	4 (27)
Ongoing, on treatment	30 (28)	18 (24)	8 (28)	19 (36)	13 (21)	6 (40)
Ongoing, in follow-up	18 17)	11 (15)	2 (7)	2 (4)	7 (11)	3 (20)
Ongoing, follow-up ended	10 (9)	15 (20)	10 (34)	11 (21)	12 (19)	2 (13)

Source: FDA Analysis

10.9 Additional PRO Results

Additional PRO results discussed in Section 7.1.6 are presented here. The source for all figures presented in this section is the Applicant's Response to the FDA Information Request dated March 27, 2025.

Figure 21: DREAMM-7 PRO-CTCAE Blurred Vision (Interference) Results (Baseline through Week 13)

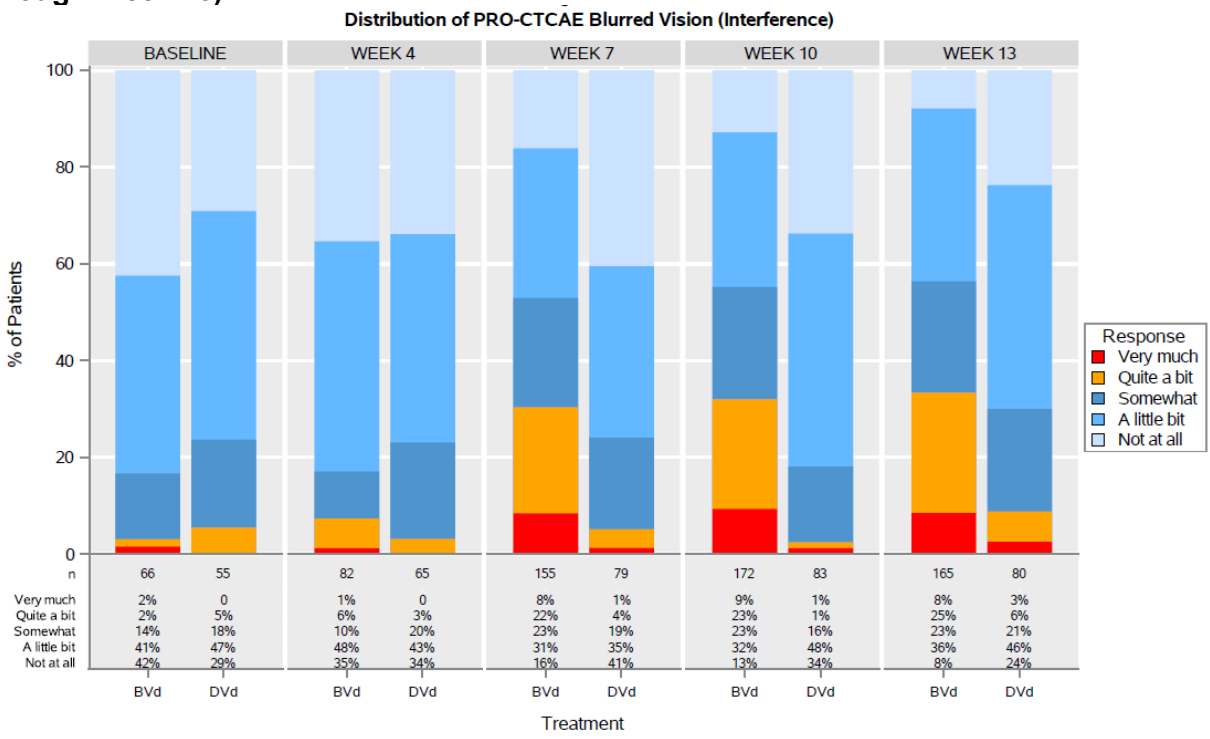


Figure 22: DREAMM-7 PRO-CTCAE Blurred Vision (Interference) Results (Week 16 through 28)

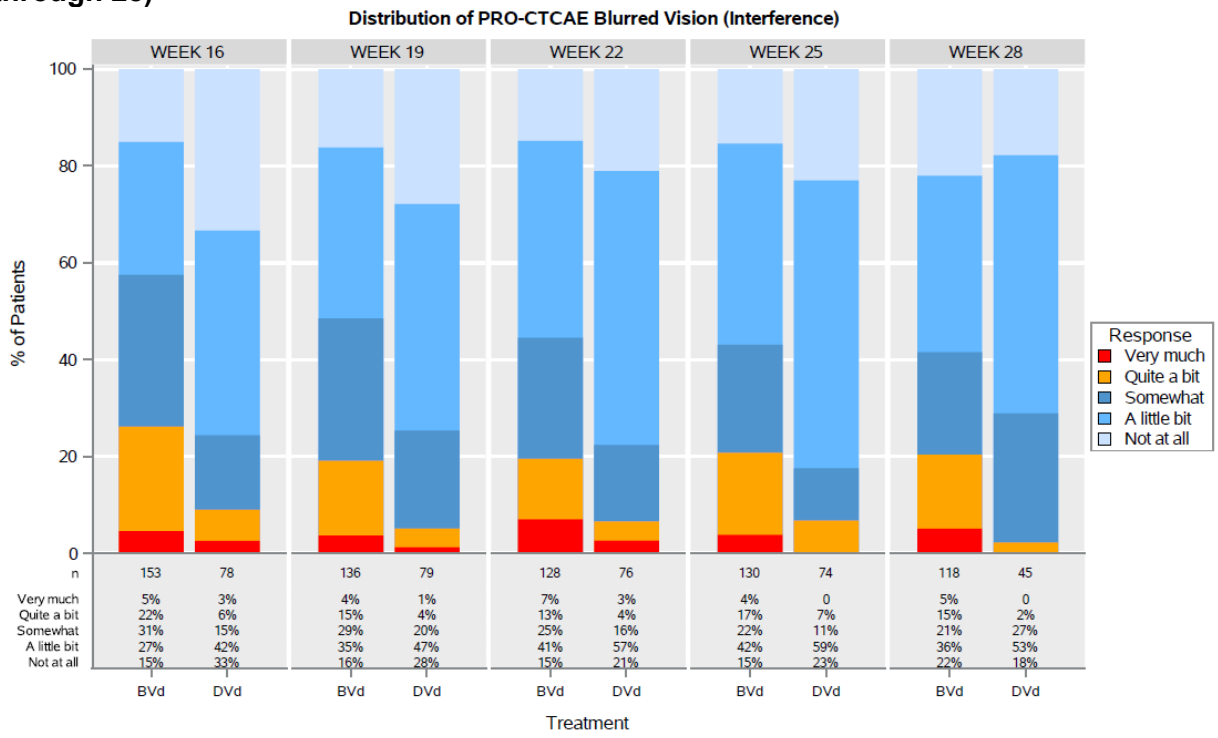


Figure 23: DREAMM-7 OSDI Vision Related Function – Reading, baseline to week 13

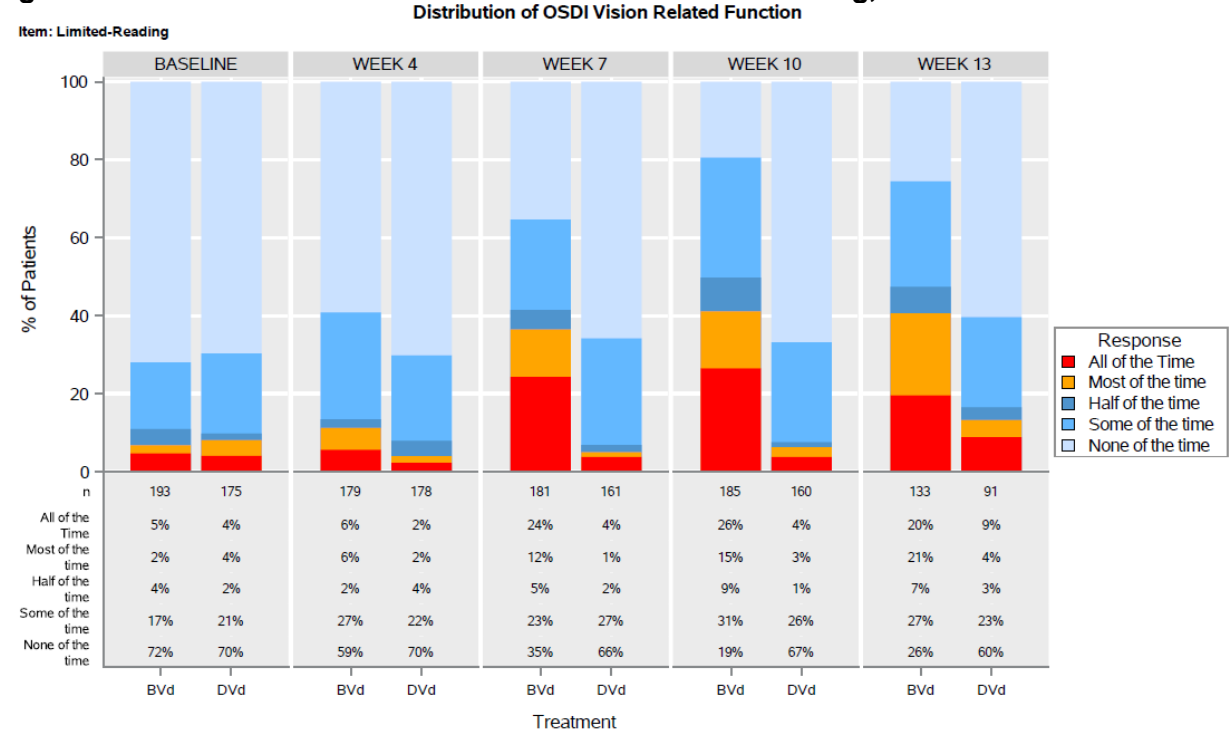


Figure 24: DREAMM-7 OSDI Vision Related Function – Reading, week 16 to week 28

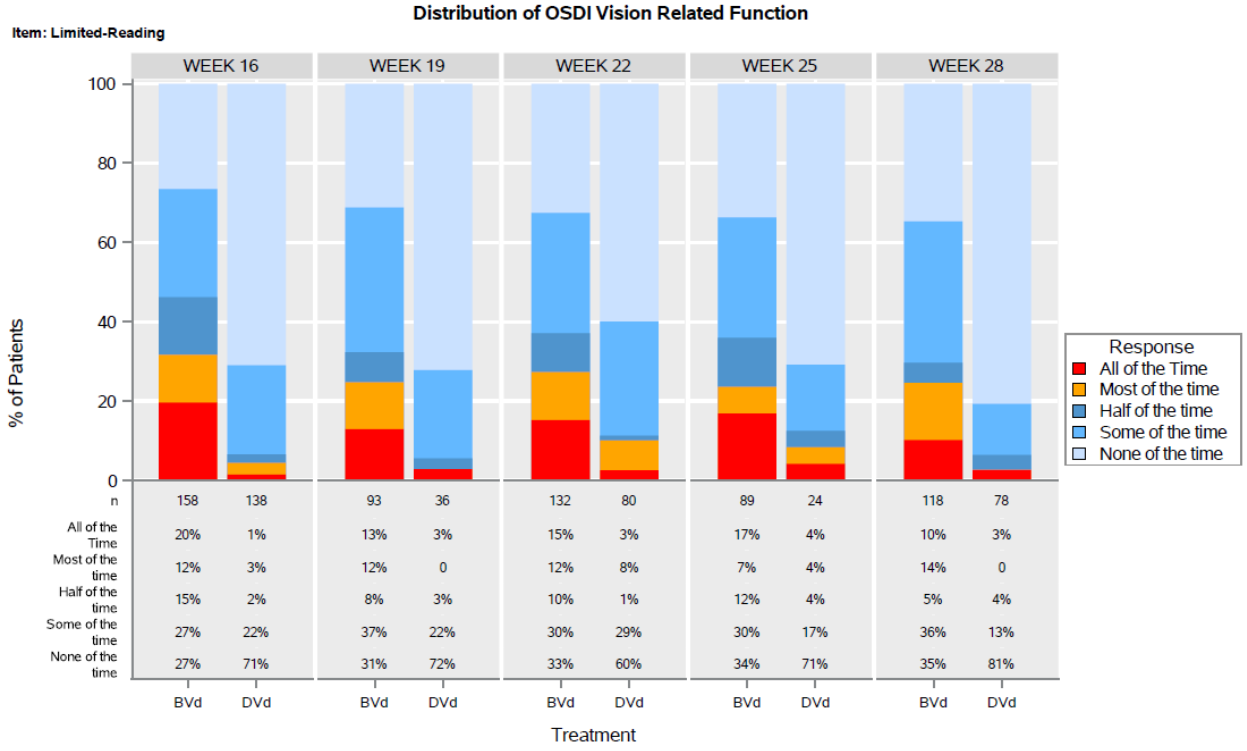


Figure 25: DREAMM-8 OSDI Vision Related Function – Reading, baseline to week 17

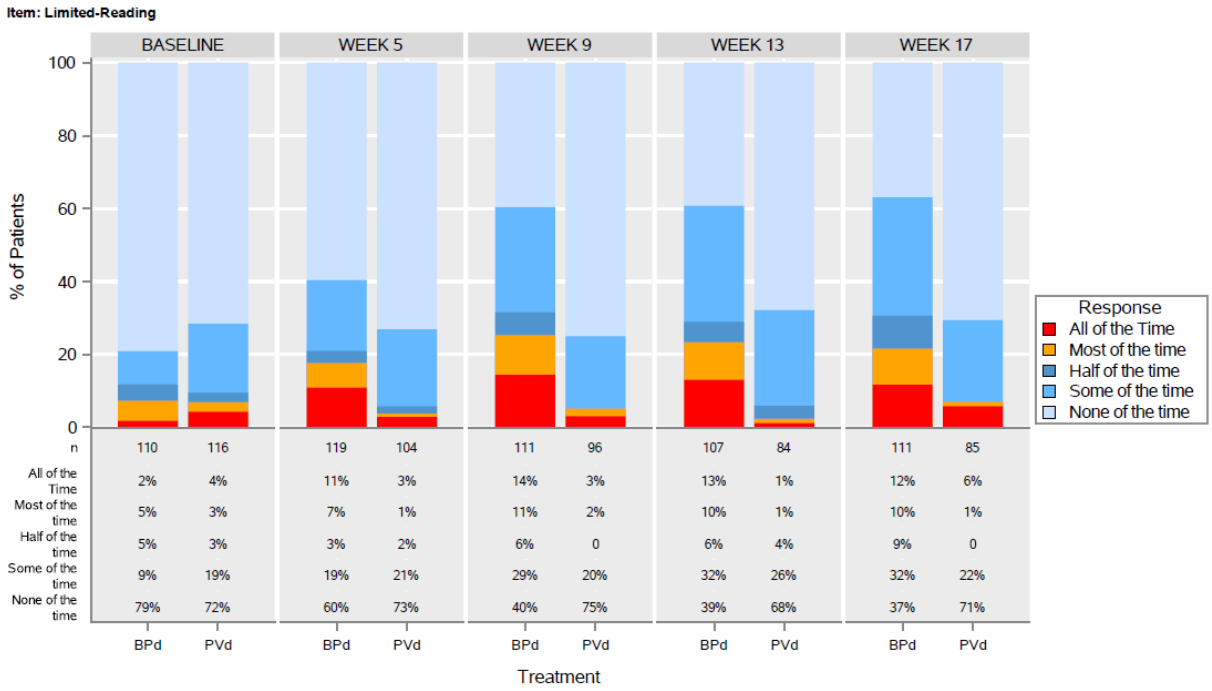


Figure 26: DREAMM-8 OSDI Vision Related Function – Reading, week 21 to week 53

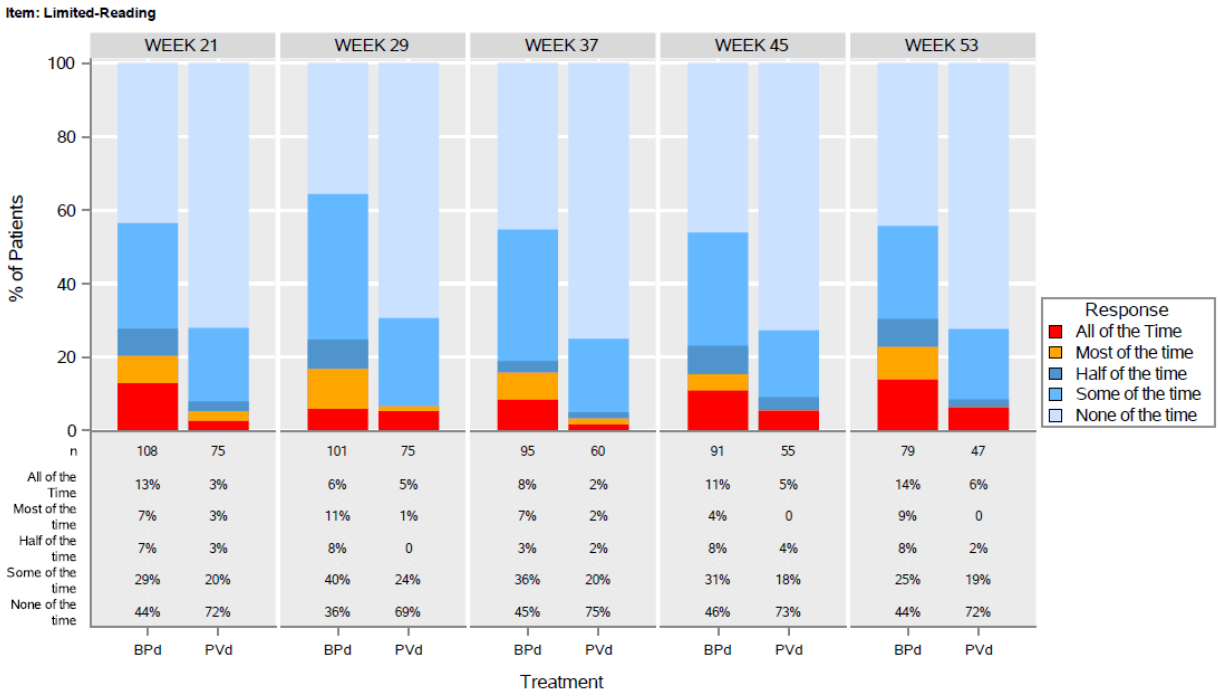


Figure 27: DREAMM-7 FACT-GP5 results, baseline to week 13

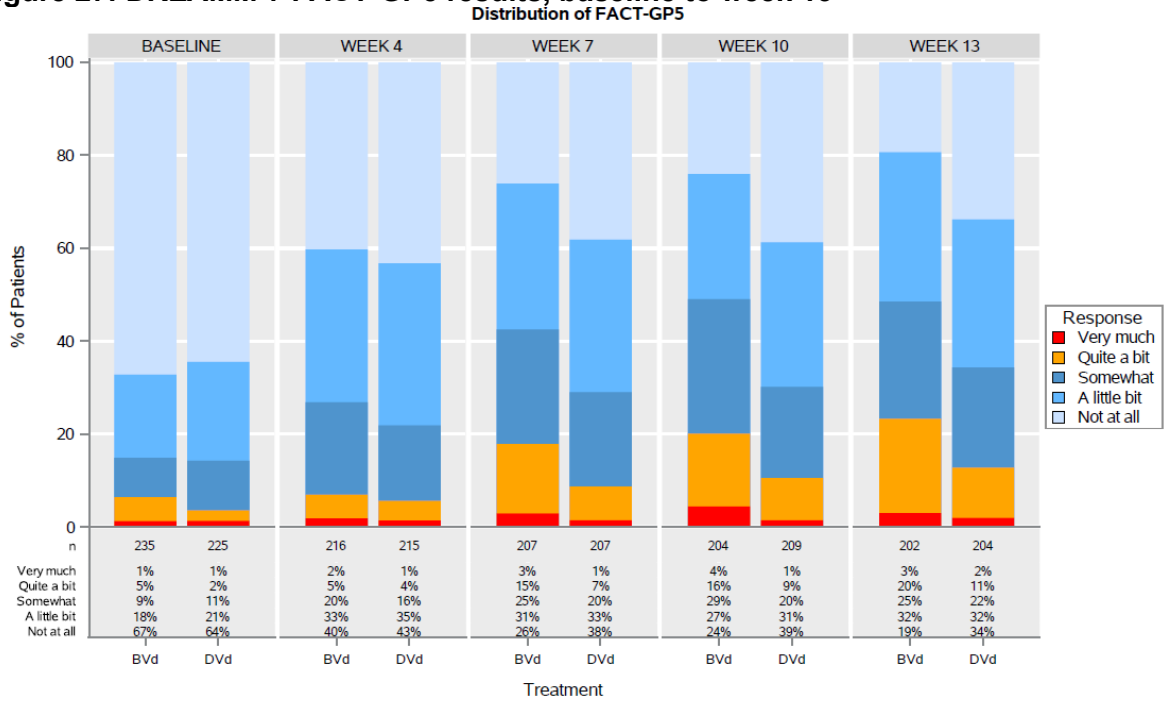
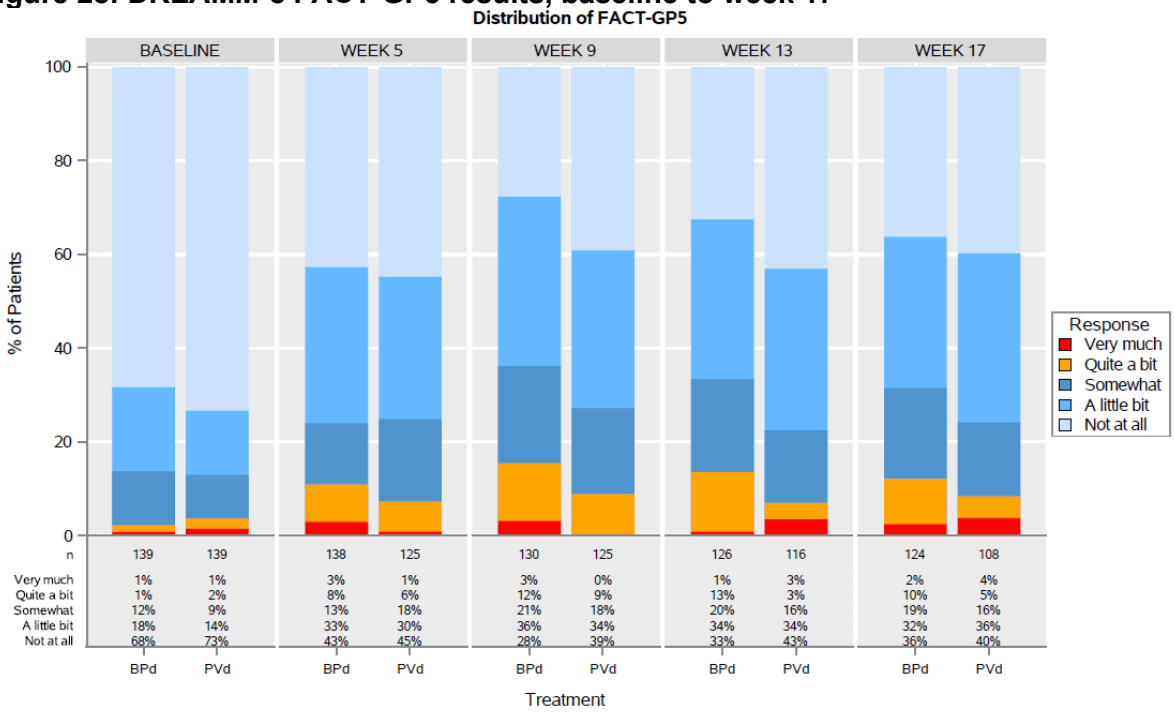


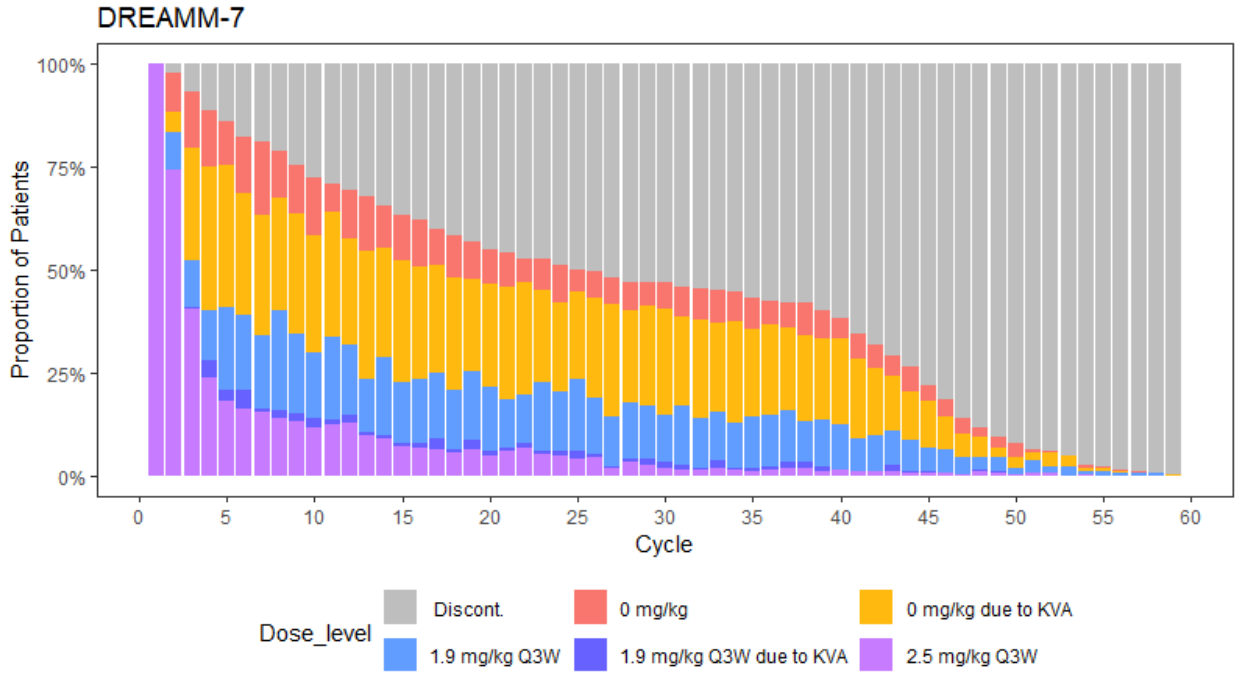
Figure 28: DREAMM-8 FACT-GP5 results, baseline to week 17



10.10 Dose Modifications Due to KVA Events

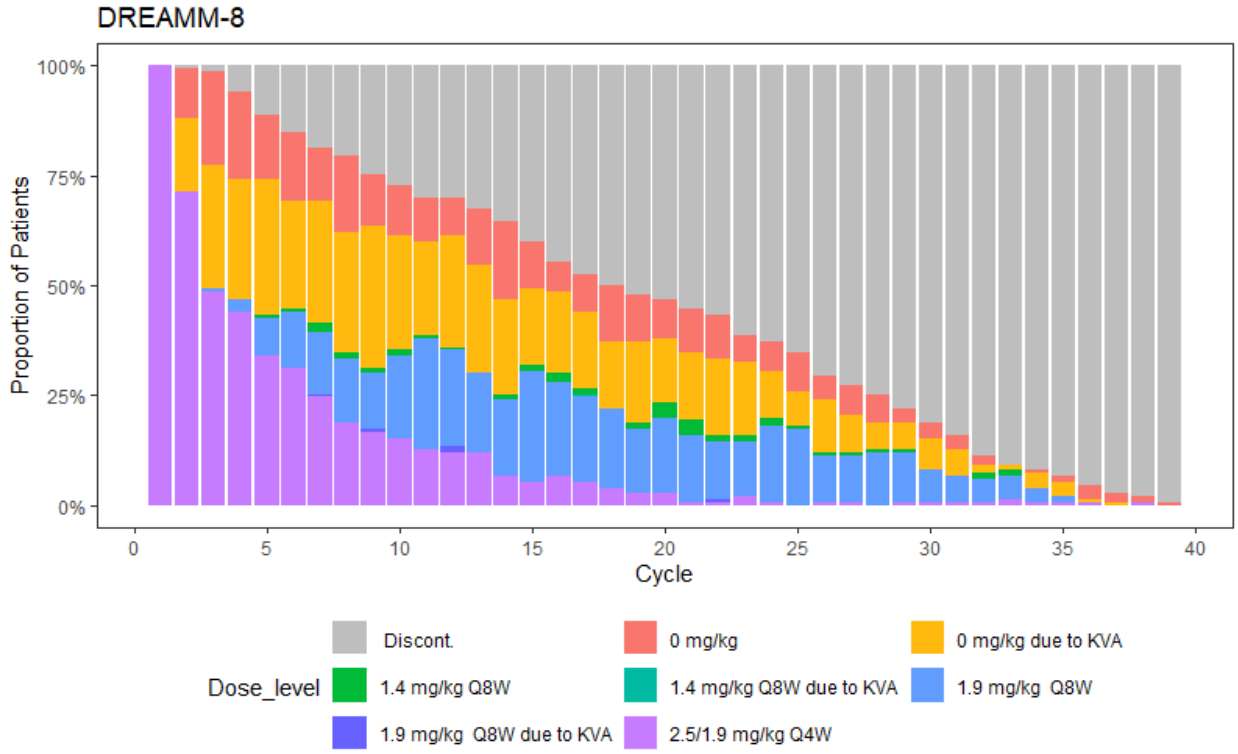
As discussed in Section 7.2.1, Figure 29 and Figure 30 depict the percentage of patients who received a given dose in each cycle of treatment, with the dose modifications due to KVA events specified, for DREAMM-7 and DREAMM-8, respectively.

Figure 29: DREAMM-7 Proportion of Patients Receiving Each Dose Level by Cycle (with KVA-Related Events Specified)



Source: FDA analysis

Figure 30: DREAMM-8 Proportion of Patients Receiving Each Dose Level by Cycle (with KVA-Related Events Specified)

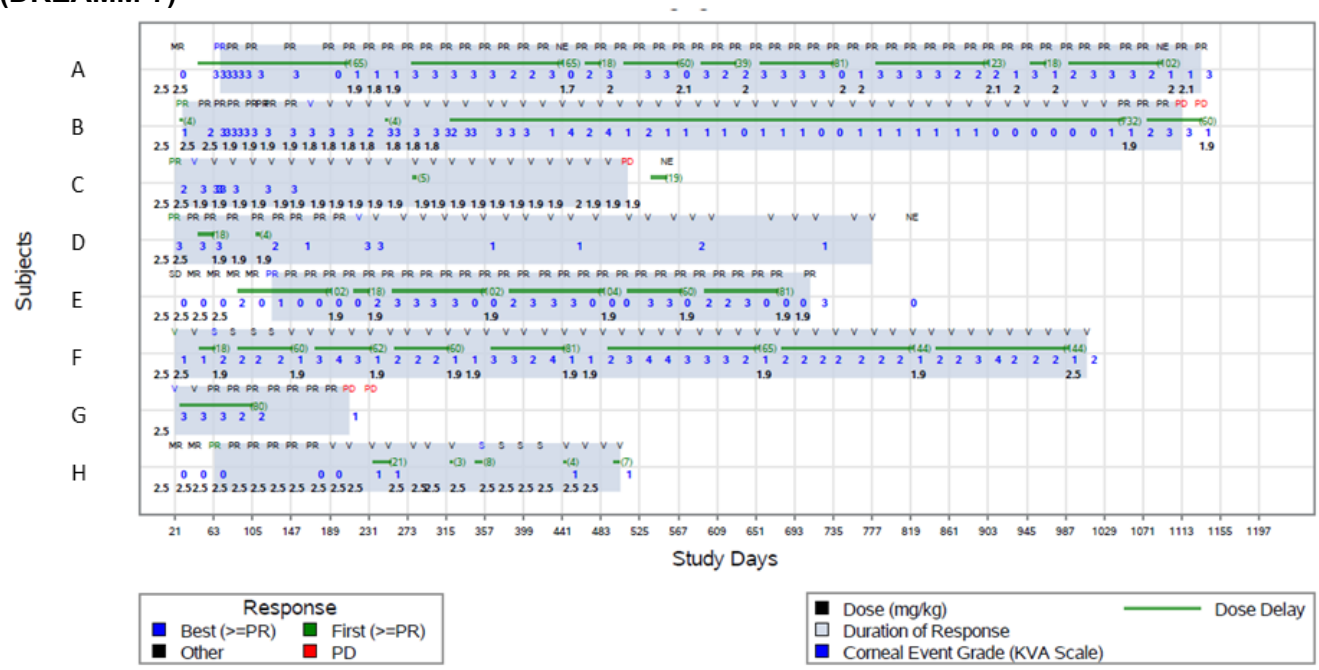


Source: FDA analysis

10.11 Patient Profiles Depicting Dose Modifications

As discussed in Section 7.2.1, Figure 31 depicts eight patient profiles from patients treated on the BVd arm in DREAMM-7. For each patient, the grade of the KVA event experienced is represented by the blue numbers, the dose of belantamab mafodotin received is represented by the black numbers, and the timepoints at which dose delays/interruptions occurred are represented by the green bars. It is notable that several patients (A, B, E, F, and G) had prolonged dose delays/interruptions due to KVA events throughout study treatment, some of whom (A, E, F) experienced recurrent events throughout treatment. While this depiction is specific to these eight patients treated on DREAMM-7, it highlights the prolonged and recurrent nature of KVA events experienced by many patients treated with belantamab mafodotin.

Figure 31: Patient Profiles Depicting Dose Modifications over Time on Treatment (DREAMM-7)



S: Stringent Complete Response, CR: Complete Response, V: Very Good Partial Response, PR: Partial Response, MR: Minimal Response, SD: Stable Disease, PD: Progressive Disease, NE: Not evaluable.
Note: 1. Dose delays are derived and presented when the time between belantamab mafodotin dose administrations, or the time from last dose to death, decision to discontinue treatment, treatment discontinuation date, start of new anti-myeloma therapy or last contact date is > 24 days for belantamab mafodotin. Confirmed IRC-Assessed Response is presented.
2. Dose delay duration reflects the delay from the expected dosing day and does not reflect the time between doses.
/mnt/code/prod/tfls/f_pp_irc_rsp_sp_kva_fda.sas 13FEB2025 14:14

Source: Applicant's Response to FDA Information Request dated February 13, 2025

10.12 PK/PD M-Protein Longitudinal Modeling and Simulations

Further details of the longitudinal PK/PD serum M-protein model used to characterize the exposure-response relationship between belantamab mafodotin exposure and drug activity, as described in Section 7.2.3, are provided below.

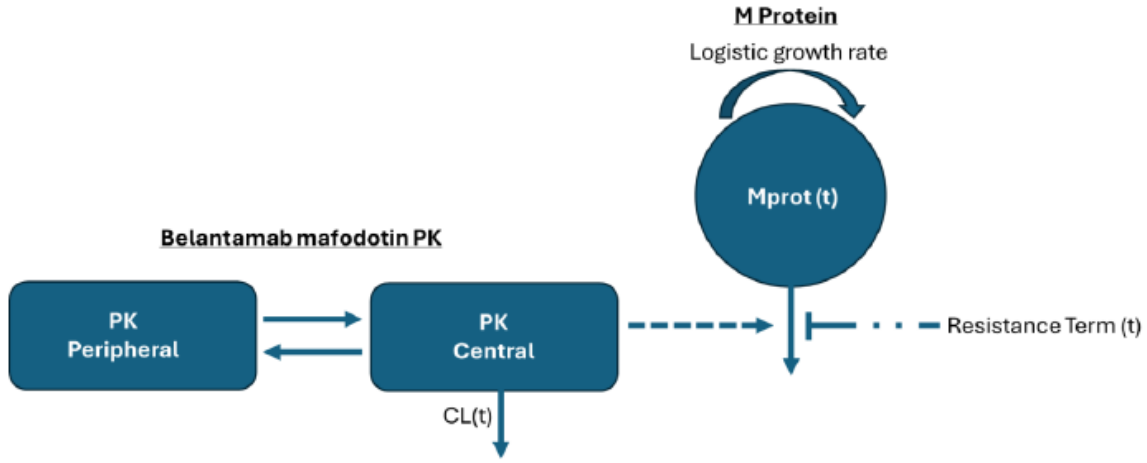
The International Myeloma Working Group (IMWG) identifies the presence of M protein in serum and/or urine, along with clonal plasma cells in the bone marrow, as a critical diagnostic criterion for multiple myeloma (MM). The dynamic changes of M protein can provide additional insights into the clinical benefits of MM treatment.

The Applicant had developed longitudinal tumor growth inhibition models to describe the kinetic changes in serum M protein in participants with RRMM following administration of belantamab mafodotin in combination with bortezomib and dexamethasone (BVd) from DREAMM-6 Arm B and DREAMM-7 and in combination with pomalidomide and dexamethasone (BPd) from DREAMM-8.

The longitudinal PK/PD models characterize the time course of serum M protein following treatment, accounting for tumor growth, drug-induced cell death, and development of resistance. The growth rate of serum M protein expressing cells with a weak Allee effect is described by a logistic model and the treatment effect driven by belantamab mafodotin concentrations is described by an exponential kill model in the elimination of the serum M protein. Resistance is represented by a standard exponential decay on the killing function. Figure 32 illustrates the model structure.

In general, this longitudinal PK/PD model provides a quantitative framework to understand the pharmacodynamic effects of this combination therapy in patients with R/R MM and this type of modeling approach may be utilized to inform future dose selection and clinical trial design.

Figure 32: Model Scheme of the Longitudinal PK/PD Model for Serum M protein

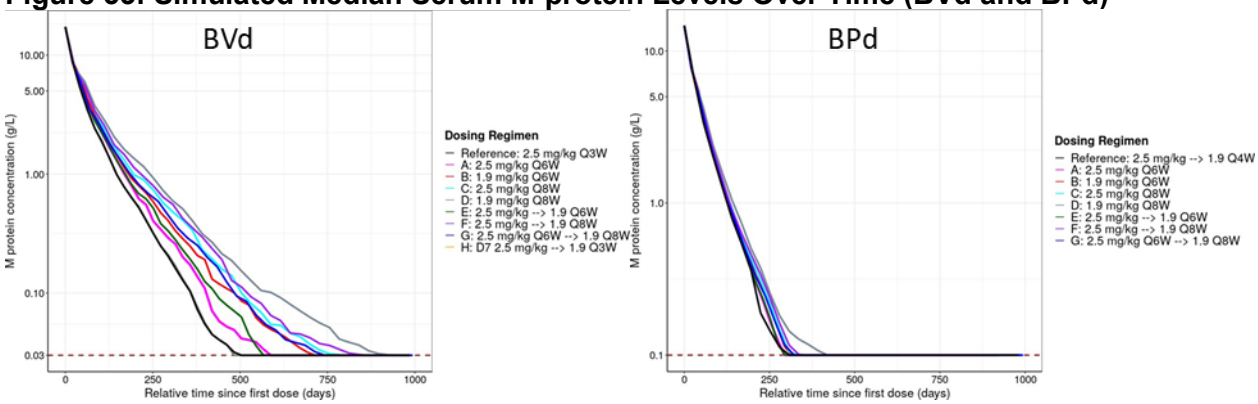


The Sponsor's longitudinal PK/PD models captured both population and individual-level data in both DREAMM-7 and DREAMM-8 studies reasonably well with acceptable agreement between observation and prediction in model evaluation, with slight overprediction of the variability for the lower serum M protein concentration range. In general, the majority of the serum M protein concentration data falls within the model prediction intervals in visual predictive check indicating model predictive ability for simulations.

Based on the final population PK and longitudinal PK/PD models, simulations were conducted using patient data from DREAMM-7 and DREAMM-8 studies. These simulations aimed to predict changes in serum M-protein levels under various dosing regimens of BVd or BPd. Efficacy measures, including Overall Response Rate (ORR) and Very Good Partial Response or better (VGPR+), were calculated using serum M protein-based response definitions from the IMWG. Partial response is defined as ≥50% reduction in M-protein from baseline and very good partial response is defined as ≥90% reduction in M-protein from baseline. The simulations also accounted for patient drop-out due to progressive disease. Patients were removed from the simulations at the time of disease progression, which was defined as an increase of >25% over the lowest on-treatment M-protein concentration, with an absolute increase of >0.5 g/dL.

The simulated serum M-protein concentration-time profiles are illustrated in Figure 33, and the simulation results of efficacy are summarized in Table 29.

Figure 33: Simulated Median Serum M-protein Levels Over Time (BVd and BPd)



While dose modifications were not incorporated into the simulation, given that they are not random and are mostly as a result of toxicities that are not predictable, as they are beyond the scope of the model, this does limit interpretability of the simulated results. Generally, simulated results will overpredict the effect of dosage regimens with high doses and more frequent administrations compared to low doses with less frequent administrations.

As expected, the simulation overpredicts the clinical outcome without considering dose modification information; however, the results provide additional insights on relative outcomes across different dosing regimens. According to the simulation, similarly high efficacy (based on ORR and VGPR+) was predicted for all dosing regimens. Marginally higher efficacy was noted with higher starting doses and shorter dosing intervals, however as noted earlier, these responses may be overestimated due to toxicities leading to dose modifications. However, in general, simulations predicted similar ORR for lower doses and longer dosing intervals compared to higher doses and shorter intervals for both the BVd and BPd regimens. The overall trends observed in the PK-PD simulation align with the results from dose-finding trials, which did not demonstrate significant efficacy losses with lower doses and longer dosing intervals.